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Clinical Research Article

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Primary Hyperparathyroidism Is Associated With Shorter QTc Intervals, but Not Arrhythmia

Latoya A. Stewart,[1] Gabrielle K. Steinl,[1] Bernice L. Huang,[2] Catherine McManus,[2] James A. Lee,[2] Jennifer H. Kuo,[2] and Marcella D. Walker[3]

[1]Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA; [2]Section of Endocrine Surgery, Columbia University Irving Medical Center, New York, NY, USA; and [3]Department of Medicine, Division of Endocrinology, Columbia University Irving Medical Center, New York, NY, USA

ORCiD numbers: 0000-0001-7898-2719 (L. A. Stewart); 0000-0002-7205-6527 (M. D. Walker).

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Abstract

Context: Primary hyperparathyroidism (PHPT) is associated with subclinical cardiovascular disease, but data regarding cardiac conduction abnormalities are limited.
Objective and Design: Retrospective cross-sectional comparison of cardiac conduction in patients with PHPT or thyroid disease (TD).
Participants and Setting: Patients ≥40 years old who underwent parathyroidectomy or thyroidectomy at a single tertiary institution from 2013 to 2018.
Methods and Outcomes: Demographics and preoperative electrocardiogram (EKG) parameters were compared using the Mann-Whitney U, chi-square test, and linear regression.
Results: A total of 1242 patients were included: 49.8% PHPT (n = 619) and 50.2% TD (n = 623). Median age was 60.5 years [interquartile range (IQR) 53.6-67.9]. Compared to controls, PHPT patients had higher median serum calcium [10.7 mg/dL (IQR 10.4-11.1) vs 9.5 mg/dL (IQR 9.3-9.8), $P < 0.001$] as expected, as well as, a higher prevalence of hyperlipidemia (49% vs 36%, $P < 0.001$) and hypertension (50.1% vs 42.2%, $P < 0.01$). Based on EKG, there was no difference in PR interval or the prevalence of arrhythmia, atrioventricular block, ST segment/T wave changes, premature ventricular complexes, right bundle branch block, or left bundle branch block after adjusting for covariates. The PHPT group had a lower mean corrected QT interval (414 ± 24) ms vs 422 ± 24 ms, $P < 0.01$), adjusted for covariates. Serum calcium predicted QTc independently of age, sex, and other covariates.
Conclusions: In the largest study to date, PHPT patients had shorter QTc intervals compared to TD controls but no increased prevalence of arrhythmia based on preoperative EKG.

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Key Words: primary hyperparathyroidism, hypercalcemia, electrocardiogram, conduction abnormalities, arrhythmia

Classical primary hyperparathyroidism (PHPT), characterized by severe hypercalcemia, is associated with increased cardiovascular mortality (1,2). The effect of the modern form of PHPT, typically associated with milder hypercalcemia, on risk of death remains unclear (3). Mild PHPT has, however, been associated with subclinical cardiovascular disease, such as hypertension, increased vascular stiffness, and left ventricular hypertrophy, among other findings (4,5). Few studies have investigated cardiac conduction abnormalities in patients with PHPT (5,6). Calcium is vital in cardiac sarcomere excitation-contraction coupling and the initiation and propagation of depolarization. During phase 2 of the cardiac action potential, calcium entry through voltage-gated channels triggers further calcium release from the sarcoplasmic reticulum and myocyte contraction. Given the role of calcium in cardiac conduction, hypercalcemia in PHPT could contribute to an increased risk of cardiac conduction abnormalities and an increased risk for arrhythmias.

The QT interval on electrocardiogram (EKG) is the time from the beginning of the QRS complex, which represents ventricular depolarization, to the end of the T wave, which indicates ventricular repolarization (7). A shortened QT interval or "short QT," first described by Bronsky et al in the 1960s, is a well-documented consequence of hypercalcemia, conferring a potential risk of arrhythmia (8). The Third National Health and Nutrition Examination Survey (n = 7828) demonstrated that both shortened and prolonged QT intervals, even within reference range, were associated with increased total and cardiac mortality risk in the general population (9). However, data regarding cardiac conduction abnormalities in a large PHPT cohort are limited, and the implications for patients with PHPT remain unclear. The frequency of clinically significant conduction abnormalities in PHPT such as left bundle branch block (LBBB), sinus and atrioventricular (AV) block, and ventricular tachycardia is unknown but have been reported in case reports of moderate to severe hypercalcemia (10-13).

