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Reversible changes of electrocardiographic abnormalities after parathyroidectomy in patients with primary hyperparathyroidism

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Abstract

Background: *Several studies have reported that primary hyperparathyroidism is a risk factor of higher cardiovascular mortality, mainly because hyperparathyroidism is related to arterial hypertension, arrhythmias, structural heart abnormalities and activation of the renin–angiotensin–aldosterone system. However, very few studies have shown the electrocardiographic changes that occur after parathyroidectomy. That was the aim of this study.*

Methods: *We studied 57 consecutive patients with primary hyperparathyroidism surgically treated. Electrocardiogram, serum electrolytes, parathyroid hormone, creatinine and albumin measures were obtained before and after surgery and were compared.*

Results: *The most common basal electrocardiographic abnormalities were left ventricular hypertrophy (LVH, 24.6%), conduction disturbances (16.3%), and short QT and QTc intervals. After surgery, a QTc interval lengthening and a tendency of T wave shortening were observed, as well as an inverse association between QTc interval and serum levels of magnesium and corrected calcium. There were no differences in LVH and conduction disturbances after surgery.*

Conclusions: *Primary hyperparathyroidism is an important factor in the development of electrocardiographic abnormalities in this population, some of which are not corrected after parathyroidectomy. Further studies are required to demonstrate what factors are associated with persistence of electrocardiographic disturbances after surgery.* (Cardiol J 2009; 16, 3: 241–245)

Key words: electrocardiogram, primary hyperparathyroidism, post parathyroidectomy

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Introduction

Primary hyperparathyroidism is considered a causal factor of increased cardiovascular mortality, mainly when it is associated with symptoms, even after successful parathyroidectomy [1, 2]. The ventricular function, especially diastolic, is commonly altered in these patients [1, 3]. It is well known that parathyroid hormone has a direct chronotropic and indirect inotropic effect on the heart [2]. In the same way, high calcium levels have been considered a cause for potential cardiac damage [1–4]. Hyperparathyroidism is also related to arterial hypertension, arrhythmias, structural heart abnormalities and activation of the renin-angiotensin-aldosterone system [1–4].

The deleterious effect of the parathyroid hormone (PTH) is not well explained. However, it has been observed that modify heart rate and coronary blood flow and increase left ventricular pressure [2].

Although it is well known that primary hyperparathyroidism is associated with structural changes and increased cardiovascular mortality, few studies have described the electrocardiographic changes before and after surgical treatment [5]. Some studies have shown that primary hyperparathyroidism and hypercalcemia are directly related to the QRS complex amplitude, duration of the ST segment, QT and QTc intervals and T wave morphology [4, 6], mainly because hypercalcemia reduces the plateau phase of the cardiac action potential and the effective refractory period [7]. Compared with control patients, it was found that the QRS complex amplitude is longer, something attributed to an increased cardiac mass. Additionally, an ST segment and QT interval shortening, associated with ventricular systole and T wave extension, have been shown [5].

The main cause of primary hyperparathyroidism is a monoclonal or polyclonal solitary adenoma [3] which can be surgically treated. Nevertheless changes after surgical removal of the adenoma have not been thoroughly characterized [8, 9]. Most changes in the electrocardiographic parameters after parathyroidectomy are related to changes of calcium serum levels. Its reduction lengthens the QT and QTc intervals. It has also been described that QTc dispersion increases and the RR-corrected QT duration decreases in these patients [10, 11].

The aim of this study is to describe the electrocardiographic characteristics and their association with biochemical parameters in patients with primary hyperparathyroidism before and after parathyroidectomy.

Methods

Study population

We carried out a cross-sectional study of 57 consecutive patients with primary hyperparathyroidism surgically treated between 1987 and 2003. Subjects were excluded if the diagnosis of primary hyperparathyroidism was inaccurate and they were under beta-blocker or antiarrhythmic treatment during the study because that might have modified the electrocardiographic parameters. The hyperparathyroidism diagnosis was made according to biochemical results (hypercalcemia, elevated PTH and normal or high calciuria) and scintigraphic abnormalities.

Serum electrolytes, calcium, magnesium, phosphorus, sodium, and potassium were obtained, as well as PTH, creatinine and albumin, before and after the parathyroidectomy.

The study was approved by the local bioethical committee and all patients gave their informed consent.

Electrocardiogram

Before and after surgery, a 12-lead electrocardiogram (ECG) was obtained with a Burdick E 350 Siemens ECG equipment with a recording paper speed of 25 mm/s. This was interpreted by two experimental cardiologists who did not know the clinical and laboratory characteristics of the patients. An average of three measurements of the analyzed variables in each electrocardiogram was done. The differences between the measurements of each were resolved by consensus.

