

## Original Investigation

# Factors That Influence Parathyroid Hormone Half-life Determining if New Intraoperative Criteria Are Needed

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**IMPORTANCE** Minimally invasive parathyroidectomy using intraoperative parathyroid hormone monitoring remains the standard approach to the majority of patients with primary hyperparathyroidism. This study demonstrates that individual patient characteristics do not affect existing criteria for intraoperative parathyroid hormone monitoring.

**OBJECTIVE** To identify patient characteristics, such as age, sex, race, body mass index (BMI), and renal function, that may affect existing criteria for intraoperative parathyroid hormone (IOPH) levels during minimally invasive parathyroidectomy.

**DESIGN** Retrospective review of a prospectively collected parathyroid database populated from August 2005 to April 2011.

**SETTING** Academic medical center.

**PARTICIPANTS** Three hundred six patients with sporadic primary hyperparathyroidism who underwent initial parathyroidectomy between August 2005 and April 2011.

**INTERVENTIONS** All patients underwent minimally invasive parathyroidectomy with complete IOPH information.

**MAIN OUTCOME AND MEASURES** Individual IOPH kinetic profiles were fitted with an exponential decay curve and individual IOPH half-lives were determined. Univariate and multivariate analyses were performed to determine the association between patient demographics or laboratory data and IOPH half-life.

**RESULTS** Mean age of the cohort was 60 years, 78.4% were female, 90.2% were white, and median BMI was 28.3. Overall, median IOPH half-life was 3 minutes, 9 seconds. On univariate analysis, there was no association between IOPH half-life and patient age, renal function, or preoperative serum calcium or parathyroid hormone levels. Age, BMI, and an age  $\times$  BMI interaction were included in the final multivariate median regression analysis; race, sex, and glomerular filtration rate were not predictors of IOPH half-life. The IOPH half-life increased with increasing BMI, an effect that diminished with increasing age and was negligible after age 55 years ( $P = .001$ ).

**CONCLUSIONS AND RELEVANCE** Body mass index, especially in younger patients, may have a role in the IOPH half-life of patients undergoing parathyroidectomy. However, the differences in half-life are relatively small and the clinical implications are likely not significant. Current IOPH criteria can continue to be applied to all patients undergoing parathyroidectomy for sporadic primary hyperparathyroidism.

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**P** primary hyperparathyroidism is defined as elevated serum calcium levels with inappropriate elevation of parathyroid hormone (PTH) levels. In the majority (75%-85%) of patients, primary hyperparathyroidism is the result of a single parathyroid adenoma; the remaining patients have involvement of more than 1 parathyroid gland (multigland hyperplasia).<sup>1</sup> Parathyroidectomy is currently the only cure for primary hyperparathyroidism. Historically, the gold standard for parathyroidectomy involved bilateral cervical exploration and identification of all parathyroid glands, with removal of only enlarged glands. With the advent of intraoperative PTH (IOPTH) monitoring and improved radiographic techniques for preoperative gland localization imaging, minimally invasive parathyroidectomy (MIP) has become the favored approach. Minimally invasive parathyroidectomy has been demonstrated to have similar success rates as bilateral exploration, with lower rates of endocrine-specific complications, such as recurrent laryngeal nerve injury and permanent hypoparathyroidism.<sup>2</sup>

Monitoring IOPTH levels involves sampling of PTH values preoperatively and intraoperatively, after resection of abnormal parathyroid glands. The definition of a successful parathyroidectomy using IOPTH data varies by institution. Two common criteria include (1) a decrease of more than 50% from the highest preexcision value (the Miami criterion) or (2) a decrease of more than 50% from the highest preexcision value and into the normal range of the PTH assay.<sup>3-5</sup> Despite the various institutional differences, all current criteria rely solely on absolute IOPTH values and few studies have investigated the effect of patient factors on IOPTH elimination that could alter these values.<sup>3,5-10</sup> Therefore, the purpose of this study was to identify patient characteristics (age, sex, race, body mass index [BMI], and/or renal function) that may affect the half-life of PTH and, if so, to determine if new criteria are needed for IOPTH monitoring during parathyroidectomy.

## Methods

### Patients

Following institutional review board approval, patient data were retrospectively collected from a single institution's prospectively collected parathyroidectomy database populated from August 2005 to April 2011. Inclusion criteria for the study were patients with sporadic primary hyperparathyroidism due to a single adenoma who underwent initial parathyroidectomy with a complete IOPTH profile, consisting of IOPTH levels assayed at 0 to 4 minutes, 5 to 9 minutes, 10 to 14 minutes, and 15 to 40 minutes after adenoma resection. Of the initial 314 patients, 8 patients were excluded because of nonstandard IOPTH profiles. The final study cohort consisted of 306 patients.

