

# Intraoperative parathormone monitoring to predict operative success in patients with normohormonal hyperparathyroidism

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**Background:** It is unclear whether parathyroidectomy guided by intraoperative parathormone (PTH) monitoring is predictive of operative success in patients with normohormonal hyperparathyroidism (nhHPT), a variant of primary hyperparathyroidism (pHPT) in which patients develop clinical manifestations similar to those of pHPT. This study examined intraoperative PTH monitoring in patients undergoing parathyroidectomy for nhHPT.

**Methods:** We performed a retrospective review of prospectively collected data from adult (age > 18 yr) patients who underwent parathyroidectomy for pHPT at 1 of 2 North American medical centres (in Calgary, Alberta, Canada, or Miami, Florida, United States) between 2007 and 2015. In patients with nhHPT, we used the criterion of an intraoperative decrease of more than 50% in PTH after abnormal gland excision. We defined operative success as continuous eucalcemia more than 6 months after parathyroidectomy.

**Results:** Of 333 patients, 38 (11.4%) had nhHPT, with mean preoperative calcium and PTH levels of 2.7 mmol/L and 53 pg/dL, respectively. An intraoperative decrease of more than 50% in PTH level was seen in 27 patients (71.0%) with nhHPT and 265 patients (89.8%) with classic pHPT at 5 minutes ( $p < 0.001$ ); the corresponding values at 20 minutes were 35 (92.1%) and 286 (96.9%). Although 5 patients (13.2%) with nhHPT did not reach this criterion until 20 minutes, the rate of operative success was still 97.0% at long-term follow-up (mean 13 mo, range 6–67 mo). Of the 38 patients, 3 (7.9%) did not have an intraoperative decrease of more than 50% in PTH level by 20 minutes. Two of the 3 achieved operative success and remained normocalcemic, and 1 developed recurrent disease at 12 months.

**Conclusion:** Parathyroidectomy guided by intraoperative PTH monitoring accurately predicted operative success in patients with nhHPT. Intraoperative PTH monitoring may also help identify multiglandular disease in patients with nhHPT, using criteria similar to those in classic pHPT, with comparable operative success.

**Contexte :** On ne sait pas si la parathyroïdectomie guidée par la surveillance peropératoire de la parathormone (PTH) permet de prédire le succès opératoire chez les patients atteints d'hyperparathyroïdie normo-hormonale (nhHPT), une variante de l'hyperparathyroïdie primaire (pHPT) qui entraîne chez les patients des manifestations cliniques similaires à celles de la pHPT. Cette étude a examiné la surveillance peropératoire de la PTH chez des patients subissant une parathyroïdectomie pour une nhHPT.

**Méthodes :** Nous avons effectué une revue rétrospective des données recueillies prospectivement auprès de patients adultes (> 18 ans) ayant subi une parathyroïdectomie pour une pHPT à l'un ou l'autre de 2 centres médicaux nord-américains (à Calgary, en Alberta, au Canada, et à Miami, en Floride, aux États-Unis) entre 2007 et 2015. Chez les patients atteints de nhHPT, nous avons utilisé le critère d'une diminution peropératoire de plus de 50 % de la PTH après l'ablation de la glande anormale. Le critère de succès opératoire consistait en une eucalcémie continue plus de 6 mois après la parathyroïdectomie.

**Résultats :** Sur 333 patients, 38 (11,4 %) avaient une nhHPT, avec des taux moyens de calcium et de PTH préopératoires de 2,7 mmol/L et 53 pg/dL, respectivement. Une diminution peropératoire de plus de 50 % du niveau de PTH a été observée chez 27 patients (71,0 %) avec nhHPT et 265 patients (89,8 %) avec pHPT classique à 5 minutes ( $p < 0,001$ ); les valeurs correspondantes à 20 minutes étaient 35 (92,1 %) et 286 (96,9 %). Bien que 5 patients (13,2 %) avec nhHPT n'aient pas

atteint ce critère avant 20 minutes, le taux de succès opératoire était encore de 97,0 % lors du suivi à long terme (moyenne 13 mois, intervalle 6–67 mois). Sur les 38 patients, 3 (7,9 %) n'ont pas eu de diminution peropératoire de plus de 50 % du taux de PTH avant 20 minutes. Pour 2 de ces 3 patients, l'opération a réussi; ils sont demeurés normocalcémiques. L'autre patient a développé une maladie récurrente à 12 mois.

