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## Is Intraoperative Parathyroid Hormone Testing in Patients with Renal Insufficiency Undergoing Parathyroidectomy for Primary Hyperparathyroidism Accurate?

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### Abstract

**Background**—Our aim was to determine whether chronic renal insufficiency (CRI) impacts intraoperative parathyroid hormone (ioPTH) monitoring during parathyroidectomy. We hypothesized that ioPTH monitoring in patients with chronic CRI would show slower decline, but still accurately predict cure.

**Methods**—A retrospective review of patients with primary hyperparathyroidism who underwent curative single adenoma parathyroidectomy. The percentage of patients reaching 50% decline of ioPTH was compared between groups stratified by renal function.

**Results**—Between 2000 and 2013, 950 patients met inclusion criteria. At five minutes, 66% of patients with CRI met curative criteria vs. 77% of normal renal function patients ( $p=0.001$ ). At ten minutes, 89% vs. 92% met criteria ( $p=0.073$ ), and by fifteen minutes, the gap narrowed to 95% vs. 97% ( $p=0.142$ ).

**Conclusions**—Despite CRI patients with primary hyperparathyroidism having slower ioPTH decline after curative parathyroidectomy, 95% met ioPTH criteria by 15 minutes. Standard ioPTH criteria can be used with CRI patients.

### Keywords

Primary hyperparathyroidism; minimally invasive parathyroidectomy; intraoperative PTH monitoring; chronic renal insufficiency

### Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the general population. It is often identified via routine laboratory testing, and only 20% of patients now present with any of the classic symptoms of kidney stones or severe bone

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disease behind the popular rhyme taught to medical students of “bones, stones, abdominal groans, psychic moans.”(1) The term asymptomatic hyperparathyroidism erroneously refers to the remainder of patients with PHPT without the classic symptoms. Other symptoms attributable to hyperparathyroidism include sleep disturbances, cardiovascular disease, neurocognitive symptoms, fatigue, muscle weakness, and peptic ulcer disease.(2) Surgery not only remains the sole definitive treatment, but is cost effective, even in asymptomatic patients.(3)

The transition from open four-gland exploration to minimally invasive parathyroidectomy has occurred following advances in imaging localization using ultrasound and 99m-technetium sestamibi radionuclide scans, and the widespread use of intraoperative parathyroid hormone (ioPTH) monitoring to predict successful resection of hyperfunctioning parathyroid tissue.(4) Multiple criteria for ioPTH have been proposed to determine when intraoperative cure is achieved.(5) While it makes clinical sense that patient factors unrelated to PHPT, such as renal function or body habitus, may play a role in the kinetics of hormone clearance, few studies have examined the effect of patient preoperative characteristics on the accuracy of ioPTH monitoring to determine cure.(6,7)

The main factor that determines the decline of serum ioPTH concentration is hormone clearance, and many providers erroneously believe that renal excretion is the main clearance mechanism for PTH. In fact, the kidneys account for only 20-30% of hormone clearance, with around 60% of clearance occurring in the liver, and the remainder rendered inactive in the periphery by oxidation of the active hormone.(8) Not surprisingly then, mixed findings are reported on the predictive effect of renal function on ioPTH kinetics.(6,7) If patients with normal renal function (NRF) clear PTH more rapidly than patients with chronic renal insufficiency (CRI), there is a potential to reduce operative time and cost by requiring fewer ioPTH measurements. Furthermore, if surgeons believe that ioPTH is less accurate in patients with CRI, they may be inclined to put less trust in the ioPTH measurements, leading to longer operative times and potentially unnecessary dissections. We hypothesized that ioPTH monitoring in patients with CRI would show slightly slower decline, but would still accurately predict cure.