Queried patient data consisted of age, sex, race, BMI (calculated as weight in kilograms divided by height in meters squared), preoperative serum calcium level, preoperative PTH level, glomerular filtration rate (GFR) (Modification of Diet in Renal Disease formula), and IOPTH concentrations with corresponding time values. All 306 patients underwent preoperative localization using cervical ultrasonography and tech-

netium Tc 99m-labeled sestamibi scans.<sup>11</sup> Since 2009, sestamibi scan was routinely performed with single-photon emission computed tomography; patients with discordant ultrasonography and sestamibi-single-photon emission computed tomography findings underwent a 4-dimensional computed tomography scan.

### Intraoperative PTH Monitoring

All patients underwent MIP with IOPTH monitoring. Our institution's IOPTH monitoring protocol consists of obtaining IOPTH levels from a peripheral blood sample following anesthesia induction and prior to neck incision (baseline), at adenoma resection (zero value), and subsequently at 5-minute intervals (5, 10, and 15 minutes) after adenoma resection. Our institution's criteria for intraoperative biochemical cure at 10 minutes after adenoma resection are defined as (1) PTH level decline of at least 50% from either the baseline or the zero value, whichever is higher, and (2) within normal immunoassay reference range. Intraoperative PTH levels were measured by the IMMULITE 1000 Turbo Intact PTH system (Diagnostic Products Corporation) from August 2005 to August 2009 and by the Roche Cobas e411 (Roche Diagnostics) from September 2009 to the present.

### Kinetic Analyses

Individual IOPTH data sets were modeled using an ideal single-phase exponential decay with an additive constant function,  $C$  (in picograms per milliliter). The model equation can be expressed as Equation 1, where  $A_o$  = constant term (in picograms per milliliter),  $k$  = decay constant (1/min), and  $t$  = time (in minutes):

$$[IOPTH](t) = A_o e^{-kt} + C \quad (1)$$

For the analysis, it was assumed that the contribution of the nonadenomatous parathyroid glands to the IOPTH profile was constant.<sup>12</sup> Least squares nonlinear regression modeling of the IOPTH data sets, based on Equation 1, was performed using an open-source implementation, ALGLIB, of the Levenberg-Marquardt algorithm in Visual Studio C++ (Microsoft).<sup>13</sup> The program yielded the kinetic decay constant,  $k$ , constant term,  $A_o$ , and constant function,  $C$ , for each patient. Correlation coefficients were calculated to verify model conformity, and IOPTH half-life values,  $\ln(2)/k$ , were then determined (Excel; Microsoft).

### Statistical Analyses

Nonparametric statistical analyses were performed because the IOPTH half-life values were nonnormally distributed in a positively skewed fashion. Nonparametric Wilcoxon rank sum test and Spearman rank correlation tests were used for univariate tests of association between patient demographics or laboratory data and IOPTH half-life. Median regression was used in multivariate analysis of IOPTH half-life. Variables in the model included those with  $P < .10$  on univariate analysis and a priori hypothesized risk factors. Median regression model selection was performed manually with a significance level of  $< .05$ . All statistical analysis was performed in SAS version 9.2 (SAS Institute Inc).

**Table. Clinical and Demographic Factors and Intraoperative Parathyroid Hormone Half-life for 306 Patients With Primary Hyperparathyroidism**

Variable	Mean (SD)	Half-life, Median	P Value
Age, y	60 (13)	...	.26 <sup>a</sup>
Sex, No. (%)			
F	240 (78.4)	3 min, 8 s	.06 <sup>b</sup>
M	66 (21.6)	3 min, 14 s	
Race, No. (%)			
White	276 (90.2)	3 min, 7 s	<.01 <sup>b</sup>
Black	26 (8.5)	3 min, 50 s	
Hispanic	4 (1.3)	2 min, 50 s	
BMI	29.50 (6.33)		
<25.00 (n = 75 [24.5%])	22.65 (1.68)	3 min	.06 <sup>b</sup>
25.00-29.99 (n = 103 [33.7%])	27.19 (1.37)	3 min, 8 s	
≥30.00 (n = 128 [41.8%])	35.38 (5.11)	3 min, 23 s	
GFR, mL/min/1.73 m <sup>2</sup>	76.46 (19.84)	...	.39 <sup>a</sup>
Preoperative serum calcium level, mg/dL	10.80 (0.71)	...	.19 <sup>a</sup>
Baseline preoperative PTH level, pg/mL	217.38 (186.63)	...	.09 <sup>a</sup>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GFR, glomerular filtration rate; PTH, parathyroid hormone. SI conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; PTH to nanograms per liter, multiply by 1. <sup>a</sup> P value determined by Spearman rank correlation test. <sup>b</sup> P value determined by Wilcoxon rank sum test.