**Conclusion :** La parathyroïdectomie guidée par la surveillance peropératoire de la PTH a permis de prédire avec précision le succès opératoire chez les patients atteints de nhHPT. La surveillance peropératoire de la PTH peut également aider à détecter une maladie multiglandulaire chez les patients atteints de nhHPT, par l'utilisation de critères similaires à ceux de la pHPT classique, avec succès opératoire comparable.

**P** rimary hyperparathyroidism (pHPT) affects about 50 per 100 000 people annually, and its clinical manifestations have adverse effects on bone, kidney and cognitive function.<sup>1,2</sup> With the advent of improved and more widespread methods of biochemical detection, neck imaging, and bone evaluation and screening, the incidence of pHPT continues to increase. The diagnosis of classic pHPT is confirmed biochemically by hypercalcemia in the setting of elevated serum parathormone (PTH) levels. Over time, the biochemical presentation of this disease has evolved, with a subset of patients presenting more frequently with biochemically mild variants of pHPT (normocalcemic hyperparathyroidism [ncHPT] or normohormonal hyperparathyroidism [nhHPT]).

Since the 1990s, there has been an increasing incidence of nhHPT as a result of a greater appreciation for subtle PTH imbalances.<sup>3–5</sup> The rate of nhHPT ranges between 5% and 21%, likely owing, in part, to variation in the upper limit of normal serum PTH level over time and between different PTH assays.<sup>3–10</sup> Despite the biochemical profile of nhHPT, affected patients have clinical manifestations of hypercalcemia similar to those of patients with classic pHPT (i.e., nephrolithiasis, bone disease, cognitive symptoms).<sup>8,11</sup> Although the underlying cause of nhHPT remains unclear, it may represent an early form of pHPT, a lower PTH set point or a technical inability to detect circulating forms of PTH with current assays.<sup>9,10,12</sup> With increased routine biochemical testing, neck imaging studies and measurements for bone mineral evaluation, patients with nhHPT currently undergo surgical treatment because of preoperative symptoms and the finding of hyperfunctioning gland(s) at parathyroidectomy.<sup>8,13</sup> It is recognized that nhHPT is a challenge to interpret and that it is a condition of abnormal parathyroid gland function in the setting of hypercalcemia.<sup>6</sup>

Some authors have described ncHPT as a forme fruste of classic pHPT in which patients develop the clinical manifestations of pHPT over time.<sup>14</sup> Patients with nhHPT who have inappropriately nonsuppressed PTH levels that lie within normal range in the setting of elevated or high-normal serum calcium levels also pres-

ent with symptoms similar to those seen in patients with classic pHPT and experience similar postoperative resolution of disease-related disorders.<sup>11,12,15</sup> Nevertheless, it remains controversial whether patients with nhHPT should undergo parathyroidectomy because the natural history of nhHPT remains poorly defined and the benefits of surgical management questioned. Although not discussed in recent guidelines,<sup>6,16</sup> patients with nhHPT often undergo surgical exploration if they meet the same symptomatic or asymptomatic criteria as patients with classic pHPT.

Many surgeons use PTH monitoring during parathyroidectomy to guide and confirm removal of all hyperfunctioning parathyroid glands. An intraoperative decrease in PTH level of more than 50% at 10 minutes, or the “Miami criterion,” is often used to guide parathyroidectomy, and this protocol has been found to be at least 98% accurate in predicting operative success in patients with classic pHPT at 6 months.<sup>17,18</sup> Given the differing biochemical profiles of patients with pHPT, determining operative success based on the Miami criterion is of interest in patients with nhHPT who have normal PTH levels preoperatively.

