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Parathyroid hormone is related to QT interval independent of serum calcium in patients with coronary artery disease

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Background: Elevated serum parathyroid hormone (PTH) is associated with increased risk of cardiovascular death, including sudden cardiac death, in patients with and without parathyroid disease. In small studies, PTH levels have been associated with changes in cardiac conduction and repolarization. Changes in the corrected QT interval (QTc) in particular are thought to be mediated by the effect of PTH on serum calcium. There is limited evidence to suggest PTH may affect cardiac physiology independent of its effects on serum calcium, but there is even less data linking PTH to changes in electrical conduction and repolarization independent of serum calcium.

Methods: ECG data were examined from the PULSE database—an observational cohort study designed to examine depression after acute coronary syndromes (ACS) at a single, urban American medical center. In all, 407 patients had PTH and ECG data for analysis.

Results: The QTc was longer in patients with elevated PTH levels compared with those without elevated PTH levels (451 ± 38.6 ms vs. 435 ± 29.8 ms; $p < .001$). The difference remained statistically significant after controlling for calcium, vitamin D, and estimated glomerular filtration rate ($p = .007$). Inclusion of left ventricular ejection fraction in the model attenuated the association ($p = .054$), suggesting that this finding may be partly driven by changes in cardiac structure.

Conclusions: In one of the largest series to examine PTH, calcium, and QT changes, we found that elevated PTH is associated with longer corrected QT interval independent of serum calcium concentration in ACS survivors.

KEYWORDS
calcium, cardiovascular risk, electrocardiogram, parathyroid hormone

1 | INTRODUCTION

Parathyroid hormone (PTH) is classically thought of as a regulator of bone and mineral metabolism, but adverse cardiovascular (CV) correlates of PTH are increasingly being reported. Several studies indicate that patients with primary hyperparathyroidism (pHPT) are at increased risk of cardiac death (Fitzpatrick, Bilezikian, & Silverberg, 2008; Ronni-Sivula, 1985; Hedback, Tisell, Bengtsson, Hedman, & Oden, 1990; Ogard, Engholm, Almdal, & Vestergaard, 2004; Palmer, Adami, Bergstrom, Akerstrom, & Ljunghall, 1987). Similarly, there is evidence that in secondary hyperparathyroidism (sHPT), elevated PTH is associated with increased CV mortality independent of classic CV risk factors (Floege et al., 2011; Block et al., 2004; Young et al., 2005; Kalantar-Zadeh et al., 2006; Wald et al., 2008; Tentori et al., 2008). Population-level data have also suggested that elevated PTH may predispose people to increased CV risk (Hagstrom et al., 2009; Sugimoto et al., 2014; van Ballegooijen et al., 2013; Bansal et al., 2014), and may also be associated with risk for sudden cardiac death (Deo et al., 2011).

Parathyroid hormone is known to affect serum calcium, which can affect cardiac physiology and may play a role in increased CV risk.

Decreases in serum calcium are thought to lead to prolongation of the QT interval (Bronsky, Dubin, Waldstein, & Kushner, 1961), and QT interval prolongation is an established risk factor for sudden cardiac death, particularly in patients with myocardial infarction (MI) (Schwartz & Wolf, 1978) and low ejection fraction (Pai & Padmanabhan, 2002).

Still, there is evidence that PTH may directly act on the cardiomyocyte, independent of serum calcium. Basic science studies have shown that PTH receptor mRNA is found in human myocardium and increases in concentration after cardiac injury (Monego et al., 2009). In patch clamp studies, PTH was found to prolong phase 2 of the cardiac action potential in guinea pig preparations when calcium concentration was held constant (Ebisawa et al., 1995). Treatment of sHPT with vitamin D was also shown to shorten the QTc even without changes in serum calcium levels (Kim et al., 2006).

Overall, data on the impact of elevated PTH on the QT interval in patients without parathyroid disease are lacking. Furthermore, previous studies examining PTH, calcium, and the QT interval are relatively small. Additional research in this area could lead to improved cardiac risk stratification or even novel, personalized therapeutic and preventative approaches to heart disease. The purpose of this analysis was to assess whether PTH was associated with QTc interval changes in a population-based study of patients without parathyroid disease. We present ECG data from a prospective cohort study of patients admitted for non-ST-segment elevation acute coronary syndromes (NSTE-ACS).

