

# Risk Factors for Intraoperative Hypertension during Surgery for Primary Hyperparathyroidism

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## Significance of the Study

- In this study the independent predictors for the occurrence of intraoperative hypertension during surgery of primary hyperparathyroidism were a history of hypertension and age. Hence, the patients at risk could be identified and the occurrence of intraoperative hypertension and its potential complications could be prevented, thereby leading to safer parathyroid surgery.

## Keywords

Primary hyperparathyroidism · Hypertension · Anesthesia · Surgery

## Abstract

**Objective:** To investigate the incidence and identify risk factors for the occurrence of intraoperative hypertension (IOH) during surgery for primary hyperparathyroidism (pHPT). **Subjects and Methods:** The study included 269 patients surgically treated between January 2008 and January 2012 for pHPT. IOH was defined as an increase in systolic blood pressure  $\geq 20\%$  compared to baseline values which lasted for 15

min. The investigated influence were demographic characteristics, surgical risk score related to physical status (based on the American Society of Anesthesiologists [ASA] classification), comorbidities, type and duration of surgery, and duration of anesthesia on IOH occurrence. The investigated factors were obtained from the patients' medical history, anesthesia charts, and the daily practice database. Logistic regression analysis was done to determine the predictors of IOH. **Results:** Of the 269 patients, 153 (56.9%) had IOH. Based on the univariate analysis, age, body mass index, ASA status, duration of anesthesia, and preoperative hypertension were risk factors for the occurrence of IOH. Multivariate analysis showed that independent predictors of IOH were a history

of hypertension (OR = 2.080, 95% CI: 1.102–3.925,  $p = 0.024$ ) and age (OR = 0.569, 95% CI: 0.360–0.901,  $p = 0.016$ ). **Conclusion:** In this study, a high percentage (56%) of the patients developed IOH during surgery for pHPT, which indicates that special attention should be paid to these patients, especially to the high-risk groups: older patients and those with a history of hypertension. Further, this study showed that advanced age and hypertension as a coexisting disease prior to parathyroid surgery were independent risk factors for the occurrence of IOH.

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## Introduction

Primary hyperparathyroidism (pHPT) is characterized by hypercalcemia, which occurs due to excessive secretion of parathyroid hormone (PTH). The pathoanatomic substrate of the disease is most commonly parathyroid adenoma (80–85%; double adenoma is found in about 5%), hyperplasia of the parathyroid glands (10–15%), and carcinoma (1%) [1].

pHPT occurs in approximately 1% of the population over 40 years of age [2]. Patients suffering from symptomatic forms of pHPT can develop various complications that might lead to poor treatment outcome, mainly due to the increased incidence of cardiovascular diseases [3]. pHPT may lead to structural and functional alterations in the cardiovascular system. Hypertension is one of the most common manifestations of such disturbances in pHPT [4]. The presence of hypertension has been reported in 20–60% of patients with pHPT [5–7]. In addition to hypertension, increased occurrence of cardiac arrhythmias was demonstrated in patients with pHPT [8], a high prevalence of left ventricular hypertrophy [9], increased stiffness of both central and peripheral arteries [10], and impairment of catecholamine response to physical stress, i.e., adrenergic dysfunction [11].

Currently, one study [12] has analyzed perioperative management difficulties, with the development of intraoperative hypertension (IOH) during parathyroidectomy. However, the study included 292 patients treated for primary, secondary, and tertiary hyperparathyroidism, of which only 96 patients belonged to the group with pHPT. Because the primary procedure for treatment of pHPT is surgical excision of the enlarged parathyroid glands [13] and since IOH might lead to various cardiovascular complications (intra- and postoperatively), the aim of this study was to investigate the incidence and identify the risk factors for the occurrence of IOH during pHPT surgery.

## Subjects and Methods

This was a retrospective study conducted between January 2008 and January 2012 at the Center for Endocrine Surgery, Clinical Center of Serbia, Belgrade. The study was approved by the Ethics Committee of the Clinical Center of Serbia, Belgrade.

A total of 269 patients >18 years surgically treated for pHPT were included in the study. The exclusion criteria were a diagnosis of pheochromocytoma, hypothyroidism, hyperthyroidism, and Conn and Cushing syndromes. The patients were divided into 2 groups: those with ( $n = 153$ ) and without IOH ( $n = 116$ ). IOH was defined as an increase of systolic blood pressure (SBP)  $\geq 20\%$  compared to the baseline values, during 15 min. The basal value of SBP was defined as the average value of all measured SBPs recorded during the preoperative evaluation of patients.

