




ORIGINAL ARTICLE

Influence of the position and size of the hyperfunctioning parathyroid gland on intraoperative PTH levels collected from the ipsilateral jugular and peripheral veins

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Abstract

Introduction: Primary hyperparathyroidism (PHPT) has an estimated prevalence of 0.78%. Its most frequent presentation is sporadic and uniglandular. In surgical treatment, the measurement of intraoperative parathyroid hormone (IOPTH) is fundamental in ensuring therapeutic success. The position and size of the hyperfunctioning parathyroid gland may influence baseline IOPTH values at different collection sites.

Objective: Examine the relationship between the position and size of the parathyroid gland and baseline IOPTH values from the ipsilateral internal jugular vein (PTH-c), peripheral vein (PTH-p), and the absolute and percentage differences between these measurements (Δ PTHc-p and $\Delta\%$ PTHc-p). **Methods:** A retrospective analysis was conducted on patients undergoing parathyroidectomy for sporadic uniglandular PHPT.

Results: Of the 300 eligible patients, 54 were males and 246 females, with a median age of 59 years. Right superior glands exhibited larger volumes and higher Δ PTHc-p and $\Delta\%$ PTHc-p values compared with the right inferior glands. Left superior glands displayed higher $\Delta\%$ PTHc-p values than the left inferior glands. Larger glands showed increased PTH-p, PTH-c, and Δ PTHp-c values. No correlation was found between volume and $\Delta\%$ PTHp-c. **Conclusion:** The position of the parathyroid gland, either superior or inferior, influences the difference between PTH-c and PTH-p values. Glandular volume correlates with Δ PTHc-p but not with $\Delta\%$ PTHc-p. Elevated $\Delta\%$ PTHc-p measurements may be of intraoperative significance, indicating a superior position of the gland.

Keywords: parathyroid glands; parathyroid neoplasms; hyperparathyroidism, primary; parathyroidectomy; parathyroid hormone.

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Introduction

Primary hyperparathyroidism (PHPT) is a common disease with a prevalence of approximately 233 cases per 100,000 women and 85 cases per 100,000 men¹. In Brazil, it is estimated to affect about 0.78% of the population². In roughly 80-90% of cases, it is sporadic and caused by a single adenoma in one of the parathyroid glands, thus presenting as uniglandular³.

For PHPT cases where surgical treatment is indicated, pre-operative evaluation can comprise imaging tests to try to locate the hyperfunctioning thyroid gland. These tests include 99mTc-SestaMIBI scintigraphy, cervical ultrasonography (US), and 4D computed tomography (CT scan). When the results of these tests are consistent and indicate the presence of uniglandular disease, it is possible to perform a focused parathyroidectomy with unilateral cervical exploration⁴.

This surgical approach gained significant traction with the possibility of intraoperative parathyroid hormone (PTH) measurement. Intraoperative PTH (IOPTH) and its practical application were initially described in 1991⁵. This technique is based on the short half-life of the PTH molecule, estimated at 3-5 min. A decrease in IOPTH serum levels is expected a few minutes after the removal of the affected gland. The most effective criterion for predicting surgical success in sporadic uniglandular PHPT is a drop of at least 50% relative to the baseline (or pre-removal) IOPTH value, 10 minutes after the gland's excision⁶.

Blood sample collection can be carried out in both peripheral veins (PTH-p) and central veins (PTH-c). PTH-c is usually obtained from the internal jugular vein ipsilateral to the suspected parathyroid gland. Studies have shown that PTH-c values are significantly higher than PTH-p values⁷⁻¹¹.

A promising approach for using IOPTH is the simultaneous collection of PTH-c from both internal jugular veins. From the discrepant result between the two sides, a preferred laterality for cervical exploration can be suggested. Various criteria have been proposed to predict this laterality, such as an absolute variation of 200 pg/mL between the two values¹², or a percentage variation of 5%, 10%, or even 20%¹³⁻¹⁷.