2 | MATERIALS AND METHODS

2.1 | PULSE database

The Prescription Use, Lifestyle, and Stress Evaluation (PULSE) study is a prospective cohort study of the mechanisms by which depression affects prognosis in acute coronary syndrome (ACS). Approval was obtained through the Institutional Review Board of Columbia University Medical Center (CUMC; New York, NY, USA), and all participants provided informed consent. Subjects were recruited from among those patients admitted to CUMC for ACS (as defined by the American Heart Association/American College of Cardiology criteria) from February 2009 through June 2010. ACS was further categorized as either ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). NSTEMI and UA were collectively termed NSTE-ACS. A total of 1087 patients were enrolled in PULSE. STEMI patients were not included in electrocardiographic (ECG) analyses to exclude significant conduction abnormalities. The remaining 955 patients (87.9%) with NSTE-ACS were included in the ECG analysis.

Patient characteristics, including CV risk factors (hypertension, diabetes, smoking, high cholesterol, or obesity) were collected via a questionnaire and confirmed or taken from electronic medical record review for conditions listed in the Charlson Index. The use of drugs was coded through chart abstraction. Major adverse CV events were identified by patient report, and verified using the electronic medical records. All-cause mortality (ACM) was also recorded according to medical records and verbal report from families; deaths were confirmed using the National Death Index. Data on depression and cardiac conduction in PULSE are published elsewhere (Whang et al., 2015, 2013).

Partway through recruitment for PULSE, collection of sera for measurement of PTH, 25-hydroxyvitamin D, and serum calcium levels were added to the study protocol to evaluate for a mediating effect between depression and CV disease. Of the 955 patients with NSTE-ACS in PULSE, serum PTH levels, 25-hydroxyvitamin D levels, and serum calcium levels were available for 414 patients, 407 of whom had ECG data (n = 407). Compared with those without PTH data, those with PTH data available were slightly younger (62.8 ± 10.5 vs. 65.5 ± 12.0 years; p < .001) and had better kidney function (estimated glomerular filtration rate (Deo et al., 2011) 74.6 ± 24.5 vs. 70.6 ± 25.9 ml/min; p = .016). They were also more likely to be men (71.0% vs. 60.6%; p = .001), obese (82.1% vs. 73.9%; p = .003), and to have had UA rather than NSTEMI (68.1% vs. 60.1%; p = .012).

2.2 | Serum markers

Serum and plasma biomarkers were measured by the CUMC Irving Institute for Translational Science core laboratory. Serum and plasma were collected on the day of anticipated hospital discharge from the index hospitalization for ACS.

Intact PTH was measured using the IMMULIT 1000 Turbo Assay (Siemens Healthcare Diagnostics, Deerfield, IL, USA), which is a two-site (C-terminus and N-terminus) immunoradiographic assay (normal range: 11–67 pg/ml, quantitative limit: 3 pg/ml, inter-assay precision: 6.30%, and intra-assay precision: 2.80%). Elevated PTH level was therefore defined as PTH > 67 pg/ml. Serum calcium and 25-hydroxyvitamin D were drawn concurrently with PTH. Calcium was determined using the COBAS INTEGRA 400 Plus colorimetric assay (Roche Diagnostics, Indianapolis, IN, USA; normal range: 8.6–10.2 mg/dl, quantitative limit: 0.4 mg/dl, inter-assay precision: 3.50%, intra-assay precision: 0.99%). Vitamin D levels, measured both as 25-hydroxycholecalciferol (25-OH-D3) and 25-hydroxyergocalciferol (25-OH-D2), were measured using the Agilent 6430 LC/MS system (Agilent, Santa Clara, CA, USA; normal range: TBA, quantitative limit: 0.5 ng/ml, inter-assay precision: <10%, intra-assay precision: <10%). For the purposes of our analysis, vitamin D levels were calculated as total vitamin D (the sum of 25-OH-D3 and 25-OH-D2). Creatinine level was also determined via the COBAS INTEGRA® 400 Plus colorimetric assay (normal range: 0.50–1.20 mg/dl, quantitative limit: 0.2 mg/dl, inter-assay precision: 2.80%, intra-assay precision: 3.10%). Serum sodium, potassium, and magnesium were also obtained using the above COBAS system (assay data not available). eGFR was calculated based on creatinine using the Chronic Kidney Disease Epidemiology Collaboration formula (Levey et al., 2009).