## Materials and Methods

An Institutional Review Board approved, prospectively collected database of consecutive parathyroidectomies was queried to identify patients with: (1) a diagnosis of primary hyperparathyroidism, (2) a curative single gland resection between November 2000 and October 2013, defined as normocalcemia (<10.2 mg/dL) at six months following surgery, (3) preoperative renal function assessment, and (4) age greater than 18. All parathyroidectomies were performed at an academic hospital by high-volume endocrine surgeons. Patients with multigland disease, autotransplantation of any parathyroid tissue, parathyroid carcinoma, reoperative parathyroid surgery, five minute ioPTH greater than baseline, multiple missing data points, follow-up < 6 months, and disease persistence or recurrence at any time were excluded. The Cockcroft-Gault equation with appropriate weight adjustment was used to classify patients as having NRF when creatinine clearance  $\geq 60$  mL/min, or CRI when creatinine clearance < 60 mL/min.(9)

Intraoperative PTH levels were obtained after induction of anesthesia (baseline) and at five, ten, and fifteen minutes post-excision, or until two sequential measurements showed falling PTH levels with at least one being < 50% of the baseline level.(10) Additional levels were drawn at the surgeon's discretion.

The ioPTH values for each patient were fit via linear regression, and slope of the fit line were determined. Values > 2 standard deviations (SD) from the mean slope in the NRF or CRI groups were excluded from analysis. Statistical analysis was carried out via Chi-squared or Student's t-tests where appropriate. The software used included Microsoft Excel and IBM SPSS Statistics for Windows Version 21.0 (Armonk, NY). A p value < 0.05 was considered statistically significant. Data were expressed as mean  $\pm$  standard error of mean (SEM) for continuous variables and percentage of total for categorical variables.

## Results

### Preoperative characteristics

A total of 950 patients met study criteria, 65% (n=621) had normal renal function and 35% (n=329) had renal insufficiency based on creatinine clearance. The patients with normal renal function had a mean creatinine clearance of  $88.1 \pm 0.9$  mL/min (range 60-272mL/min) and the patients with CRI had mean creatinine clearance of  $46 \pm 0.6$  mL/min (range 21-59mL/min) ( $p < 0.001$ ). Patients with CRI were older ( $72 + 0.6$  vs.  $56 \pm 0.4$  years,  $p < 0.001$ ), more often female (90% vs. 74%,  $p < 0.001$ ), and had significantly higher 25-hydroxy vitamin D [25(OH)D] levels (34 vs. 29ng/mL,  $p < 0.001$ ). No statistically significant difference was seen for preoperative serum calcium (11.1 vs. 11.0mg/dL), PTH (131 vs. 122pg/mL), and phosphate levels (2.9 mg/dL for both) (Table 1).

### Intraoperative findings

Initially, NRF and CRI patients had similar ioPTH absolute fall rates between 0-5 minutes (21.2 vs. 20.8pg/min,  $p = 0.867$ ) and 5-10 minutes (3.2 vs. 3.4pg/min,  $p = 0.511$ ) following adenoma resection. Only between 10-15 minutes did CRI fall rates exceed those in the NRF group (2.0 vs. 1.4pg/min,  $p = 0.028$ ). Although the mean slope of the linear regression fit to CRI ioPTH values was steeper, this was not significant (-7.8 vs. -7.4,  $p = 0.392$ ). This trend was not explained by discordant baseline ioPTH values between CRI and NRF patients (168 vs. 160pg/mL,  $p = 0.550$ ).

When comparing relative percent decline from mean baseline ioPTH levels, the mean PTH for NRF patients had dropped to 39% of baseline at 5 minutes compared to CRI patients, whose mean PTH level at 5 minutes was 44% of baseline ( $p < 0.001$ ). This trend continued at 10 minutes (28% vs 33%,  $p < 0.001$ ) and at 15 minutes (23% vs 29%,  $p < 0.001$ ) (Figure 1). A different way of looking at this is to determine how many patients met the 50% drop in ioPTH at each time point. While CRI patients were less likely to meet intraoperative curative criteria (>50% drop from baseline) at five minutes (66 vs. 77%,  $p < 0.001$ ), no differences were observed after ten (89 vs. 92%,  $p = 0.073$ ) and fifteen minutes (95 vs. 97%,  $p = 0.141$ ). A small number of patients did not meet criteria at the end of 15 minutes, and on

further analysis, these were mostly patients who had high-normal baseline PTH levels that fell, but did not quite reach to 50% threshold.