Other known EKG abnormalities associated with hypercalcemia of various etiologies include a prolonged PR interval, representing the length of time from the start of atrial depolarization to the start of ventricular depolarization; a prolonged QRS duration, indicating the length of ventricular depolarization; and ST segment/T wave changes (14). T-wave morphology changes that have been described in non-PHPT severe hypercalcemia include inverted, biphasic, and notched T waves (15). A retrospective review of hospitalized patients with hypercalcemia of various etiologies (corrected serum calcium > 12 mg/dL; n = 89) matched to normocalcemic controls showed shortened QT/QTc intervals, longer QRS duration and PR intervals, more ST segment/T-wave abnormalities, and more instances of J point elevation, an indicator of early repolarization, in the hypercalcemic group but reported no arrhythmic events (16). A matched study of PHPT patients (n = 139) showed that calcium levels were significantly correlated to higher QRS amplitude, shorter ST segment duration, shorter QT interval, and longer T wave duration after adjusting for age, sex, and antihypertensive use (8).

Given the paucity of data in patients with the modern form of PHPT, we aimed to assess cardiac conduction abnormalities in a large cohort of patients with PHPT. We compared preoperative QT/QTc interval values and other quantitative EKG parameters between patients with PHPT and controls with thyroid disease. We also compared the frequency of arrhythmia, premature ventricular beats, AV block, and other measures reported on EKG between the 2 groups. We hypothesized that hypercalcemia would be associated with shorter QT intervals.

Methods

Study Design, Subjects, and Data Collection

We conducted a retrospective review of the electronic medical records of patients 40 years of age and older who underwent parathyroidectomy for PHPT or thyroidectomy for nontoxic goiter at Columbia University Irving Medical Center between January 1, 2013 and August 9, 2018. This age group was selected because patients over 40 years old routinely have EKGs performed as part of their preoperative clinical assessment. We included both those with hypercalcemic PHPT and normocalcemic PHPT, both of which are recognized as biochemical phenotypes of PHPT by the Fourth and Fifth International Conferences on PHPT (17). Hypercalcemic PHPT was defined by persistent elevation of serum total calcium and/or ionized calcium with elevated or inappropriately normal parathyroid hormone on at least 3 labs obtained at different time periods. Normocalcemic PHPT was classified by normal total serum and ionized calcium levels with concomitant elevation in parathyroid hormone, after exclusion of other causes of secondary hyperparathyroidism [vitamin D deficiency, hydrochlorothiazide use, renal insufficiency, liver disease; hypercalciuria, thiazide diuretic or lithium use; and other

metabolic bone diseases (eg, Paget's disease) (18)]. We included those with normocalcemic PHPT to assess the relative roles of serum calcium vs PTH on QT interval within the PHPT group and the impact of normocalcemic PHPT on QT intervals. Patients with pacemakers and hypo-/hyperthyroidism were excluded. Patients were also excluded if they had no preoperative EKG report available, if the report was not legible or lacking numerical data, or if the EKG values provided were erroneous and outside of the physiological range.

Data on patient demographics, medical comorbidities, medication use, baseline laboratory values, and EKG parameters prior to surgery were extracted from the medical record. Comorbidities, medications, and race/ethnicity data were obtained from physician notes, clinic questionnaires, and patient report. Consistent with the typical preoperative workup, laboratory values and EKG reports were obtained at the host institution and outside facilities. Hypercalcemia severity was classified based on preoperative calcium levels: mild hypercalcemia (10.4-11.9 mg/dL), moderate hypercalcemia (12-13.9 mg/dL), and severe hypercalcemia (>13.9 mg/dL). EKG interpretations were largely acquired from machine readings and qualitative indices were corroborated through formal review whenever possible. EKG parameters included rhythm, heart rate, axis, PR interval (normal: 120-200 ms), QRS duration (normal: 80-100 ms), QT/QTc intervals, and presence of heart block, left and right bundle branch block, ST interval changes, T-wave changes, and premature ventricular contractions (PVCs). Corrected QT interval calculated using Bazett's formula was determined as a means of standardization: $QTc = QT/\sqrt{(60/HR)}$. Measurements were obtained from preoperative 12-lead EKG tracings. The study was approved by the Columbia University Irving Medical Center Institutional Review Board.

Statistical Analysis

All statistical analyses were performed using RStudio v 1.4.1103 (www.rstudio.org, Boston, MA, USA). The Shapiro-Wilk test was first applied to assess normality. Associations between continuous variables were examined using the Spearman rank-order correlation test. Preoperative patient characteristics and EKG parameters were compared using the Mann-Whitney U nonparametric test for continuous variables, and the chi squared test was used for categorical variables. Multivariable linear regression and logistic regression were used to compare differences in EKG parameters between the PHPT and control groups adjusting for variables that differed between groups on univariable analysis. A 2-tailed P-value < 0.05 was considered statistically significant.