This study evaluated the utility of intraoperative PTH monitoring and whether a decrease in PTH level of more than 50% during parathyroidectomy can be used to predict operative success in patients with nhHPT. We hypothesized that the intraoperative PTH level can be used to accurately predict operative success in patients with nhHPT and that the criterion of achieving an intraoperative decrease of more than 50% in PTH level may be applied to this population.

## METHODS

We conducted a retrospective cohort study using databases from 2 tertiary medical centres in Calgary, Alberta, Canada, and Miami, Florida, United States, between 2007 and 2015. Approval was granted by the University of Miami research ethics board and the University of Calgary Conjoint Health Research Ethics Board. All patients underwent parathyroidectomy guided by intraoperative PTH monitoring.

Study patients were older than 18 years and had a diagnosis of pHPT based on preoperative serum calcium and PTH levels. Patients with classic pHPT were defined by preoperative PTH levels greater than 65 pg/dL and hypercalcemia. Patients with preoperative PTH levels of 65 pg/dL or less, with elevated or near-normal calcium levels, were considered to have nhHPT. The last outpatient PTH level measured before surgery was used to categorize patients.

Data reviewed included patient demographic characteristics, intraoperative PTH dynamics, and pre- and postoperative serum calcium and PTH levels. All patients underwent parathyroid localization studies via sestamibi (MIBI) scans or ultrasonography, or both, preoperatively. Data regarding other imaging modalities and correlation with intraoperative findings were not collected. All patients were followed for a minimum of 6 months after parathyroidectomy. Patients with secondary, tertiary or familial hyperparathyroidism, multiple endocrine neoplasia syndromes, renal insufficiency, parathyroid carcinoma, concurrent thyroid surgery or redo parathyroid surgery were excluded from the study.

Patient selection for parathyroidectomy was determined in accordance with previously published guidelines for the operative indications for pHPT.<sup>13</sup> Patients underwent focused parathyroidectomy or bilateral neck exploration based on preoperative imaging and surgeon preference.

The criterion used to predict successful parathyroidectomy was an intraoperative decrease of more than 50% in PTH level from the highest preincision or pre-excision level 10 minutes after excision of all abnormal parathyroid tissue.<sup>7</sup> If there was an insufficient decrease in PTH level at 10 minutes, the operation was converted to bilateral neck exploration or the PTH level was measured at 20 minutes, at the surgeon's discretion.<sup>6,13,18</sup> Patients who did not show a decrease of more than 50% in PTH level by 20 minutes underwent bilateral neck exploration.

In patients in whom bilateral neck exploration was performed, additional abnormal-appearing glands were removed, followed by intraoperative PTH measurement. In Miami, multiglandular disease was defined as persistently elevated intraoperative PTH levels despite removal of 1 hypersecreting gland at the time of initial operation or when removal of a single gland resulted in operative failure. In Calgary, multiglandular disease was defined as more than 1 histologically enlarged hypercellular gland identified intraoperatively or when removal of a single gland resulted in operative failure.

We defined operative success as eucalcemia more than 6 months after parathyroidectomy, and operative failure as hypercalcemia greater than the reference range more than 6 months after parathyroidectomy. We defined recurrent disease as hypercalcemia and PTH levels above the normal reference range more than 6 months after successful parathyroidectomy.

Statistical analysis

We used the Student *t* test and the  $\chi^2$  test to perform statistical analysis. A *p* value < 0.05 was considered statistically significant.

RESULTS

Of 333 patients identified from the joint databases, 295 (88.6%) had classic pHPT, and 38 (11.4%) had nhHPT (Table 1). There were no differences in age or sex between the 2 groups. Preoperative calcium values (2.7 mmol/L v. 2.8 mmol/L) and PTH values (53 pg/dL v. 145 pg/dL) were significantly lower in the nhHPT group than in the classic pHPT group (*p* < 0.001 for both) (Table 2). All patients underwent preoperative imaging, 296 (88.9%) with ultrasonography, 259 (77.8%) with sestamibi scintigraphy, and 233 (70.0%) with both modalities.