ECGs were analyzed for heart rate, PR and QTc (heart rate — corrected QT with Bazett's formula) interval duration, width of the QRS complex, T wave abnormalities, U wave presence, and left ventricular hypertrophy. ECG abnormalities were defined according to the following established criteria: sinus bradycardia (< 60 bpm); PR interval prolongation (> 200 ms); QRS widening (> 100 ms); QTc prolongation (> 440 ms); ST segment depression, horizontal or downsloped ST segment with or without ST-J depression (0.05 mV); ST segment elevation, upward convexity of the ST segment (0.1 mV) with or without ST-J elevation; T wave abnormalities: low voltage, isoelectric or negative T waves in leads in which they are normally upright or that are abnormally tall and peaked; prominent U wave (top > 25% of the highest T wave in precordial leads); and left ventricular hypertrophy, Sokolow's Index [12]: in men, RVL + SV3 > 3.5 mV; in men < 40 years of age, TV1 > 0 mV; in men > 40 years

of age, TV1 0.2 mV; in women, TaVL + SV3 > 2.5 mV (or > 1.2 or TV1 > 0 mV in women < 40 years of age); and in women > 40 years of age, TV1 > 0.2 mV [10].

Statistical analysis

Continuous variables are expressed as mean ± ± standard deviation and categorical as proportions. For comparison between basal measurement and after surgery, Student's *t*-test and Pearson's χ^2 test were used. A value of $p < 0.05$ was considered statistically significant. For the statistical analysis a SPSS INC program (Version 15.0) was used.

Results

Fifty seven patients were included, 53 (93%) female, 4 (7%) male. The average age was 54.7 ± ± 14.16 years old. The hyperparathyroidism cause was adenoma in 96.5% of the cases.

The most frequent electrocardiographic abnormalities observed in basal measurements were: left ventricular hypertrophy (LVH) in 15 patients (26.3%), conduction disorders in 15 patients (26.3%), and QRS axis left deviation (8.08 ± 41.1 degrees). Short QT (363.46 ± 60.31 ms) and QTc (404.27 ± 36.5 ms) intervals were also observed.

Basal PTH levels were elevated (283.83 ± ± 528.88 pg/mL), serum calcium was high (11.33 ± ± 1.92 mg/dL) as well as corrected calcium for albumin (11.74 ± 2.19), and serum levels of creatinine (2.02 ± 5.49 mg/dL). The phosphorus value was 2.45 ± 0.47 mg/dL (Table 1). An inverse association between QTc and the serum level of magnesium ($r = –0.372$, $p = 0.02$) was found.

During post-surgery follow-up, a significant lengthening of QTc interval was observed ($p = 0.04$), and a T wave shortening, although it does not reach statistical significance ($p = 0.09$). After the surgery, only three (20%) of the 15 did not have LVH patterns, and six patients without LVH before the surgical resection developed ECG abnormalities suggesting LVH during follow-up. Those patients who developed or did not show regression of LVH criteria after surgery had higher basal PTH levels than those who did not develop it or showed 'LVH regression' ($p < 0.0001$) (Table 2).

In addition, 50% of patients with basal ECG suggesting ischemia and 40% of those who had basal conduction disturbances normalized their electrocardiogram during post-surgery follow-up. However there is no statistically significant difference.

Table 1. Characteristics before surgery.

Gender — F/M	53 (93%)/4 (7%)
Age (years)	54.7 ± 14.16
Hyperparathyroidism causes:	
Carcinoma	2 (3.5%)
Hyperplasia	1 (1.8%)
Adenoma	55 (96.5%)
Electrocardiogram:	
Ischemia	4 (7%)
Left ventricular hypertrophy	15 (26.3%)
Conduction disorders	14 (24.6%)
Right bundle branch block	2 (3.5%)
Left anterior hemiblock	9 (16.1%)
Left posterior hemiblock	2 (3.6%)
First degree AVB	2 (3.6%)
Frequency [beats/min]	73.3 ± 16.87
P wave [ms]	83.1 ± 16.8
P axis [degrees]	44.5 ± 20.1
QRS [ms]	79.3 ± 18
QRS axis [degrees]	8.08 ± 41.1
AT axis [degrees]	34.46 ± 17.83
QT [ms]	363.45 ± 60.31
QTc [ms]	404.27 ± 36.5
T wave [ms]	3.35 ± 1.12
Biochemical:	
Calcium [mg/dL]	11.33 ± 1.92
Corrected calcium [mg/dL]	11.74 ± 2.19
Phosphorus [mg/dL]	2.45 ± 0.47
Sodium [mg/dL]	137.58 ± 17.27
Potassium [mg/dL]	4.04 ± 0.95
Magnesium [mg/dL]	2.5 ± 0.58
PTH [pg/mL]	283.82 ± 528.88
Creatinine [mg/dL]	2.02 ± 5.49
Albumin [g/dL]	3.55 ± 1.56

AVB — atrioventricular blocks; PTH — parathyroid hormone

Regarding biochemical changes, a decrease of PTH ($p < 0.0001$), calcium ($p < 0.0001$), corrected calcium ($p < 0.0001$), and phosphorus ($p < 0.001$) (Table 3) was observed.