Results

A total of 1380 consecutive patient records meeting inclusion criteria were identified. Of these, 138 records were excluded for the following reasons: missing EKG (n = 59), no numerical data (n = 48), not legible (n = 21), paced rhythm (n = 4), machine error (n = 2), and duplicate (n = 4). The remaining 1242 records (PHPT group = 619, thyroid disease controls = 623) were analyzed.

Demographics

The demographic composition of the cohort was predominantly white race (64.5%), non-Hispanic (73.7%), and female (80.8%), with a median age at surgery of 60.5 years [interquartile range (IQR) 53.6-67.9] (Table 1). Patients with PHPT were slightly older and more likely to be white and non-Hispanic. There was no between-group difference based on sex. Within the thyroid disease group, 77.7% and 22.3% underwent total thyroidectomy and hemithyroidectomy, respectively. All patients in the thyroid disease group were euthyroid. In patients within the PHPT group, surgical pathologic findings were consistent with parathyroid hyperplasia, enlarged glands, and/or adenomata.

Medical History

There were no between-group differences in self-reported history of coronary artery disease, myocardial infarction, atrial fibrillation, arrhythmia, asthma, chronic obstructive pulmonary disease, or chronic kidney disease (Table 2). The most commonly reported arrhythmias based on history were PVCs and supraventricular tachycardias. Compared to controls, a higher proportion of patients in the PHPT group had a history of hyperlipidemia (48.8% vs 36.2%, $P < 0.001$) and hypertension (50.1% vs 42.2%, $P < 0.01$) (Table 2).

As shown in Table 2, there was no difference in the use of the following medications between the PHPT and control groups: nitrates, diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, amiodarone, digoxin, beta blockers, aspirin or other antiplatelet agents, anticoagulants, bisphosphonates, selective estrogen receptor modulators, cinacalcet, antidepressants, or albuterol. The frequency of use of calcium channel blockers, levothyroxine, vitamin D supplements, and amphetamine-dextroamphetamine were higher in the PHPT group, whereas the use of calcium supplements was higher in the control group (Table 2).

Table 1. Comparison of demographic data between patients with primary hyperparathyroidism and thyroid disease

Variable	Total (n = 1242)	PHPT (n = 619)	Control (n = 623)	*P*-value
Age at surgery	60.5 (53.6-67.9)	61.6 (54.7-68.8)	59.5 (52.8-66.7)	<0.01
Race				<0.001
White	801 (64.5)	443 (71.6)	358 (57.5)	
Black/African American	102 (8.2)	50 (8.1)	52 (8.4)	
Asian	36 (2.9)	12 (1.9)	24 (3.9)	
Native Hawaiian/Pacific Islander	1 (0.1)	1 (0.2)	0	
Mixed Race	24 (1.9)	7 (1.1)	17 (2.7)	
American Indian/Alaskan Native	1 (0.1)	1 (0.2)	0	
Unknown	277 (22.3)	105 (17.0)	172 (27.6)	
Ethnicity				<0.001
Non-Hispanic	915 (73.7)	502 (81.1)	413 (66.3)	
Hispanic	144 (11.6)	59 (9.5)	85 (13.6)	
Unknown	183 (14.7)	58 (9.4)	125 (20.1)	
Sex				0.65
Male	238 (19.2)	115 (18.6)	123 (19.7)	
Female	1004 (80.8)	504 (81.4)	500 (80.3)	
Surgery type				NA
Hemithyroidectomy	139 (11.2)	0	139 (22.3)	
Total thyroidectomy	484 (39.0)	0	484 (77.7)	
Parathyroidectomy	619 (49.8)	619 (100)	0	

Values represent n (%) or median (interquartile range).
Abbreviations: PHPT, primary hyperparathyroidism; NA, not applicable.

Laboratory Values

Preoperative median serum calcium (IQR) [10.7 (10.4-11.1) vs 9.5 (9.3-9.8) mg/dL, normal: 8.8-10.3 mg/dL, $P < 0.001$] and PTH values [90 (66-122.2) vs 42 (35.75-50.35) pg/mL, normal: 15.1-85.7 pg/mL, $P < 0.001$] were significantly higher in the PHPT group (Table 3). However, serum PTH levels were only available for 19/623 (3%) controls. Within the PHPT group, 24% had a serum calcium measurement within the normal range, 73% had mild hypercalcemia (10.4-11.9 mg/dL), 3% had moderate hypercalcemia (12-13.9 mg/dL), and <1% had severe hypercalcemia (>13.9 mg/dL) on the day of measurement. There were no differences in serum albumin, creatinine, glomerular filtration rate, magnesium, or vitamin D levels. Ionized calcium measurements were available for only 0.5% of controls and were not assessed further. Serum thyroid-stimulating hormone was also higher in the PHPT group, but within the normal range for both groups (Table 3).