2.3 | ECG and cardiac measures

Twelve-lead ECGs were acquired during initial hospitalization using a Marquette MAC-PC ECG (Marquette Electronics, Milwaukee, WI USA) calibrated at 10 mm/mV with a paper speed of 25 mm/s. ECGs were excluded from analysis if not in normal sinus to exclude

significant conduction or repolarization abnormality, or for complete LBBB with a QRS duration >120 ms. ECG parameters that were included in the analysis included heart rate (HR), PR interval, and *P*-, *R*-, and *T*-wave axes. QT interval was obtained based on the raw ECG HR and QT interval using Bazett's correction: QTc = QT interval/√(60/HR), hereafter QTc, morphologic features such as ST-segment depressions, ST elevations, T-wave inversions (excluding leads aVR and V_1), and J point elevation were coded as well, as evidence of repolarization abnormality. RBBB was also noted. Evidence of left ventricular strain pattern, defined as the presence of >1 mm ST depression and/or T-wave inversion in any lateral lead (I, aVL, V_5, or V_6) along with LVH according to the Cornell criteria (RaVL+SV_3 + [6 mV in women] ⩾28 mV) was also assessed. Results of the relationship between ECG left ventricular strain pattern and depression in the PULSE study are published elsewhere (Whang et al., 2015).

Left ventricular ejection fraction was obtained from reports in the subjects' medical records from echocardiogram, left ventriculogram, or multigated acquisition (MUGA) scan obtained during the index hospitalization for ACS. LVEF was available for most but not all patients in the sample (*n* = 361).

2.4 | Statistical analyses

All analyses were performed using SPSS Version 22 software (IBM Corp., Armonk, NY, USA). Baseline characteristics were compared using chi-square tests for categorical variables and independent sample *t* tests for continuous variables. Continuous variables were also compared with linear regression. Multivariate analysis of covariance (ANCOVA) was performed to compare QTc in those with and without elevated PTH after controlling for covariates. The covariates included were serum calcium, 25-hydroxyvitamin D, and eGFR, as these parameters are known to impact PTH concentration. As LVEF influences QTc, it was also included as a covariate in the subset of patients for whom data were available. Three ANCOVA models were generated: (1) controlling for serum calcium only; (2) controlling for serum calcium, 25-hydrxoyvitamin D, and eGFR; and (3) controlling for serum calcium, 25-hydroxyvitamin D, eGFR, and LVEF in the subgroup for whom LVEF was available. A two-tailed *p* value < .05 was considered significant. Mean values are reported with the standard deviation.

3 | RESULTS

3.1 | Baseline characteristics

Baseline characteristics for individuals with and without elevated PTH are shown in Table 1. There were no between-group differences with respect to sex, race, or classic clinical CV disease risk factors. In addition, there were also no differences in aspirin use, statin use, beta-blocker use, history of MI, or type of ACS (NSTEMI vs. UA). Antidepressant use did not differ between groups. There was no difference in ACM between the group with and without elevated PTH (six deaths [6.3%] in the elevated PTH group, compared to 10 [3.1%] in the normal PTH group [*p* = .22]) but PTH was 70% higher on average in those who experienced ACM compared with those who did not experience ACM during the study period (97.2 ± 141.0 pg/ml vs. 57.1 ± 60.2 pg/ml; *p* = .016).