Studies addressing the use of IOPTH have not thoroughly explored the influence of the location (either superior or inferior) and size of the diseased parathyroid gland on PTH-c levels in the ipsilateral internal jugular vein, or its possible discrepancy with PTH-p or PTH-c levels in the contralateral internal jugular vein. This information can have clinical relevance and potentially contribute to decision-making and surgical treatment success.

Objective

Investigate whether variables such as the position and size of the hyperfunctioning parathyroid gland are associated with a greater discrepancy in the baseline IOPTH values collected from the ipsilateral internal jugular vein compared with those taken from the peripheral vein, in patients undergoing parathyroidectomy to treat sporadic uniglandular PHPT.

Materials and methods

Patients with a clinical diagnosis of PHPT who underwent parathyroidectomy at the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo, from January 2015 to May 2023, were selected using the institution's electronic medical record system.

For inclusion in the analysis, the disease of the resected parathyroid was confirmed by histopathological evaluation. Patients who had more than one or no parathyroid gland removed, or with missing IOPTH data, were excluded.

Clinical and epidemiological data from the assessed patients were collected.

At least five intraoperative blood samples were collected from all patients following the institution's routine care. They were sequentially named as follows: sample 1 - baseline PTH from peripheral vein (PTH-p); sample 2 - baseline PTH from central vein (PTH-c); sample 3 - pre-removal PTH of the diseased gland; sample 4 - 10-min post-removal PTH; sample 5 - 15-min post-removal PTH. In this study, only samples 1 and 2 were evaluated.

Sample 1 (PTH-p) was collected during anesthetic induction through puncture of a peripheral vein in the upper limbs, lower limbs, or anterior jugular vein, with no predefined laterality. Sample 2, as well as all other samples, were collected during the surgical procedure through direct puncture and under visualization of the internal jugular vein ipsilateral to the suspected parathyroid gland.

Venous blood samples (3-5 ml) were collected in tubes without anticoagulants, immediately transported to the laboratory, and centrifuged at room temperature before analysis. The intact PTH molecule was analyzed using an electrochemiluminescence immunoassay, with a reference range of 10 to 65 pg/mL. Values above the assay's upper detection limit (>5000 pg/mL) were reported as 5000 pg/mL.

The absolute difference between the PTH-c and PTH-p values (Δ PTHc-p) and the percentage variation between them ($\Delta\%$ PTHc-p) were calculated.

The pre-removal positioning of the parathyroid glands was recorded in the surgical description, indicating their laterality and whether their position was compatible with the upper, lower, or intrathyroidal parathyroid. Thus, patients were classified as follows: 1. Right inferior parathyroid (RIPT); 2. Right superior parathyroid (RSPT); 3. Left inferior parathyroid (LIPT); 4. Left superior parathyroid (LSPT); and 5. Intrathyroidal parathyroid (ITPT).

All resected parathyroid glands were measured immediately after removal using a millimeter ruler, and their height, width, and length were recorded in millimeters. These measures were registered in the surgical description.

For analysis of the parathyroid gland size, the estimated volume was calculated simply by multiplying the three recorded dimensions. This measure corresponds to the volume of a parallelepiped and does not represent the real volume or actual weight of the gland but was used as a method for relative comparison. The estimated volume was described in mm³ units.

It was impossible to measure the dimensions of the intrathyroidal parathyroid glands intraoperatively, so the volume variable was not assessed in this group.

For statistical analysis, qualitative and quantitative variables were compared, including gender, age, position and estimated volume of the parathyroid gland, PTH-c, PTH-p, Δ PTHc-p, and $\Delta\%$ PTHc-p.

After verifying the normality of continuous variable distribution (Kolmogorov-Smirnov test), the unpaired *t*-test (normal distribution) or the Mann-Whitney test (non-parametric distribution) was applied for inference. When at least one variable had a non-parametric distribution, the median was presented as a measure of central tendency, and the first and third quartiles (Q1-Q3) were used as measures of dispersion.

For multiple comparisons, Analysis of Variance (ANOVA) or the Kruskal-Wallis test was employed, as appropriate. In the case of significant differences, the Dunn test was applied for multiple comparisons. Qualitative variables were presented as absolute and relative frequency, and the Fisher's Exact test was used for inference.