### Postoperative findings

Mean follow up time was longer in CRI patients (23.7 vs. 18.6 months,  $p < 0.001$ ). Six month postoperative calcium, by our own inclusion criteria, were normal, but PTH was significantly higher in patients with renal insufficiency (59 vs. 45 pg/mL;  $p = 0.002$ ).

### Discussion

We present here preoperative and intraoperative details for 950 patients with PHPT that underwent curative single adenoma excision. To our knowledge this is the largest study examining renal function as a predictor of ioPTH decline. We found that CRI predicts blunted ioPTH fall slightly, but after ten minutes, 89% of patients with CRI met intraoperative cure criteria, and at 15 minutes 95% met criteria. All of these patients ultimately were cured based on normal calcium at 6 months. Previous groups have reported a 9-12% rate of ioPTH failing to decline by 10 minutes in patients who ultimately were cured.(7,11) There was no clinically significant difference in meeting ioPTH criteria for cure between the patients with CRI vs NRF. Further subgroup analysis of the 99 patients with creatinine clearance  $< 40$  ml/min was not significantly different, and by 10 minutes, 88% of patients with the most severe decline in renal function still met cure criteria. Since the minority of PTH clearance is by the kidney, even substantially impaired renal function is unlikely to meaningfully impact ioPTH criteria,(8) and standard ioPTH criteria can be applied.

Failure to achieve a 50% decline in PTH levels in the operating room can lead to operative decision making problems for the surgeon. Many surgeons choose to draw additional levels, particularly if they feel that the patient may have some factors that slow the rate of decline of PTH. We demonstrated that this is a reasonable approach for patients with CRI who fail to meet standard ioPTH criteria, since the ioPTH continues to decline after 10 minutes, while patients with normal renal function begin to level off slightly at that time. It is possible that it may be more cost effective to eliminate the 5 minute level altogether in patients with CRI, since fully 1/3 of these patients did not meet cure criteria at this time point. An alternative approach to the patient with failure to meet ioPTH criteria is to perform a bilateral exploration. This may be quicker and more cost effective if turn-around times for processing ioPTH samples are slow, but may lead to unnecessary dissection and possible resection of normal glands.

Other patient characteristics that may influence PTH rate of decline include age, adenoma weight, and body mass index. Gannage-Yared, et al. found that the most important negative predictor was adenoma weight in their review of 108 patients, but they also noted that decreased GFR altered the rate of decline.(7) A larger study of 306 patients by Leiker, et al. did not confirm similar variables to predict ioPTH half-life.(6) The authors reported that renal function was not an independent predictor of ioPTH kinetics, but BMI, particularly when looked at together with patient age, was significant. However, the study authors concluded that current ioPTH criteria are still applicable to patients regardless of BMI. Our

current analysis is larger and more complete in terms of follow up than these studies, and confirms that current ioPTH criteria seem to work well for a broad range of patients.

The current study has limitations, mostly pertaining to its retrospective design. For comparison purposes, we chose to look at only single adenoma patients cured at six months. This does not mirror the population of patients with primary hyperparathyroidism that a typical surgeon would see, but we felt it was necessary to exclude multi-gland disease patients and patients with persistent or recurrent disease in order to address our study hypothesis that ioPTH would successfully predict cure in patients with CRI. We also chose to look solely at renal function and PTH kinetics without adjusting for other known factors that influence PTH kinetics such as age, BMI and gland weight. We have previously published results from this same cohort of patients that gland weight and preoperative serum PTH and calcium levels do play a role in interpretation of ioPTH values,<sup>(12)</sup> and feel that the results of the current study should be interpreted within this context.

## Conclusions

In summary, ioPTH criteria are met slightly more slowly in patients with primary hyperparathyroidism and CRI, so surgeons should alter expectations for operative time and ioPTH monitoring. If criteria are being used that only call for a 10 minute level to be drawn, especially in patients with CRI, consideration should be given to waiting an additional 5 minutes and drawing a 15 minute level before making a final interpretation. The overwhelming majority of patients who ultimately are cured, regardless of renal function, meet ioPTH criteria within 15 minutes of adenoma excision. Standard ioPTH criteria may be applied regardless of renal function.