EKG Parameters

With respect to findings on 12-lead EKG, there were no significant differences in the recorded rhythm between the 2 groups. Specifically, the frequency of normal sinus rhythm, sinus bradycardia or tachycardia, and atrial fibrillation did not differ. As shown in Figure 1, there was also no difference in the occurrence of first or second degree AV block, ST-segment or T-wave changes, PVCs (extra beats originating in the ventricles), or right bundle branch block. In unadjusted analyses, the PHPT group had a higher prevalence of LBBB (3.9% vs 1.8%, $P < 0.05$) compared to controls (Fig. 1). As shown in Figure 2, the PHPT group also had a lower median heart rate, longer PR interval, and shorter QT [386 (368-406) ms vs 398 (376-418) ms, $P < 0.001$] and QTc interval [412 (395.8-426.9) ms vs 426 (410-441.5) ms, $P < 0.001$]. There were no significant differences in axis or QRS duration. In adjusted models (Figs. 1 and 2), PHPT was not associated with the frequency of LBBB, heart rate, PR interval, or uncorrected QT, but QTc remained significantly shorter in the PHPT group (414 ± 24 ms vs 422 ± 24 ms, adjusted *P*-value < 0.01).

Calcium levels were significantly correlated with QT ($\rho = -0.20$, $P < 0.001$) and QTc ($\rho = -0.28$, $P < 0.001$) interval but not with other quantitative EKG parameters. Within the PHPT group, we also observed shorter QT (IQR) [384 (368-402.8) ms vs 388 (372-414.5) ms, $P < 0.05$] and QTc intervals [410 (394.6-425.7) ms vs 416 (400.1-428.7) ms, $P < 0.05$] in PHPT patients with elevated serum calcium measurements compared to those with values in the normal range. Furthermore, PHPT patients with normal serum calcium measurements had shorter QT [388 (372-414.5) ms vs 398 (376-418) ms, $P < 0.001$] and QTc [416 (400.1-428.7) ms vs 426 (410-441.5) ms, $P < 0.001$] intervals than controls. Using univariable linear regression analysis, serum

Table 2. Cardiovascular comorbidities and medication use

Variable	Total (n = 1242)	PHPT (n = 619)	Control (n = 623)	*P*-value
Condition				
Coronary artery disease	61 (4.9)	31 (5.0)	30 (4.8)	0.98
Myocardial infarction	11 (0.9)	8 (1.3)	3 (0.5)	0.22
Hyperlipidemia	526 (42.5)	301 (48.8)	225 (36.2)	<0.001
Atrial fibrillation	33 (2.7)	15 (2.4)	18 (2.9)	0.74
Arrhythmia	15 (1.2)	8 (1.3)	7 (1.1)	0.81
Asthma	86 (6.9)	46 (7.4)	40 (6.4)	0.56
COPD	27 (2.2)	16 (2.6)	11 (1.8)	0.43
Chronic kidney disease	27 (2.2)	18 (2.9)	9 (1.5)	0.12
Hypertension	572 (46.1)	310 (50.1)	262 (42.2)	<0.01
Cardiovascular medication use				
Nitrates	6 (0.5)	2 (0.3)	4 (0.6)	0.69
Diuretics	167 (13.5)	76 (12.3)	91 (14.6)	0.27
ACEi/ARB	393 (31.6)	207 (33.4)	186 (29.9)	0.20
Amiodarone	1 (0.1)	1 (0.2)	0 (0)	1.0
Digoxin	5 (0.4)	4 (0.7)	1 (0.2)	0.37
Beta blocker	196 (15.8)	95 (15.4)	101 (16.2)	0.73
Calcium channel blocker	194 (15.6)	111 (17.9)	83 (13.3)	<0.05
Aspirin/Antiplatelet	263 (21.2)	140 (22.6)	123 (19.7)	0.24
Anticoagulant	33 (2.7)	19 (3.1)	14 (2.3)	0.47
Endocrine medication use				
Levothyroxine	173 (13.9)	111 (17.9)	62 (10.0)	<0.001
Calcium supplementation	108 (8.7)	42 (6.8)	66 (10.6)	<0.05
Vitamin D supplementation	377 (30.4)	211 (34.1)	166 (26.7)	<0.01
Bisphosphonates	46 (3.7)	28 (4.5)	18 (2.9)	0.17
SERMs	7 (0.6)	3 (0.5)	4 (0.6)	1
Cinacalcet	4 (0.33)	4 (0.66)	0 (0)	0.13
Other medications				
Antidepressant	188 (15.1)	105 (17.0)	83 (13.3)	0.09
Amphetamine-dextroamphetamine	11 (0.9)	10 (1.6)	1 (0.2)	<0.05
Albuterol	56 (4.5)	30 (4.9)	26 (4.2)	0.66