Correlations were analyzed using the Spearman test.

A significance level of 5% ($p \leq 0.05$) was adopted for the calculated value of the descriptive level in statistical tests.

This study is part of a research project approved by the institution's Research Ethics Committee (CAEE 41758720.2.0000.0068) for the retrospective analysis of electronic medical records.

Results

The initial study sample comprised 330 patients with sporadic PHPT who underwent parathyroidectomy. Thirty subjects were excluded from the study: 13 patients who had more than one parathyroid gland resected, 2 patients who had no parathyroid glands excised, and 15 patients who had missing IOPTH data. Therefore, 300 patients were deemed eligible for analysis (Figure 1).

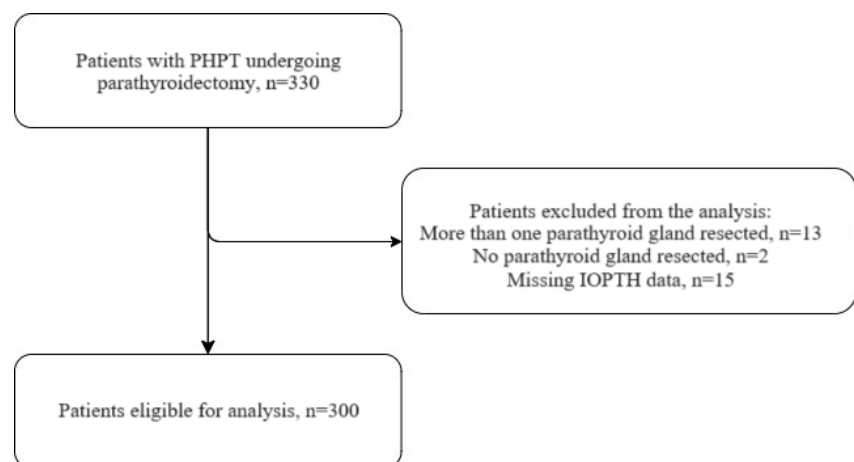


Figure 1. Composition of the sample.

Descriptive data of the population and the comparison between sexes are presented in Table 1. Of the 300 patients analyzed, 54 (18%) were male and 246 (82%) were female. The median age was 59 years (Q1-Q3 51.2-68).

Table 1. Descriptive data of the sample and comparison between sexes.

Demographic data				
	Total	Sex M	Sex F	p-value
Patients, n (%)	300 (100)	54 (18)	246 (82)	-
Age (year), mdn (Q1-Q3)	59 (51.2-68)	57 (44.8-65.3)	60 (52-68)	0.08
Position of the resected parathyroid gland				
	Total, n = 300	Sex M, n = 54	Sex F, n = 246	p-value
RIPT, n (%)	77 (25.7)	11 (20.4)	66 (26.8)	-
RSPT, n (%)	73 (24.3)	12 (22.2)	61 (24.8)	-
LIPT, n (%)	76 (25.3)	17 (29.8)	59 (24.0)	-
LSPT, n (%)	63 (21.0)	13 (24.1)	50 (20.3)	-
ITPT, n (%)	11 (3.7)	1 (1.8)	10 (4.1)	-
Estimated volume of the resected parathyroid gland and IOPTH values				
	Total	Sex M	Sex F	p-value
Gland volume, mm ³ mdn (Q1-Q3)	1600 (720-3750)	2548 (960-7106)	1440 (654-3375)	0.02
PTH-p, pg/mL mdn (Q1-Q3)	156.5 (111-301)	188.5 (102.8-463.3)	151.5 (111.8-27.3)	0.30
PTH-c, pg/mL mdn (Q1-Q3)	252 (47.3-764.3)	347.5 (120-1192)	248.5 (150-644.8)	0.53
ΔPTHc-p, pg/mL mdn (Q1-Q3)	58 (9-330.5)	64 (10.5-523.5)	58 (8.75-294.8)	0.36
Δ%PTHc-p, % mdn (Q1-Q3)	31.1 (4.3-114.8)	35.5 (5.4-136.3)	33.1 (6-161.2)	0.85