Mean peak preincision/pre-excision intraoperative PTH values were significantly higher in patients with classic pHPT than in those with nhHPT (263 pg/dL v. 133 pg/dL, *p* < 0.05). Twenty-seven patients (71.0%) in the nhHPT group and 265 patients (89.8%) in the classic

Table 1. Mean preoperative calcium and parathormone levels in patients with normohormonal hyperparathyroidism and primary hyperparathyroidism at the 2 study centres

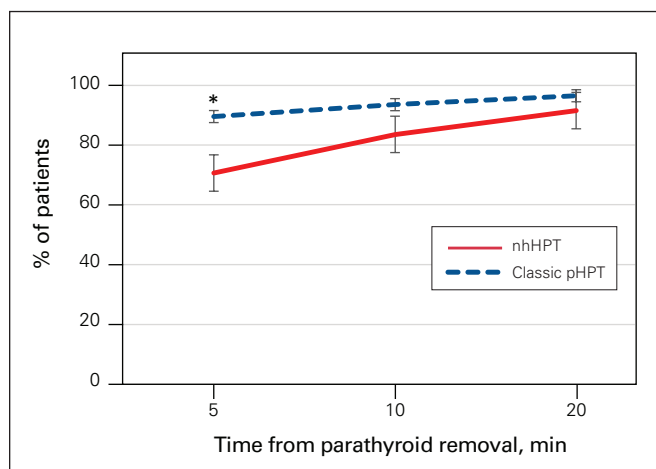
| Group; variable                               | Centre; no. (%) of patients* |                         |
|---|------------------------------|-------------------------|
|   | Calgary<br><i>n</i> = 62     | Miami<br><i>n</i> = 271 |
| <b>Classic pHPT (<i>n</i> = 295)</b>          | 47 (75.8)                    | 248 (91.5)              |
| Preoperative calcium level, mean ± SD, mmol/L | 2.8 ± 0.2                    | 2.8 ± 0.2               |
| Preoperative PTH level, mean ± SD, pg/dL      | 113 ± 50                     | 151 ± 60                |
| <b>nhHPT (<i>n</i> = 38)</b>                  | 15 (24.2)                    | 23 (8.5)                |
| Preoperative calcium level, mean ± SD, mmol/L | 2.6 ± 0.1                    | 2.7 ± 0.1               |
| Preoperative PTH level, mean ± SD, pg/dL      | 52 ± 10                      | 54 ± 9                  |

nhHPT = normohormonal hyperparathyroidism; pHPT = primary hyperparathyroidism; PTH = parathormone; SD = standard deviation.  
\*Except where noted otherwise.

Table 2. Patient demographic characteristics

| Characteristic                                | No. (%) of patients*           |                        |                |
|---|--------------------------------|------------------------|----------------|
|   | Classic pHPT<br><i>n</i> = 295 | nhHPT<br><i>n</i> = 38 | <i>p</i> value |
| Age, mean ± SD, yr                            | 59 ± 14                        | 58 ± 10                | 0.5            |
| Female sex                                    | 239 (81.0)                     | 28 (73.7)              | 0.3            |
| Preoperative calcium level, mean ± SD, mmol/L | 2.8 ± 0.2                      | 2.7 ± 0.1              | < 0.001        |
| Preoperative PTH level, mean ± SD, pg/dL      | 145 ± 61                       | 53 ± 9                 | < 0.001        |
| Preoperative eucalcemia                       | 7 (2.4)                        | 2 (5.3)                | 0.3            |

nhHPT = normohormonal hyperparathyroidism; pHPT = primary hyperparathyroidism; PTH = parathormone; SD = standard deviation.  
\*Except where noted otherwise.