Values represent n (%) or median (interquartile range)

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; PHPT, primary hyperparathyroidism; SERM, selective estrogen receptor modulator.

Table 3. Laboratory values

Laboratory value	Normal range[a]	Total (n = 1242)	PHPT (n = 619)	Control (n = 623)	*P*-value
Sodium, mEq/L	137-145	140 (139-142)	140 (138-142)	140 (139-142)	<0.05
Potassium, mEq/L	3.5-5.1	4.3 (4.1-4.6)	4.4 (4.1-4.6)	4.3 (4.1-4.6)	<0.001
Magnesium, mg/dL	1.6-2.4	2.1 (2-2.2)	2.1 (2-2.2)	2.2 (2.0-2.3)	0.41
Calcium, mg/dL	8.8-10.3	10 (9.5-10.7)	10.7 (10.4-11.1)	9.5 (9.3-9.8)	<0.001
Albumin, mg/dL	3.9-5.2	4.3 (4.2-4.5)	4.4 (4.2-4.5)	4.3 (4.1-4.5)	0.11
PTH, pg/mL	15-86	88 (63-121)	90 (66-122.2)	42 (35.8-50.4)	<0.001
Creatinine, mg/dL	0.5-0.95	0.8 (0.7-0.92)	0.79 (0.7-0.91)	0.8 (0.7-0.9)	0.18
GFR, mL/min	>60	60 (60-84)	60 (60-86)	60 (60-81)	0.07
GFR < 60 mL/min		133 (11.0)	68 (11.1)	65 (10.9)	
GFR < 30 mL/min		6 (0.5)	3 (0.5)	3 (0.5)	
TSH, mIU/L	0.4-4.8	1.52 (0.9-2.3)	1.67 (1-2.3)	1.34 (0.9-2.2)	<0.05
Vitamin D, ng/dL	30-100	30.3 (23-38)	30.4 (23.2-37.8)	30.3 (22.6-38.9)	0.95

Values represent n (%) or median (interquartile range).

Abbreviations: GFR, glomerular filtration rate; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

[a]Normal range at Columbia University Irving Medical Center.