Caption: n = Number; M = Male; F = Female; mdn = Median; Q1 = 1st Quartile; Q3 = 3rd Quartile; RIPT = Right Inferior Parathyroid; RSPT = Right Superior Parathyroid; LIPT = Left Inferior Parathyroid; LSPT = Left Superior Parathyroid; ITPT = Intrathyroidal Parathyroid; PTH = Parathyroid Hormone; IOPTH = Intraoperative PTH; PTH-p = Baseline PTH from Peripheral Vein; PTH-c = Baseline PTH from Central Vein; ΔPTHc-p = Absolute Difference Between PTH-c and PTH-p Values; Δ%PTHc-p = Percentage Variation Between PTH-c and PTH-p Values.

The distribution of parathyroid glands according to their position was as follows: RIPT = 77 (25.7%), RSPT = 73 (24.3%), LIPT = 76 (25.3%), LSPT = 63 (21%), and ITPT = 11 (3.7%). No significant difference in frequency between men and women was observed in the multiple comparisons.

The median estimated volume of the resected parathyroid gland was 1600 mm³ (Q1-Q3 720-3750). Regarding gender, the median estimated volume was 2548 mm³ (Q1-Q3 960-7106) for men and 1440 mm³ (Q1-Q3 654-3375) for women. There was a statistically significant difference in the estimated volume of the parathyroid between men and women (p=0.02).

Comparisons between gland position, estimated volume, and IOPTH values are described in Table 2. A statistically significant difference was observed between the estimated volume of RIPT and RSPT ($p=0.04$), but no significant differences were found between the other positions of the parathyroid glands. When comparing gender with the estimated volume of the parathyroid gland according to its position, a statistically significant difference was observed between the estimated volumes of LIPT between men and women ($p=0.001$).

Table 2. Comparison between the position of the resected parathyroid gland, estimated volume, and IOPTH values.

Comparison between the position of the resected parathyroid gland, estimated volume, and IOPTH values				
	Volume	Sex M	Sex F	p-value
RIPT, mm ³ mdn (Q1-Q3)	1163 (645.8-2690)	1061 (787.5-4328)	1188 (596.3-2370)	0.56
RSPT, mm ³ mdn (Q1-Q3)	1944 (920-5540)	1876 (465-5526)	1944 (1036-5544)	0.48
LIPT, mm ³ mdn (Q1-Q3)	1496 (600-3150)	3450 (1704-9180)	1053 (483-2725)	0.001
LSPT, mm ³ mdn (Q1-Q3)	2097 (732-4494)	2592 (960-15500)	2080 (644-4863)	0.30
Comparison between the position of the resected parathyroid gland and IOPTH values				
	PTH-p, pg/mL	PTH-c, pg/mL	ΔPTHc-p, pg/mL	Δ%PTHc-p, %
RIPT, mdn (Q1-Q3)	157 (111.5-232)	238 (138.5-456.5)	55 (2.5-147.5)	28% (1.6%-107.2%)
RSPT, mdn (Q1-Q3)	158 (102-428.5)	389 (165.5-896)	117 (29.5-460.5)	55% (16.5%-170.2%)
LIPT, mdn (Q1-Q3)	151 (116.1-268.8)	204 (130-526.3)	34.5 (-1.75-144)	12.2% (-4.3%-49.3%)
LSPT, mdn (Q1-Q3)	151 (112-328)	367 (146-1746)	54 (0-902)	41.1% (0%-276.3%)
ITPT, mdn (Q1-Q3)	156 (101-360)	292 (123-508.3)	98 (22-208)	92.1% (21.7%-184.4%)

Caption: *n* = Number; *M* = Male; *F* = Female; *mdn* = Median; *Q1* = 1st Quartile; *Q3* = 3rd Quartile; *RIPT* = Right Inferior Parathyroid; *RSPT* = Right Superior Parathyroid; *LIPT* = Left Inferior Parathyroid; *LSPT* = Left Superior Parathyroid; *ITPT* = Intrathyroidal Parathyroid; *PTH* = Parathyroid Hormone; *IOPTH* = Intraoperative PTH; *PTH-p* = Baseline PTH from Peripheral Vein; *PTH-c* = Baseline PTH from Central Vein; Δ PTHc-p = Absolute Difference Between PTH-c and PTH-p Values; $\Delta\%$ PTHc-p = Percentage Variation Between PTH-c and PTH-p Values.