Discussion

Solitary adenoma, as reported in literature [3], represented the most common etiology in this group of patients (96.5%).

We found a significant lengthening of QTc, which can be directly associated with the significant calcium serum reduction, as previously reported [4, 6, 7].

Table 2. Paratohormone concentrations before and after surgery according to hypertrophy after surgery.

	With LVH	Without LVH	p_h	p_t	p_{hxt}
N	18	34			
Basal PTH	810.7 ± 763.6	382.8 ± 557			
Post surgical PTH	117.1 ± 160.8	103.6 ± 154.6			
Total	511.19 ± 648.9	107.6 ± 155	0.047	0.025	< 0.0001

p_h, p_t, p_{hxt} — significance level for H — LVH, t — before and after surgery; h x t — HVI x before and after surgery; LVH — left ventricular hypertrophy, PTH — parathyroid hormone

Table 3. Pre and post parathyroid adenoma resection differences.

	Basal	Post surgery	p
Heart rate [beats/min]	72.78 ± 17.17	75.55 ± 18.1	0.3
P wave [ms]	80 ± 20	98 ± 120	0.4
QRS [ms]	79 ± 20	115 ± 190	0.18
T wave [ms]	3.38 ± 1.1	3.09 ± 1.3	0.09
P wave voltage [mV]	0.15 ± 0.17	0.14 ± 0.21	0.79
AQRS [degrees]	8.82 ± 41.1	5.1 ± 39.6	0.31
AT [degrees]	33.13 ± 15.7	34.88 ± 17.1	0.6
QT [ms]	362.12 ± 61.6	372.5 ± 45.9	0.34
QTc [ms]	401.4 ± 37	414.8 ± 32.3	0.04
Calcium [mg/dL]	11.5 ± 1.3	9.2 ± 1.02	< 0.0001
Corrected calcium [mg/dL]	11.9 ± 1.5	9.7 ± 1.3	< 0.0001
Phosphorus [mg/dL]	2.4 ± 0.5	3.5 ± 0.55	< 0.001
Sodium [mg/dL]	140 ± 3.1	139.8 ± 3.7	0.8
Potassium [mg/dL]	4.05 ± 0.95	3.9 ± 0.43	0.4
Magnesium [mg/dL]	2.4 ± 0.6	2.6 ± 0.6	0.12
Parathyroid hormone [pg/mL]	511.19 ± 648.9	107.6 ± 159.9	< 0.0001
Creatinine [mg/dL]	1.35 ± 1.2	1.3 ± 0.9	0.6
Albumin [g/dL]	3.5 ± 0.85	3.5 ± 0.9	0.82

Although many previous studies associate the most of the deleterious cardiac effects observed in this group of patients with the high serum calcium levels [1–4], we observed no significant post-surgery reduction in the number of patients with LVH ECG criteria, ischemia and conduction disturbances, even when the serum calcium reduction observed after surgical treatment was statistically significant.

This observation might be explained as a deleterious effect caused by other factors that do not disappear after parathyroidectomy, and could be associated with higher pre-surgical PTH levels per se. Perhaps the interval after surgery is somehow related to the correction of ECG changes.

An increased cardiovascular mortality has been reported in patients with parathyroidectomy between ten years before and one year after surgery, when it equals that of the general population [7]. That increase in mortality cannot be associated with cardiac arrhythmias since, in spite of the electrocardiographic changes found in most patients with primary hyperparathyroidism; those changes could not be related to an increase in the incidence of supraventricular and/or ventricular rhythm disturbances [8]. Although it is well known that these patients have many metabolic abnormalities that can explain this increased mortality [4], it is poorly understood why it remains increased after parathyroidectomy. Possibly it can be explained by a direct PTH cardiovascular effect, which, once present, persists even though PTH normalizes after surgery. Short QT syndrome is related to mutations in the genes encoding the L-calcium channel, especially in CACNA1C and CACNB2b. These mutations induce a loss of function that shortens QT interval [13–15]. Perhaps elevated calcium levels related to hyperparathyroidism induce an abnormal calcium channel regulation that persists after surgical correction. This warrants further investigation involving long follow-up intervals.

Conclusions

Primary hyperthyroidism is an important factor in the development of electrocardiographic changes in this population, some of which can be explained by electrolytic disorders. Electrocardiographic disorders remain or could be developed after post-surgery follow-up. Further studies are required to demonstrate that other factors determine the absence of regression of these electrocardiographic disturbances and keep cardiovascular mortality increased in this group of patients after surgical treatment.

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