TABLE 1 Baseline demographics and cardiovascular risk factors by PTH level

	Normal PTH (*n* = 315)	Elevated PTH (*n* = 92)	*P* value
Age (years)	62.3 ± 10.6	64.5 ± 10.4	.072
Female (%)	89 (28)	30 (33)	.419
Race			
White (%)	214 (69)	53 (58)	.507
Black (%)	56 (18)	22 (24)	
Asian/Pacific islander (%)	4 (1)	2 (2)	
Other/more than one (%)	38 (12)	14 (16)	
BMI > 25 kg/m^2 (%)	255 (81)	79 (86)	.354
History of HTN (%)	251 (80)	77 (84)	.219
History of diabetes (%)	108 (34)	44 (48)	.121
Total cholesterol (mg/dl)	168.7 ± 49.6	164.4 ± 54.4	.483
Smoker (%)	169 (54)	48 (52)	.813
Aspirin use (%)	218 (69)	65 (71)	.449
Statin use (%)	199 (62)	62 (65)	.350
Beta-blocker use (%)	168 (53)	54 (57)	.275
Antidepressant use (%)	26 (8)	5 (5)	.257
History of MI (%)	88 (28)	34 (37)	.236
ACS type (NSTEMI, %)	98 (31)	29 (32)	.518
All-cause mortality (%)	10 (3.1)	6 (6.3)	.220

ACS, acute coronary syndrome; BMI, body mass index; eGFR, estimated glomerular filtration rate; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PTH, parathyroid hormone; QTc, QT interval corrected using Bazett's formula; UA, unstable angina.
± standard deviation.

Parathyroid hormone was also evaluated as a continuous variable. PTH was inversely related to serum calcium (*r* = −.14; *p* = .004), total serum 25-hydroxyvitamin D (*r* = −.091; *p* = .033), and eGFR (*r* = −.42; *p* < .001). PTH was not associated with any other demographic, CV, or biochemical factors.

3.2 | Calciotropic factors

Serologic analyses for those with and without elevated PTH are shown in Table 2. As expected, mean PTH level in the elevated PTH group was more than three times higher than that in the normal PTH group (126 ± 110 pg/ml vs. 39 ± 14 pg/ml; *p* < .001). Serum calcium was lower in the group with elevated PTH (9.1 ± 0.6 mg/ml vs. 9.3 ± 0.5 mg/ml; *p* = .004) although the mean levels were within normal range in both groups. Both total 25-hydroxyvitamin D (21.9 ± 10.3 ng/ml vs. 25.1 ± 10.3 ng/ml; *p* = .007) and eGFR (56.2 ± 26.6 ml/min vs.

TABLE 2 Calciotropic factors and biochemical evaluation by pth level

	Normal PTH	Elevated PTH	*p* value
PTH (pg/ml)	38.6 ± 14.4	126.1 ± 109.8	<.001*
Serum calcium (mg/dl)	9.27 ± 0.51	9.09 ± 0.62	.004*
Total vitamin D (ng/ml)	25.1 ± 10.3	21.9 ± 10.3	.007*
Serum sodium (mEq/L)	139 ± 2.63	139 ± 2.94	.569
Serum potassium (mEq/L)	4.26 ± 0.46	4.35 ± 0.49	.138
Serum magnesium (mg/dl)	1.98 ± 0.30	1.99 ± 0.32	.774
eGFR (ml/min)	80.2 ± 20.9	56.2 ± 26.6	<.001*
CKD stage III or higher (%)	57 (19)	53 (57)	<.001*
CKD stage V (%)	1 (0.3)	6 (6.5)	<.001*

± Standard deviation.
eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.
*$p < .05$.

80.2 ± 20.9 ml/min; $p \leq .001$) were lower in those with elevated PTH. There were also higher rates of CKD stage III or greater, as well as of CKD stage V. There were no significant differences in serum sodium, potassium, or magnesium between the two groups.