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Summary sentences: Successful minimally invasive parathyroidectomy relies on decline of intraoperative parathyroid hormone levels to a pre-determined level. Renal function may play a role in the kinetics of the decline of parathyroid hormone, but most patients with impaired renal function still achieve levels consistent with cure. Standard intraoperative parathyroid hormone criteria can be applied to patients with chronic renal insufficiency.

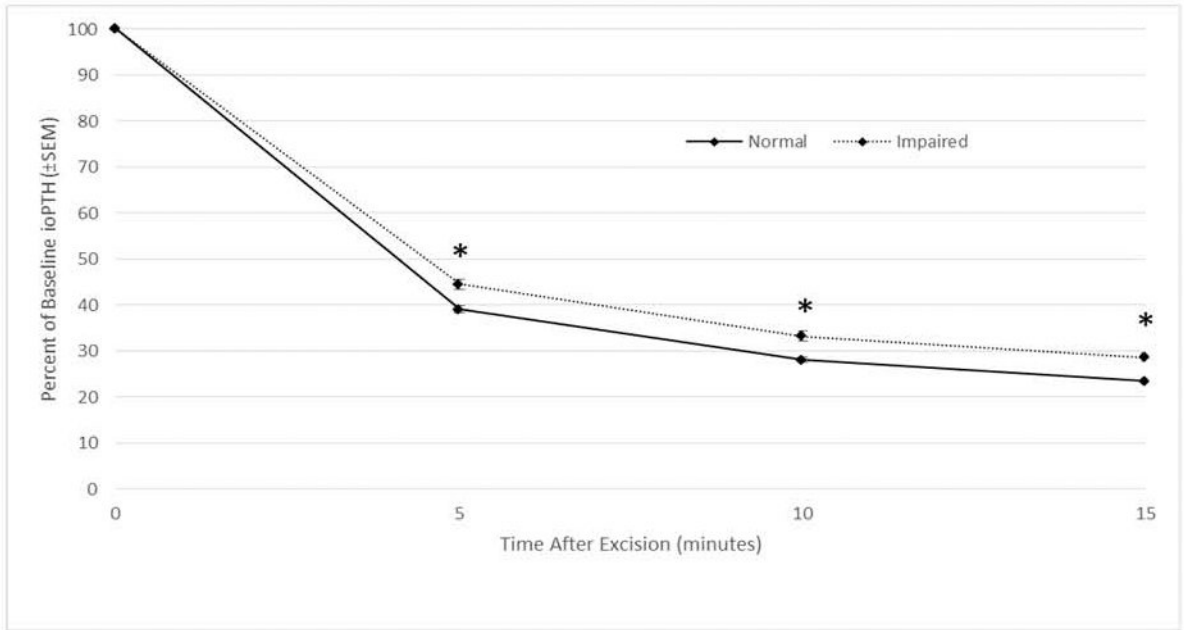
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**Figure 1.** Intraoperative PTH kinetics for single gland resection disease based on preoperative renal function ( $\pm$  standard error). (\*  $p < 0.05$ )

**Table 1****Preoperative Demographics**

Preoperative demographics of patients with primary hyperparathyroidism and normal (Creatinine clearance > 60 mL/min) or impaired (Creatinine clearance < 60 mL/min) renal function. Standard error of the mean (SEM).

	Normal ( $\pm$ SEM)	Impaired ( $\pm$ SEM)	P value
Patients	621	329	
Age (years)	56 $\pm$ 0.4	72 $\pm$ 0.6	< <b>0.001</b>
Female (%)	74	90	< <b>0.001</b>
Creatinine clearance (mL/min)	88.1 $\pm$ 0.9	45.6 $\pm$ 0.6	< <b>0.001</b>
Calcium (mg/dL)	11.0 $\pm$ 0.0	11.1 $\pm$ 0.0	0.248
Phosphate (mg/dL)	2.9 $\pm$ 0.1	2.9 $\pm$ 0.0	0.910
PTH(pg/mL)	122 $\pm$ 3	131 $\pm$ 4	0.082
25(OH)D(ng/mL)	29 $\pm$ 0.6	34 $\pm$ 1	< <b>0.001</b>