There was a statistically significant difference in the Δ PTHc-p values when comparing the RIPT and RSPT glands ($p=0.02$). When comparing LIPT and LSPT, no statistically significant difference was observed ($p=0.09$). For $\Delta\%$ PTHc-p values, there was a statistically significant difference both in the comparison of RIPT and PTSD ($I=0.04$) and the comparison of LIPT and LSPT ($p=0.005$). No significant differences in the values were found in the multiple comparisons between the other positions of the parathyroid glands.

A statistically significant positive correlation was observed between the estimated volume of the parathyroid gland and the PTH-p ($p < 0.0001$), PTH-c ($p < 0.0001$), and Δ PTHc-p ($p = 0.0007$) values. However, no correlation was found between the estimated volume and $\Delta\%$ PTHc-p ($p = 0.34$) (Figure 2).

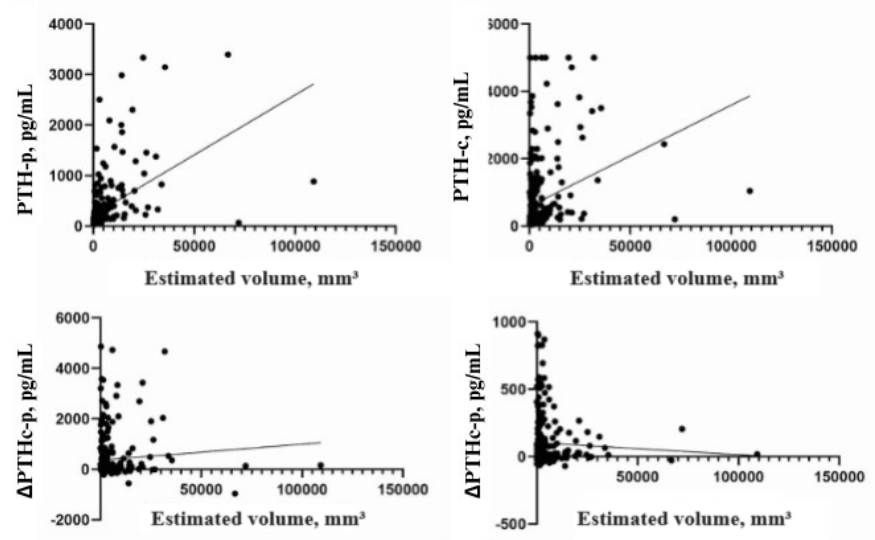


Figure 2. Comparison between the estimated volume of the resected parathyroid gland and IOPTH values.

In the analysis of the relationship between age and the estimated volume of the parathyroid gland, a statistically significant negative correlation was observed ($p < 0.0001$) (Figure 3).

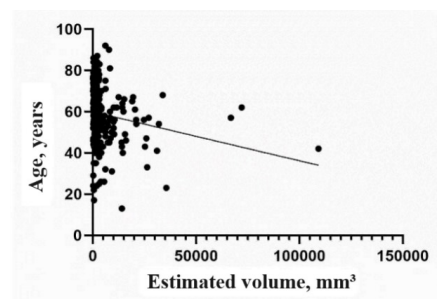


Figure 3. Comparison between the estimated volume of the resected parathyroid gland and age.

Discussion

In the present study, we observed a patient population with sporadic uniglandular PHPT akin to data previously reported in the literature. We verified a similar frequency of involvement of the four parathyroid glands.

We identified a frequency of 3.7% of intrathyroidal parathyroid glands, which agrees with data from other case series¹⁸. We did not find any cases of other ectopic positions of the parathyroid in our sample. This may be partly attributed to varying criteria to classify ectopia. In our institution, the mere location of the gland within the thymus is not considered as ectopia unless it is below the brachiocephalic vein. Therefore, glands located in the thymic horn are regarded as topical.