3.3 | ECG findings

ECG findings for those with and without elevated PTH are shown in Table 3. HR was on average 4.5 bmp higher in those with elevated PTH (71.7 bpm vs 67.2 bpm, $p = .002$). It was also more common for patients with normal PTH levels to be bradycardic (HR < 60 bpm), while it was more common for patients with elevated PTH levels to be tachycardic (HR > 100 bpm; see Table 3). Patients with elevated PTH had a QTc interval that was longer on average (451 ± 38.6 ms vs. 435 ± 29.8 ms; $p < .001$). They also had a more rightward *T*-wave axis (62.0° ± 71.8° vs. 44.1° ± 55.2°; $p = .011$) although the average *R*-wave axis were not significantly different. ST-segment depressions were more commonly observed in patients with elevated PTH (23.9% vs. 14.3%; $p = .029$). QRS duration was not significantly different among patients with and without elevated PTH. RBBB was also no more common among the two groups. LV strain pattern was more common in patients with elevated PTH (20.7% vs 8.9%; $p = .002$). LVEF was also lower in patients with elevated PTH compared with patients with normal PTH levels (47.6% ± 13.9% vs. 51.6% ± 11.0%; $p = .007$). When assessed as a continuous variable, PTH was positively correlated with QTc ($r = .13$; $p = .010$) and negatively associated with LVEF ($r = -.166$; $p = .001$).

3.4 | Adjusted analyses

Adjusted analyses (ANCOVA) comparing the QTc in those with and without elevated PTH after controlling for covariates are shown in Table 4. The mean QTc remained higher in the group with elevated PTH compared with those with normal PTH after controlling for serum calcium alone (Model 1) and after controlling for serum calcium, total 25-hydroxyvitamin D, and eGFR (Model 2). In Model 3, after controlling for calcium, vitamin D, eGFR, and LVEF (in the subset of patients with LVEF data, $n = 361$), the difference was attenuated and reduced to borderline significance ($F = 3.73$; $p = .054$).

TABLE 3 Electrocardiographic parameters and LVEF by PTH level

	Normal PTH	Elevated PTH	*p* value
Heart rate (bpm)	67.2 ± 11.3	71.7 ± 14.2	.002*
HR > 100 bpm (%)	1 (0.3)	4 (4.3)	.006*
HR < 60 bpm (%)	92 (29.2)	22 (23.7)	.006*
QT interval (ms)	414 ± 37.0	417 ± 44.1	0.582
QTc (ms)	435 ± 29.8	451 ± 38.6	<.001*
R-axis (degrees)	14.0 ± 37.5	−11.2 ± 46.0	.541
T-axis (degrees)	44.1 ± 55.2	62.0 ± 71.8	.011*
QRS duration (ms)	96.9 ± 19.4	99.0 ± 22.2	.387
QRSD 100–120 ms (%)	63 (20)	18 (20)	.996
QRSD > 120 ms (%)	34 (11)	10 (11)	.996
RBBB	10 (3.2)	2 (2.2)	.275
ST depression (%)	45 (14)	22 (24)	.029*
Strain pattern (%)	28 (9)	19 (21)	.002*
LVEF (%)	51.6 ± 11.0	47.6 ± 13.9	.007*

HR, heart rate; LVEF, left ventricular ejection fraction; PTH, parathyroid hormone; QTc, QT interval corrected using Bazett's formula.
*$p < .05$.
± Standard deviation.

4 | DISCUSSION

Our results indicate that in a population of patients with NSTE-ACS, elevated PTH level is associated with longer QTc. Our data suggest that this relationship is independent of serum calcium concentration. Although previous studies have examined the relationship between QTc, PTH, and calcium in patients with pHPT (and to a lesser extent in sHPT from renal failure), this study is among the largest to examine this topic, and also uses a population without known parathyroid disease. Our data are novel in that they suggest that the impact of PTH on QTc is not explained by serum calcium concentration alone.

In our study, we also found that patients with elevated PTH had increased incidence of LV strain pattern, and on average they had a rightward deviated T-wave axis. This further adds evidence to the idea that PTH may affect cardiac conduction and repolarization. We also found that patients with elevated PTH had increased HR, and also that patients with elevated PTH had increased incidence of tachycardia and lower incidence of bradycardia. Although these findings could be partly explained by confounding variables, such as renal function, our findings suggest that PTH may be associated with other changes in cardiac function.