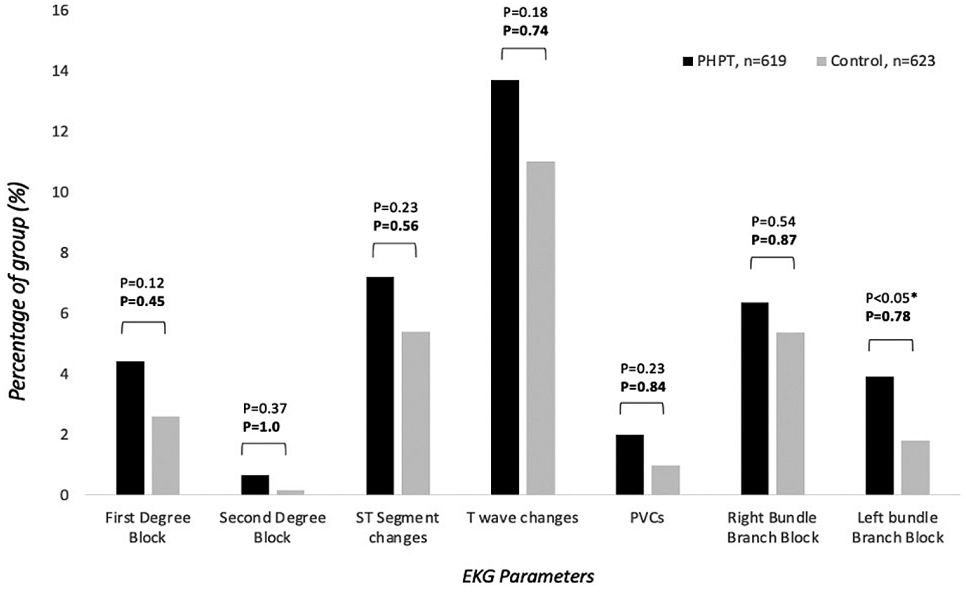

Figure 1. Comparison of the frequency of electrocardiogram (EKG) interval and waveform abnormalities between patients with primary hyperparathyroidism (PHPT) and controls. Black indicates the PHPT group and gray represents the control group. Top and bottom (bold) *P*-values represent unadjusted and adjusted *P*-values, respectively. Presence of left bundle branch block was only significantly different in unadjusted model; 12-lead EKG rhythm (normal sinus rhythm, sinus tachycardia, sinus bradycardia, arrhythmia) was not statistically different between the 2 groups in unadjusted or adjusted analysis (not shown). Abbreviation: PVC, premature ventricular contraction.

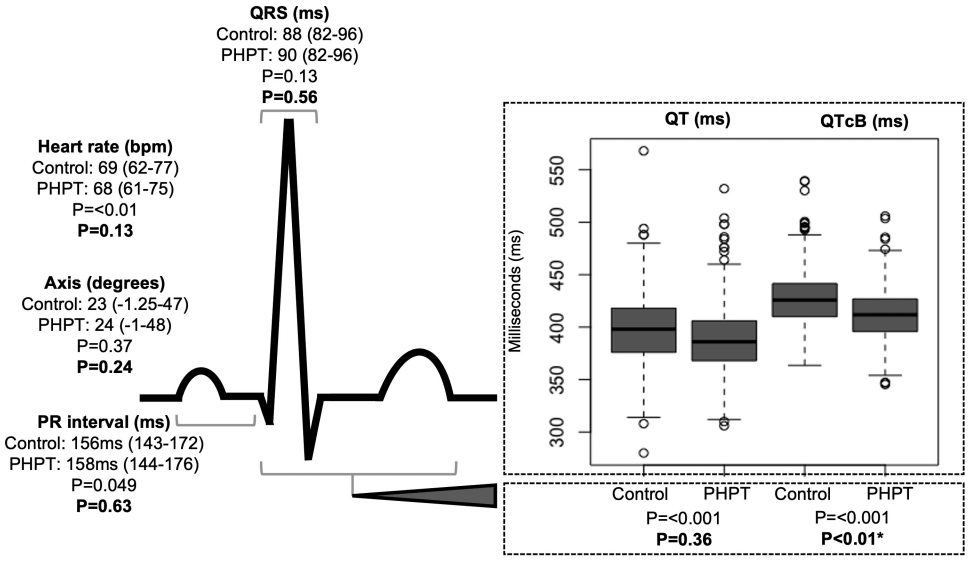

Figure 2. Schematic indicating electrocardiogram intervals and a comparison of QTc measurements in primary hyperparathyroidism and control groups. *indicates *P*-value remains significant after adjustment for covariates. Values represent median (interquartile range); *P*-values from unadjusted and adjusted (bold) models. There was a significant difference in QTcB interval between the groups in unadjusted and adjusted models. Abbreviation: QtcB, QT interval with Bazett correction.

calcium was a significant predictor of both the QT [(unadjusted β = −7.96 (95% CI: −10.0, −5.9), $P < 0.001$] and QTc interval [unadjusted β = −9.05 (95% CI: −10.7, −7.4), $P < 0.001$]. The β is interpreted to mean that for each 1 mg/dL increase in calcium, QTc interval decreased by 9.05 ms.

On multivariable analysis, serum calcium level was a significant predictor of decreased QTc interval [adjusted β = −9.4 (95% CI: −11.1, −7.7), $P < 0.001$]. Serum potassium [adjusted β = −6.0 (95% CI: −9.5, −2.5), $P < 0.001$] and history of hypertension [adjusted β = −6.6 (95% CI: −9.6, −3.6), $P < 0.001$] were also significant predictors of