The frequency of involvement of each position of the diseased gland showed no significant variation regarding sex and age. However, it was observed that men had larger hyperfunctioning glands than women, especially the LIPT. We found no prior records of this in the literature. Moreover, a negative correlation was identified between age and the estimated volume of the gland. These results suggest the existence of a distinct biological behavior of sporadic uniglandular PHPT among these population groups. A more comprehensive analysis might pinpoint an age cutoff or age ranges that enable the detection of biological behavior differences in the future, which may be useful for clinical considerations.

Most studies using the IOPTH technique do not mention the superior or inferior position of the hyperfunctioning parathyroid gland. It is assumed that superiorly positioned parathyroid glands may present higher PTH-c levels when collected from the internal jugular vein because of the venous drainage pattern of these glands. Both inferior and superior parathyroids usually drain into the ipsilateral inferior thyroid vein, which typically tributaries to the ipsilateral brachiocephalic vein. However, in some cases, superior parathyroids might drain into the superior or middle thyroid veins, which tend to be tributaries of the ipsilateral internal jugular vein^{19,20}.

In this study, we found significant differences in the values of the estimated volume of the parathyroid, Δ PTHc-p, and $\Delta\%$ PTHc-p when comparing the RIPT and RSPT glands, and in $\Delta\%$ PTHc-p when comparing the LIPT and LSPT glands, with higher values observed in the superior glands.

Although the discrepancy in the variation values between PTH-c and PTH-p on the right side can be attributed to the glandular volume difference between RIPT and RSPT, the finding of higher $\Delta\%$ PTHc-p values also in the superior left position corroborates the hypothesis of a different venous drainage pattern between superiorly and inferiorly positioned glands, regardless of the side.

Based on the described findings, we suggest that $\Delta\%$ PTHc-p might have intraoperative utility as additional information to guide surgical exploration. Elevated values of this measure might suggest the presence of a hyperfunctioning gland in a superior position. This approach could be especially useful in patients with negative localization tests but requires further studies.

Regarding the estimated volume of the resected gland, we observed a positive correlation between the volume and PTH-p, PTH-c, and Δ PTHc-p; however, no correlation with $\Delta\%$ PTHc-p was found.

We believe that the behavior of Δ PTHc-p and $\Delta\%$ PTHc-p might be analogous to the PTH-c gradient collected simultaneously from the internal jugular veins,

as assessed in studies investigating this criterion as a predictor of laterality. Initially, PTH-p values are expected to be similar to the PTH-c of the internal jugular vein contralateral to the hyperfunctioning parathyroid gland. Additional studies are needed to evaluate if these measures can be useful for surgery lateralization.

This study presents a broad cohort of patients monitored in a tertiary center, with a standardized care routine that includes IOPTH collection and detailed recording of intraoperative data, such as the size and position of the parathyroid gland.

Study limitations include the simplified method used to calculate the volume of the parathyroids, the upper detection limit of IOPTH in the laboratory assay used, and the fact that it is a single-center study, meaning the findings need confirmation in other populations to be generalized. The study did not evaluate perioperative imaging or laboratory data, nor the drop in IOPTH. Subsequent studies can explore the relationship between the described findings and these other variables.

Conclusion

In patients with sporadic uniglandular PHPT, we observed that the RSPT glands have a larger volume, as well as higher Δ PTHc-p and $\Delta\%$ PTHc-p values, compared with the RIPT glands. Meanwhile, the LSPT glands display higher $\Delta\%$ PTHc-p values compared with those of the LIPT glands.

It is suggested that elevated $\Delta\%$ PTHc-p measures might be of intraoperative significance, indicating a potential superior position of the gland to be resected.

There is a relationship between larger parathyroid glands and higher PTH-p, PTH-c, and Δ PTHp-c values; however, there is no correlation between gland volume and $\Delta\%$ PTHp-c.

It was observed that men have larger parathyroid glands compared to women. Additionally, a negative correlation between age and gland volume was identified.

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