**Fig. 1.** Proportion of patients with classic primary hyperparathyroidism (pHPT) and normohormonal hyperparathyroidism (nhHPT) who had an intraoperative decrease of more than 50% in parathormone level 5, 10 and 20 minutes after parathyroid removal. \* $p < 0.001$ . Error bars represent standard deviations.

pHPT group had a decrease of more than 50% in PTH level at 5 minutes ( $p < 0.001$ ) (Figure 1). The corresponding values at 10 minutes were 32 (84.2%) and 277 (93.9%), and at 20 minutes, 35 (92.1%) and 286 (96.9%), both non-significant differences.

Of the 24 patients with nhHPT with PTH values at 20 minutes, 19 (79%) achieved a decrease of more than 50% in PTH level by 10 minutes. Of the 5 remaining patients, 3 (12%) had a decrease of more than 50% in PTH level at 20 minutes, and 2 (8%) had decreases of 40% and 49% at 20 minutes; both of the latter patients underwent bilateral neck exploration with 1 gland removed, and both were eucalcemic at most recent follow-up (8 mo and 58 mo). In 1 patient (4%), owing to a technical issue, only 1 PTH measurement was obtained intraoperatively, showing a decrease of 38%. This patient had 1 gland removed and was eucalcemic at 6 months but was found to have a recurrence at 12 months. All patients with nhHPT with an intraoperative decrease of more than 50% in PTH level by 20 minutes were eucalcemic at a mean follow-up duration of 13.6 months.

A higher proportion of patients with nhHPT than with classic pHPT underwent bilateral neck exploration (12 [31.6%] v. 55 [18.6%]); however, the difference was not statistically significant ( $p = 0.06$ ). Three patients (7.9%) in the nhHPT group had multiglandular disease; all 3 had 2 glands removed and achieved an intraoperative decrease of more than 50% in PTH level by 10 minutes. One of these patients had bilateral neck exploration, and 2 had unilateral neck exploration. Thirty-two patients (11.0%) in the classic pHPT group had multiglandular disease. Of the 32, 2 had 1 gland removed; the other hyperfunctioning gland was not identified. Twenty-nine patients had 2 glands removed, and 1 patient had 3 glands removed. There was no significant difference in the

number of glands removed or incidence of multiglandular disease between the nhHPT and classic pHPT groups.

The rate of operative success was 99.0% (292/295) among patients with classic pHPT and 97.4% (37/38) among those with nhHPT.

## DISCUSSION

We observed a rate of nhHPT of 11%. This value is consistent with published rates of 0.3%–22.5%.<sup>3,19,20</sup> In our nhHPT group, an intraoperative decrease of more than 50% in PTH level by 10 or 20 minutes accurately predicted operative success at a mean follow-up duration of 13.6 months. At 10 minutes, 84% of patients with nhHPT achieved this criterion, compared to 94% of those with classic pHPT. The corresponding values at 20 minutes were 92% and 97%. These trends in intraoperative PTH dynamics suggest a slower rate of PTH decrease in patients with nhHPT than in those with classic pHPT. This is similar to the results of Alhefdhi and colleagues,<sup>21</sup> who found that 4.9% of patients with mild hyperparathyroidism did not achieve an intraoperative decrease of more than 50% in PTH level until 20 minutes. Trinh and colleagues<sup>22</sup> compared rates of decrease in intraoperative PTH level between patients with classic pHPT and those with nhHPT, and found a direct association between baseline PTH level and rate of intraoperative PTH degradation. Although the physiologic basis for this more gradual decline of intraoperative PTH level in patients with nhHPT remains unclear, a possible explanation is that, in patients with lower preoperative PTH levels, there may be less suppression of normally functioning parathyroid glands, leading to a slower relative decrease in PTH level intraoperatively.