Table 4. Multivariable model of QT interval

Model	Predictors	β (95% CI)	*P*-value	Model adjusted R^2 and *P*-value
QTc interval (entire cohort)				
	Serum calcium, per mg/dL	−9.4 (−11.1, −7.7)	<0.001	Model $R^2 = 0.113$ $P = 2.2 \times 10^{-16}$
	Age, per year	0.05 (−0.1, 0.2)	0.54	
	Ethnicity	−2.5 (−5.2, 0.2)	0.06	
	Potassium, per mEq/L	−6.0 (−9.5, −2.5)	<0.001	
	Hypertension	−6.6 (−9.6, −3.6)	<0.001	
	Hyperlipidemia	−1.4 (−4.4, 1.7)	0.38	
QTc interval (excluding patients taking medications that may affect QT interval)				
	Serum calcium, per mg/dL	−9.0 (−10.9, −7.1)	<0.001	Model $R^2 = 0.100$ $P = 2.2 \times 10^{-16}$
	Age, per year	0.1 (−0.1, 0.3)	0.24	
	Ethnicity	−2.8 (−5.8, 0.2)	0.07	
	Potassium, per mEq/L	−4.5 (−8.5, −0.5)	0.03	
	Hypertension	−6.2 (−9.5, −2.9)	<0.001	
	Hyperlipidemia	0.2 (−3.2, 3.5)	0.93	
QTc interval (PHPT group alone)				
	Serum calcium, per mg/dL	−8.0 (−10.8, −5.2)	<0.001	Model $R^2 = 0.069$ $P = 5.68 \times 10^{-09}$
	Age, per year	0.15 (−0.1, 0.4)	0.17	
	Ethnicity	−3.7 (−7.9, 0.6)	0.09	
	Potassium, per mEq/L	−3.5 (−8.4, 1.3)	0.15	
	Hypertension	−6.2 (−10.2, −2.2)	<0.01	
	Hyperlipidemia	−1.01 (−5.0, 3.0)	0.62	
QTc Interval (PHPT group excluding patients with normocalcemic PHPT)				
	Serum calcium, per mg/dL	−7.9 (−11.8, −3.9)	<0.001	Model $R^2 = 0.058$ $P = 4.7 \times 10^{-6}$
	Age, per year	0.3 (0.1, 0.6)	0.01	
	Ethnicity	−2.0 (−6.9, 3.0)	0.44	
	Potassium, per mEq/L	−3.3 (−8.7, 2.2)	0.24	
	Hypertension	−5.7 (−10.4, −1.0)	0.02	
	Hyperlipidemia	−0.3 (−5.1, 4.6)	0.92	

Abbreviation: PHPT, primary hyperparathyroidism.

QTc interval, but age, ethnicity, and hyperlipidemia were not. Use of cardiovascular, endocrine, and other medications was not associated with QTc interval in the model. Excluding those taking medications that might affect the QT interval (albuterol, amiodarone, antidepressants) did not appreciably change the model or significance of serum calcium in the model (Table 4).

Furthermore, when evaluating the PHPT group alone, serum calcium [adjusted β = −8.0 (95% CI: −10.8, −5.2), $P < 0.001$], and history of hypertension [adjusted β = −6.2 (95% CI: −10.2, −2.2), $P < 0.01$], remained significant predictors of decreased QTc interval, while serum potassium did not (Table 4). PTH level was not a significant predictor in the model. Excluding those with normal calcium, potassium level was no longer significant, but calcium remained a significant predictor while age became a significant predictor (Table 4).

Discussion

In the largest study assessing cardiac conduction to date, we compared preoperative EKG parameters between patients with PHPT and controls with thyroid disease. We found that patients with PHPT have shorter QTc intervals and calcium levels were a predictor of shorter QTc intervals. Although short QT interval has been associated with arrhythmia in other settings, we found no difference in the frequency of arrhythmia in patients with PHPT compared to controls, based on EKG. Our findings are reassuring regarding the effects of PHPT on the occurrence of clinically significant conduction abnormalities and arrhythmia in modern PHPT. Given that EKG provides only a one-time snapshot of cardiac conduction, we cannot rule out the possibility that longer term monitoring might reveal differences in paroxysmal arrhythmias that were not shown here.

Inclusion of a normocalcemic PHPT group in our analysis allowed us to assess the relative contributions of serum calcium vs PTH on the QT interval. While we hypothesized hypercalcemia was associated with shortened QT interval, there are data to suggest PTH is also related to QT interval independent of serum calcium in the general population (19). Our results show that QT intervals are shorter in those with hypercalcemic vs normocalcemic PHPT,

indicating a clear role for serum calcium. Of note, however, patients with normocalcemic PHPT had shorter QT intervals than controls, which may suggest an independent role for PTH. Alternatively, a recent study indicated that even in patients with normocalcemic PHPT, serum calcium levels are higher than in controls without normocalcemic PHPT (20). Further work is needed to clarify the basis for the shortened QT interval in patients with normocalcemic PHPT. Our findings however add to the very limited data available regarding the cardiovascular manifestations of this important biochemical phenotype.