TABLE 4 Analysis of covariance: QTc according to PTH level controlling for covariates

	Variables included	Normal PTH	Elevated PTH	F statistic	*p* value
Unadjusted	None	435.2 ± 29.8	451.0 ± 38.6	10.4	.001*
Model 1	Ca	435.2 ± 32.0	450.8 ± 32.1	16.7	<.001*
Model 2	Ca, Vit D, eGFR	436.1 ± 33.3	447.7 ± 35.4	7.35	.007*
Model 3[a]	Ca, Vit D, eGFR, LVEF	437.0 ± 31.8	445.6 ± 33.6	3.73	.054

± Standard deviation.

Ca, serum calcium; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PTH, parathyroid hormone; QTc, QT interval corrected using Bazett's formula; Vit D, total vitamin D.

*$p < .05$.

[a]$n = 361$.

A molecular mechanism to explain how PTH might affect cardiac structure and repolarization remains unclear. Still, PTH receptor mRNA has been identified in rat myocardium (Urena et al., 1993), as well as in human ventricular myocytes after MI (Monego et al., 2009) suggesting that PTH could work directly on the myocardium, independent of calcium. Patch-clamp studies in animal models have demonstrated a modulating effect of PTH on cardiac repolarization through changes in both serum and intracellular calcium concentration (Ebisawa et al., 1995). In vitro studies of human cardiac tissue have demonstrated that parathyroid hormone fragments may also have activity on cardiac catecholamine receptors, and can increase cardiac automaticity and heart rate (Potthoff et al., 2011). We similarly found that elevated PTH was associated with increased HR in our study. It is reasonable to suspect that PTH could affect cardiac repolarization in addition to chronotropy, as changes in serum and intracellular calcium concentration are critical to cardiac pacemaker action potentials as well as repolarization, and PTH serves as a "master" endocrine regulator of serum calcium concentrations. Further research in this area may improve our understanding of the pathophysiology of PTH in heart disease.

A few clinical studies have examined the relationship between PTH and cardiac conduction and repolarization abnormalities. Two small studies found that premature ventricular beats were more common in pHPT during exercise testing; in one study, this resolved after parathyroidectomy (Pepe et al., 2013), although, in the other, this persisted even after parathyroidectomy (Nilsson, Aberg, Rastad, & Lind, 2000). Conversely, one small study found no increased incidence of events on Holter monitoring in pHPT (Rosenqvist, Nordenstrom, Andersson, & Edhag, 1992). Several studies have shown that patients with pHPT and hypercalcemia have a short QT interval and that the QT interval prolongs and normalizes after parathyroidectomy with normalization of serum calcium concentration (Bronsky et al., 1961; Pepe et al., 2013; Rosenqvist et al., 1992; Lind, Ridefelt, Rastad, Akerstrom, & Ljunghall, 1994; Lind & Ljunghall, 1994) but these are small studies. In contrast, in sHPT the QT interval is prolonged, which is thought to be because of decreased calcium concentration (Bronsky et al., 1961). One study found that after treatment for sHPT with vitamin D, the QTc shortened with treatment as the PTH level came down although calcium levels did not change (Kim et al., 2006). Overall, there are relatively few studies examining PTH and QTc, and our study represents one of the largest ones to date.

At the population level, elevated levels of PTH have been associated with worse CV outcomes. In a large population-based study of Swedish men, elevated PTH was associated with both increased risk of cardiac death (Hagstrom et al., 2009) and hospitalization for heart failure (Hagstrom et al., 2010). Similar findings were observed in two small population studies in Japanese (Sugimoto et al., 2009) and Dutch patients (van Ballegooijen et al., 2013). In a large, multiethnic population cohort study, elevated serum PTH was associated with increased incidence of heart failure exacerbation as well as left ventricular hypertrophy independent of classical CV risk factors (Bansal et al., 2014). Analysis of the same cohort also found that PTH was associated with vascular dysfunction independent of serum calcium concentration (Bosworth et al., 2013). Recently, a large population-based cohort study found a relationship between elevated serum PTH and sudden cardiac death (Deo et al., 2011). Our study suggests a possible mechanistic link—prolonged QTc and thus repolarization—between elevated PTH and sudden cardiac death.