In the present study, all patients with nhHPT who did not have an intraoperative decrease of more than 50% in PTH level at 10 minutes but achieved this decrease by 20 minutes had operative success at 6 months. Graves and colleagues<sup>23</sup> examined intraoperative PTH kinetics in patients with mild hyperparathyroidism and found that there was a trend toward a longer time to achieve an intraoperative decrease of more than 50% in PTH level in those with nhHPT than in those with classic pHPT. Among patients with nhHPT who did not have an intraoperative decrease of more than 50% in PTH level by 10 minutes, the median time to reach this criterion was 25 minutes. Khan and colleagues<sup>24</sup> reported that PTH measurement at 20 minutes significantly reduced the need for bilateral neck exploration in patients with classic pHPT by enabling more patients to reach an intraoperative decrease of more than 50% in PTH level. Based on these findings, it is reasonable to extrapolate that measuring the PTH level at 20 minutes during parathyroidectomy may optimize operative success in patients with nhHPT.

The rate of in the nhHPT group in our study, 8%, is lower than values reported in the literature (12%–59%).<sup>8,11,10,19,21</sup> In 1 report, a rate of multiglandular disease of 29% was found in patients with nhHPT, higher than that seen in classic pHPT.<sup>25</sup> In another study, multivariate analysis did not show any statistically significant association of multiglandular disease with any pHPT variant (classic pHPT 16.5% v. ncHPT 21.7% v. nhHPT 9.1%).<sup>26</sup> The observed variability in multiglandular disease rates in these studies is likely multifactorial and includes factors such as population; sample size; varied definitions of multiglandular disease based on quantitative assessment (i.e., intraoperative PTH level) versus qualitative assessment (i.e., size, colour, histologic features); surgeon experience, judgment and preference; and initial surgical approach used.<sup>10–12,18,19</sup>

The rate of bilateral neck exploration among our patients with nhHPT was higher than that for patients with classic pHPT (32% v. 19%). Similar findings were reported in other surgical series showing a rate of bilateral neck exploration of 54% but no difference in multiglandular disease between the classic pHPT, ncHPT and nhHPT groups.<sup>26</sup> The reported use of bilateral neck exploration in patients with nhHPT varies (50%–91%),<sup>8,10,19,25</sup> but because many surgeons use it as the standard initial operative approach, it is difficult to extrapolate its correlation to multiglandular disease.

### Limitations

Although our study is limited by its retrospective nature, the fact that it combined patient populations from 2 North American cities may have helped overcome some inherent biases. The reported upper limit of normal for PTH varies between 40 pg/dL and 72 pg/dL, reflecting different assays used in different centres.<sup>8,10,19,21</sup> The upper limit of normal used in this study, 65 pg/dL, represents the threshold for normal in the majority of patients and an approximate median of values reported in the literature. However, the specific PTH value is less important than the recognition that patients with normal or slightly elevated PTH levels can still be candidates for parathyroidectomy guided by intraoperative PTH monitoring. The accuracy of preoperative localization studies was not available in this data set and would be an area of interest in subsequent analysis. Although patients were followed for at least 6 months, this interval may not have been long enough to detect recurrent hyperparathyroidism. Future studies would ideally have a larger sample of patients with nhHPT, with prospective data collection and long-term follow-up. Finally, recognizing that PTH levels can be influenced by multiple variables, it would be beneficial to have creatinine and vitamin D levels to compare between patient populations.

### CONCLUSION

A decrease of more than 50% in PTH level during parathyroidectomy in patients with nhHPT accurately predicted operative success at a mean follow-up duration of 13.6 months. However, the rate of decrease in PTH level in this group was slower than that in patients with classic pHPT, which suggests that PTH measurement at 20 minutes may be required to observe a decrease of more than 50% in patients with nhHPT. Intraoperative PTH monitoring may also help identify multiglandular disease in patients with nhHPT, using criteria similar to those in classic pHPT, with comparable operative success.

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**Competing interests:** None declared.

**Contributors:** B. Azab, J. Pasiaka and J. Lew designed the study. B. Azab, O. Picado Roque, J. Pasiaka and J. Lew acquired the data, which all authors analyzed. H. Stuart, B. Azab, J. Pasiaka and J. Lew wrote the manuscript, which B. Azab, O. Picado Roque, J. Pasiaka and J. Lew critically revised. All authors gave final approval of the article to be published.

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