The QT interval indicates action potential duration, and a shortened QT interval represents accelerated repolarization which may occur increased activity of repolarizing currents or decreased activity of depolarizing currents (21). High serum calcium decreases ventricular conduction velocity and shortens the effective refractory period, which theoretically may increase the likelihood of reentry and ventricular arrhythmia (13). Indeed, there are reports of ventricular tachycardia and sudden cardiac death in the setting of hypercalcemic crisis related to PHPT and severe non-PHPT-mediated hypercalcemia (13,22). The effects of mild hypercalcemia related to the modern form of PHPT on conduction and arrhythmic risk are less clear.

Several studies have reported shortened QT intervals in patients with PHPT (23,24). Similar to our study, a recent smaller study indicated postmenopausal women with PHPT (n = 26) had a lower QTc interval than controls; the clinical significance of shortened QT intervals in PHPT remains unclear. Like our study, this study showed no evidence of arrhythmia but did show a higher prevalence of PVCs and supraventricular premature contractions during 24-h EKG monitoring. After randomization to parathyroidectomy or observation, there was a subsequent reduction in PVCs/supraventricular premature contractions 6 months after surgery (23). On the other hand, another study (n = 30) showed fewer PVCs in patients with PHPT compared to controls (25). Like our study, other limited data indicate effects on QT interval but no increase in the prevalence of arrhythmias such as supraventricular or ventricular arrhythmias in PHPT (24).

Reports of AV nodal dysfunction in PHPT are rare, although degeneration of the electrical conduction system from calcification has been suspected as a potential causative factor (11,12,26,27). We found no evidence of AV nodal dysfunction based on similar PR intervals and similar frequencies of first- and second-degree AV block in cases and controls after adjusting for covariates. Similarly, another small retrospective study of patients with PHPT [mean serum calcium of 11.4 mg/dL (2.85 mmol/L), n = 20] showed no high grade AV block preoperatively (24). We found that the prevalence of LBBB was higher in PHPT than the controls, but this was related to age and not PHPT and was attenuated and no longer significant after adjusting for covariates. Although there are case reports of ST segment elevations in severe hypercalcemia, there are fewer reported occurrences in the setting of mild hypercalcemia (28-31). In this study, we did not find a higher prevalence of ST elevations among patients with PHPT. This was not unexpected given participants were generally healthy enough to undergo preoperative evaluation for surgery.

Our study has several limitations. This analysis was based on retrospective data collected for clinical purposes. Since our institution is a large, tertiary referral center, EKGs were performed at various facilities due to convenience. Representative of the usual clinical preoperative workup, there was heavy reliance on machine interpretation and calculations with few independent formal reviews of the EKG tracings by cardiologists. Findings were based on a single preoperative EKG rather than Holter monitoring, which may have been able to detect differences not captured with a standard 12-lead EKG. Moreover, although the Bazett correction is the best method to standardize measurement of the QT interval, it can overestimate the QT interval at higher heart rates and underestimate at lower heart rates (9,21). About one fourth of patients had normocalcemic, rather than, hypercalcemic PHPT. While this may be considered a limitation, it allowed assessment of the relative roles of serum calcium vs PTH on QT interval and provides data regarding the cardiovascular manifestations of normocalcemic PHPT, a recognized biochemical phenotype of PHPT, for which current information is severely limited. The analysis was unchanged after excluding those with normocalcemic PHPT. Further, we lacked data regarding serum calcium levels in the majority of the control group. However, based on the prevalence of hyper- and hypocalcemia in the general ambulatory population, we would expect >99% of controls to have normal serum calcium values. Our main analysis included patients taking medications that could, in theory, affect cardiac conduction or QT interval. However, none of these medications were associated with QT interval in our analysis and results were unchanged after excluding those on medications in categories that may affect QT interval.

Despite these limitations, there are important strengths to our study. This analysis represents the largest evaluation of cardiac conduction in PHPT and included a multiethnic population. Additionally, we comprehensively accounted for cardiovascular comorbidities, medications, and electrolyte disturbances that might influence the risk of arrhythmia (13,14,24,32-34). In addition, the control group was selected from the same population as the PHPT group and was generally well-matched, thereby increasing its validity as a comparator.

Conclusion

PHPT is associated with shortened QTc interval, but we found no association with arrhythmia or other indices of cardiac conduction based on EKG. While the results are reassuring, further studies are needed to investigate the long-term consequences of short QTc in PHPT, specifically, the lifetime risks of developing clinically significant cardiac events and mortality.

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Additional Information

Correspondence: Marcella Walker, MD, Division of Endocrinology, 180 Fort Washington Ave, 9th Floor #904, Columbia University Irving Medical Center, New York, NY 10032, USA. Email: mad2037@cumc.columbia.edu.

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