## Results

### Cohort Summary Statistics

The **Table** summarizes the characteristics of the study cohort. Median age of the cohort was 60 years (interquartile range [IQR], 53-69 years) and 78.4% were female. The majority of patients (90.2%) were white, 8.5% were black, and 1.3% were Hispanic. The median BMI of the cohort was 28.3 (IQR, 25.0-32.7); 24.5% were normal weight or underweight (BMI <25), 33.7% were overweight (BMI 25-29.99), and 41.8% were obese (BMI ≥30). Cohort median GFR was 75.2 mL/min/1.73m<sup>2</sup> (IQR, 65.5-85.8 mL/min/1.73m<sup>2</sup>); 18% had a GFR less than 60 mL/min/1.73 m<sup>2</sup>. The median preoperative serum calcium level was 10.7 mg/dL (IQR, 10.3-11.3 mg/dL) (to convert to millimoles per liter, multiply by 0.25) and the median baseline preoperative PTH level was 169.5 pg/mL (IQR, 118.0-169.5 pg/mL) (to convert to nanograms per liter, multiply by 1). No patient was taking cinacalcet at the time of surgery; 39 patients (13%) were taking a bisphosphonate at the time of surgery.

### Kinetic Analyses

On kinetic analysis, Equation 1 was shown to fit individual IOPTH data with high conformity, as validated by a nonlinear regression correlation coefficient IQR of 0.9978 to 0.9999. The median calculated IOPTH half-life for the entire cohort was 3 minutes, 9 seconds (IQR, 2 minutes, 37 seconds to 4 minutes; mean, 3 minutes, 28 seconds). Calculated IOPTH half-life values were independent of the immunoassay implemented (*P* = .11).

### Statistical Analyses

There was an association between race and IOPTH half-life (**Table**); black patients demonstrated a longer IOPTH half-life than white patients (3 minutes, 50 seconds vs 3 minutes, 7 seconds; *P* < .01). Hispanic patients had a shorter IOPTH half-life (2 minutes, 50 seconds) but the small Hispanic sample size

(*n* = 4) limited our ability to make any inferences for this subset of the population. There was a trend toward an association between BMI and IOPTH half-life (*P* = .06); patients with a higher BMI had a longer IOPTH half-life. Similarly, there was a trend toward an association between sex and IOPTH half-life; men had a median IOPTH half-life that was 6 seconds longer than women (3 minutes, 14 seconds vs 3 minutes, 8 seconds; *P* = .06). There was no association between IOPTH half-life and patient age, renal function, preoperative serum calcium or PTH levels, or preoperative use of bisphosphonates.

Race, sex, and BMI along with a priori variables GFR and age plus an age × BMI interaction factor were then considered in multivariate analysis. Controlling for these factors, race, sex, and GFR were not significant. Significant predictors of IOPTH half-life were BMI (*P* = .04) and the age × BMI interaction factor (*P* < .001) with the final median IOPTH half-life model as given in Equation 2, where *A<sub>c</sub>* = (age - 60) and *B<sub>c</sub>* = (BMI - 30):

$$\text{Half-life}(A_c, B_c) = 3.21 - 0.0025 \times A_c + 0.0020 \times B_c - 0.0021 \times A_c \times B_c \rightarrow \quad (2)$$

Median IOPTH half-life increases with increasing BMI, but the predictive value of BMI declines with increasing age (Equation 2 and **Figure**). Therefore, the effect of BMI is negligible once a patient is older than 55 years, because the effect of BMI was not statistically significant until the age × BMI interaction was considered.

### Postoperative Follow-Up

At the time of last follow-up, the median calcium level for the study cohort was 9.4 mg/dL (range, 7.4-11.3 mg/dL) and median PTH level was 22.6 pg/mL (range, 2.5-200.1 pg/mL). No patient had persistent disease and only 1 patient (0.3%) had a known recurrence, defined as both a serum calcium level and PTH level more than the upper limit of normal, at last follow-up, with a serum calcium level of 11.3 mg/dL and PTH level of 75 pg/mL (IOPTH half-life, 2 minutes, 40 seconds). Median follow-up was 835 days (2.3 years; median, 6-2193 days [0.02-6.0 years]).