Our data indicate that the relationship between PTH and cardiac conduction may in part be mediated by lower LVEF. Although the attenuation of the effect after controlling for LVEF may be due in part to the lower number of subjects with LVEF data available, it is possible that the difference was reduced due to a mediating effect between PTH and LVEF. Several studies have suggested that in pHPT, PTH is associated with increased left ventricular mass (LVM), which is related to LVEF. Some studies found that the increase in LVM regresses after parathyroidectomy (Piovesan et al., 1999; Osto et al., 2012; Agarwal et al., 2013) although other studies have not found this association (Pepe et al., 2013; Nilsson et al., 2000; Almqvist et al., 2002; Ambrogini et al., 2007; Persson et al., 2011; Dominiczak et al., 1990; Sato et al., 1995; Barletta et al., 2000; Nappi et al., 2000; Nilsson, Aberg, Rastad, & Lind, 2005; Farahnak et al., 2010; Walker et al., 2012; Luigi et al., 2012; Stefenelli et al., 1997; Walker et al., 2010). In particular, there is debate over whether mildly elevated PTH is associated with cardiac anatomic changes or whether more severe PTH elevation is necessary. Furthermore, it is unclear whether the effect of PTH on LVM in pHPT is mediated by hypertension (which is more common in patients with pHPT than in the general population), or whether there is a direct effect of PTH on the myocardium. We also found that elevated PTH was associated with electrocardiographic strain pattern on ECG, which can be seen in hypertension. A recent meta-analysis in patients with pHPT indicated that parathyroidectomy reduced LVM in pHPT and higher

preoperative PTH levels were associated with greater improvements although baseline blood pressure did not moderate the effect of parathyroidectomy on LVM (McMahon et al., 2015). Overall, in addition to being consistent with past reports indicating that PTH affects cardiac structure, our data suggest that this effect may also possibly impact repolarization.

Our study has several limitations. The data we present are cross sectional, and thus we cannot conclude that the relationship between PTH and QTc is causal. Our study only examined individuals with ACS; therefore, our findings may not be generalizable to patients without ACS. In addition, QTc is only one measure of cardiac repolarization. Furthermore, our study is also limited in that PTH data were added to the study design partway through enrollment. We also found that patients with elevated PTH also had worse renal function (elevated PTH is known to be associated with CKD), which can increase cardiovascular risk. Thus, conclusions about any increase in cardiovascular risk in those with elevated PTH must account for differences in renal function. Certain other serum markers, such as pro-BNP also might have been helpful in characterizing the severity of illness of the patients with elevated PTH. Similarly, although our study found other changes in ECG parameters, including ECG strain pattern, certain parameters—namely additional measures of LVH, such as Sokolow-Lyon criteria or Framingham criteria for LVH—were not assessed, nor were other ECG markers of electrical dysfunction, such as fascicular blocks. In addition, while our study also included data on whether patients were taking certain drugs that affect CV outcomes such as aspirin, statins, and beta-blockers, and drugs that affect the QTc, like antidepressants, our study lacked data on other drugs of interest, such as diuretics and antiarrhythmics. In the end, our data are hypothesis generating.

Our study has several strengths as well. The PULSE database examines patients with NSTE-ACS, which represents a growing proportion of patients with ACS. Moreover, studying the pathophysiology of PTH in patients without a diagnosis of pHPT has broader implications for a larger patient population. Another strength is that the number of ECGs we were able to analyze is larger than many prior studies examining the relationship between PTH and heart disease, and represents one of the largest studies examining the relationship between PTH and QTc. Our study also adjusted for several mediators and confounders. Importantly, our findings suggest a possible mechanistic link—increased QTc—between PTH and SCD that was missing in past studies. Our work suggests PTH may be an important marker for increased CV risk in patients after NSTE-ACS although obtaining PTH as a disease marker may be practically challenging. Further work could help improve our understanding of the mechanisms by which PTH impacts QTc and lead not only to a better understanding of the pathophysiology of PTH in patients with heart disease, but could also lead to novel, targeted therapeutics.

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DISCLOSURE

The authors report no conflicts of interest in this work.

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