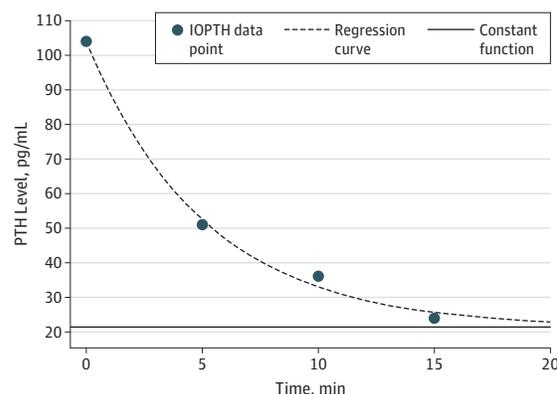
## Discussion

Since the introduction of MIP, various criteria for IOPTH monitoring have been proposed. The 2 most commonly used are (1) the Miami criterion (decrease of >50% from the highest pre-precision value at 10 minutes following parathyroid removal) and (2) a 10-minute postexcision decrease of more than 50% and into the normal range.<sup>3-5</sup> However, none of the previously published criteria account for patient characteristics, such as GFR or BMI, that might affect PTH elimination. One recent study by Cisco et al<sup>10</sup> examined the impact of race on IOPTH kinetics and found that African American patients had higher initial preexcision and 5-minute postexcision values, with similar 10-minute postexcision values, suggesting altered IOPTH kinetics, although no formal modeling was performed. In this study, the PTH elimination profiles of 306 patients who underwent MIP with IOPTH monitoring for primary HPT were analyzed to potentially identify preoperative predictors of IOPTH elimination that might affect intraoperative biochemical determination of cure. On multivariate analysis, statistically significant predictors of IOPTH half-life included BMI and an age × BMI interaction factor.

To our knowledge, this study of kinetic modeling of each individual patient's IOPTH elimination during parathyroidectomy is the largest of its kind in the published literature.<sup>12,14-17</sup> Our finding of a mean IOPTH half-life of 3 minutes, 28 seconds is consistent with previous studies. In a 2-phase model, Maier et al<sup>14</sup> reported a first-phase mean IOPTH half-life of 3 minutes, 24 seconds (Nichols Institute Diagnostics assay), and in a single-phase model, similar to the model used in this study, Bieglmayer et al<sup>16</sup> reported mean IOPTH half-life values ranging from 3 minutes, 18 seconds to 3 minutes, 42 seconds (Nichols Laboratories, Diagnostic Products Corporation, and Roche-Diagnostics assays, respectively).

Selection of a kinetic model that most closely approximated the IOPTH elimination data of the cohort was paramount to quantifying IOPTH elimination in this study. Previous IOPTH kinetic studies have implemented either a multiexponential decay model (multiphase) or a single-exponential decay model.<sup>12,14,17</sup> Maier et al<sup>14</sup> used a 2-phase exponential decay model; however, this required multiple IOPTH data points that were not obtained in our cohort. Two single-phase models dependent on first-order kinetics have previously been described. Libutti et al<sup>17</sup> used the preexcision PTH level as the initial data point, required 3 intraoperative data points, and assumed that the nonadenomatous glands' contribution to serum PTH level immediately increased as a function of the intraoperative decay constant,  $k$ , and time after adenoma resection. In contrast, in the model used by Bieglmayer et al,<sup>16</sup> the initial data point was the PTH level at the time of adenoma resection, 4 intraoperative data points were required, and it was assumed that the nonadenomatous glands' contribution to serum PTH level was constant after adenoma resection. Both of these models yielded identical IOPTH half-lives in an ideal setting.<sup>16,17</sup> However, in the operative setting, potential parathyroid gland manipulation during parathyroidectomy likely alters the true IOPTH profile and would thus exclude use of the preoperative PTH level as the initial data point in attaining the most accurate IOPTH

Figure. A Single Patient's Intraoperative Parathyroid Hormone (IOPTH) Profile



Fitted to Equation 1 ( $[IOPTH](t) = A_0 e^{-kt} + C(t)$ , where  $A_0$  = constant term [in picograms per milliliter],  $k$  = decay constant [1/min], and  $t$  = time [in minutes]) by nonlinear regression. PTH indicates parathyroid hormone.

elimination profile. Therefore, this study used a model similar to Bieglmayer et al in the analysis of IOPTH kinetics.

Only 1 previous study has investigated the predictors of IOPTH elimination. Gannagé-Yared et al<sup>9</sup> evaluated 108 patients with primary HPT who underwent MIP and determined that elderly age and reduced renal function (Modification of Diet in Renal Disease formula GFR <60 mL/min/1.73m<sup>2</sup>) were independent preoperative predictors of a slower decrease in IOPTH concentration between the PTH values at baseline and 10 minutes after adenoma resection. In this study, however, GFR was not found to be an independent predictor of IOPTH half-life on univariate or multivariate analysis. The results of this study do show BMI and an age × BMI interaction factor to be predictors of IOPTH half-life on multivariate analysis. The relationship between BMI and PTH metabolism is unclear. Animal models have shown that the hepatic Kupffer cell is a major determinant of the first phase of PTH elimination, which corresponds to the elimination phase of our model.<sup>18,19</sup> Therefore, it is possible that patients with higher BMI, perhaps because of a higher likelihood of steatohepatitis, may have reduced hepatic metabolism of PTH.<sup>20</sup>

There are several limitations to this study, including those inherent to a retrospective medical record review. Furthermore, recorded times for IOPTH blood draws were approximate and may not reflect exact intervals; therefore, the calculated IOPTH half-life may be inaccurate. However, since the predicted half-life differences were short (seconds), this limitation was not likely to affect the outcomes of this study.

In conclusion, patient race, sex, and renal function were not independent predictors of IOPTH half-life in patients with primary hyperparathyroidism undergoing parathyroidectomy. Interestingly, BMI and an age × BMI interaction factor may predict IOPTH half-life. However, predicted IOPTH half-life differences based on BMI are small, on the order of seconds, thus limiting the translation of the findings into clinical practice. Furthermore, the overall success rate in this cohort

of patients was more than 99%, providing further evidence that these relatively small differences in IOPTH half-life are not clinically significant. Given these findings, it is recommended that

current IOPTH criteria should continue to be applied to all patients undergoing parathyroidectomy for sporadic primary hyperparathyroidism.

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#### Invited Commentary

## Intraoperative Parathyroid Hormone Criteria

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**Primary hyperparathyroidism is due** to a single adenoma in 80% to 85% of patients and to multiple enlarged parathyroid glands in 15% to 20% of patients, and management of this anatomical disparity is one crux of expertise in parathyroid surgery.



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Because imaging tests do not reliably diagnose or exclude multiglandular disease, 2 strategies have been shown over decades to achieve high rates of operative cure: 4-gland exploration and focused dissection with intraoperative parathyroid hormone monitoring. Additionally, minimally invasive techniques combined with intraoperative parathyroid hormone monitoring

have been shown to improve quality of life, decrease morbidity, shorten operative time, and shorten hospital stay.<sup>1-6</sup>

Both methods still occasionally fail, and today's parathyroid surgeons continue to seek a perfect algorithm that identifies multiglandular disease without increasing costs or morbidity. Leiker and colleagues<sup>7</sup> commendably set out to examine a new question, whether patient factors can affect parathyroid hormone half-life, thus impacting intraoperative parathyroid hormone monitoring criteria for adequate resection. They report several fascinating and potentially useful findings. First, calculated parathyroid hormone half-life is independent of the parathyroid hor-

mone immunoassay type used. Second, parathyroid hormone half-life increases with increasing body mass index, particularly in young patients. Third, parathyroid hormone half-life is independent of bisphosphonate use, biochemical disease severity, and, surprisingly, renal function. However, the article also has a flaw. Multiglandular disease that has been missed at exploration typically presents as biochemical persistence or recurrence detected in long-term follow-up, which is why the time-tested proof that only a single adenoma was present is durable cure. Because some of the studied patients had as little as 6 days of postoperative follow-up, the presented data do not verify the premise that

all studied patients indeed had a single adenoma and we therefore cannot assume all to be cured.

Taken together, the valuable findings described by Leiker et al will help us to further refine an already highly successful approach. These findings also serve to highlight new challenges in the current management of primary hyperparathyroidism. Over decades, for example, the biochemical, and anatomical, presentation of primary hyperparathyroidism has become more subtle while some patient factors that hinder success, such as obesity, are better recognized.<sup>8,9</sup> Endocrine surgeons are by definition detail oriented and outcome based and continue to pursue the Holy Grail for our patients, the perfect operative outcomes.

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