All operations were performed under general endotracheal anesthesia. Patients were premedicated 20 min prior to surgery (using 0.1 mg/kg midazolam and 0.5 mg atropine given intramuscularly). During anesthesia induction, all patients received 0.05–0.1 mg fentanyl and 1.5 mg/kg propofol. In order to facilitate tracheal intubation, 1.1 mg/kg succinylcholine was used and further relaxation was achieved with 0.5 mg/kg rocuronium. Anesthesia was maintained with fentanyl (5  $\mu\text{g}/\text{kg}$ ) and a mixture of gases: air (2 L/min), oxygen (2 L/min), and sevoflurane in appropriate concentrations.

Noninvasive blood pressure, heart rate, and oxygen saturation were recorded in anesthesia charts every 5 min, and cardiac rhythm was monitored using continuous ECG monitoring. IOH was marked from the moment of anesthesia induction until extubation of the patient.

General characteristics of the patients, coexisting diseases, anesthesia, and surgery characteristics were obtained using the patients' medical records, anesthesia charts, and daily practice database. The following factors were investigated: the influence of age, gender, body mass index (BMI), ASA status (the surgical risk score related to physical status based on the American Society of Anesthesiologists classification), type of surgery (extirpation of the adenoma/subtotal parathyroidectomy), duration of the procedure (min), time under general endotracheal anesthesia (min), and coexisting diseases (hypertension, cardiac rhythm disturbances, cardiomyopathy, ischemic heart disease, diabetes mellitus, dyslipidemia, and renal dysfunction) on the occurrence of IOH.

### Statistical Analysis

Statistical analyses were performed using SPSS 22.0 (Chicago, IL, USA). Numerical variables are expressed as mean values  $\pm$  SD, while the other categorical variables are shown as absolute numbers and percentages. The normality of data distribution was checked by a one-sample Kolmogorov-Smirnov test. A Student  $t$  test was used to compare mean values of the parametric features and a Mann-Whitney test was used to compare the nonparametric parameters. A Pearson  $\chi^2$  test and McNemar test were used to compare the differences in frequency of categorical features. All variables that were statistically significant in univariate analysis, at the level of significance of  $p < 0.05$ , were included in the multivariate logistic regression analysis.

**Table 1.** Basic characteristics of patients

IOH	
With	153 (56.9)
Without	116 (43.1)
Gender	
Male	36 (13.4)
Female	233 (86.6)
Age, years	56.79 ± 12.65
BMI	
≤20	15 (5.6)
20.01–25	102 (38.1)
>25.01	151 (56.3)
ASA status	
I	21 (7.8)
II	171 (63.6)
III	77 (28.6)
Duration of surgery, min	41.03 ± 17.06
Duration of anesthesia, min	50.56 ± 18.21
Degree of IOH	
≥140 mm Hg	203 (75.5)
<140 mm Hg	66 (24.5)

Values are presented as *n* (%) or means ± SD. BMI, body mass index; ASA, physical status based on American Society of Anesthesiologists classification; IOH, intraoperative hypertension.

## Results

Of the 269 patients, 153 (56.9%) had IOH. The youngest patient was 19 years old and the oldest was 83 years old. The median age was 59 years and there were 233 females (86.6%) and 36 males (13.4%). The mean duration of surgery was 41.03 ± 17.06 min, and the mean time under general endotracheal anesthesia was 50.56 ± 18.21 min. Of the 269 patients, 171 (63.6%) were classified as ASA II status and 151 (56.3%) had a BMI ≥25; regarding the degree of IOH, 203 (75.5%) had SBP values ≥140 mm Hg. The basic characteristics of the patients are presented in Table 1.

The comparative characteristics of patients with and without IOH are shown in Table 2. There was no significant difference regarding gender. In general, patients with IOH were statistically significantly older. Also, a significant number of patients older than 61 years had IOH (*n* = 82; 53.6%). Significantly more patients with ASA III status were in the group with IOH compared to the group without IOH (*n* = 50 [32.37%] vs. *n* = 27 [23.3%], *p* = 0.009). In the group with IOH, there were statistically significantly more patients with BMI >25 (*n* = 96 [63.2%] vs. *n* = 55 [47.4%], *p* = 0.006). Significantly more patients with IOH had preoperative hypertension compared to

**Table 2.** Comparative characteristics of patients with and without intraoperative hypertension

	IOH		<i>p</i> value
	with	without	
Gender			0.863
Male	20 (13.1)	16 (13.8)	
Female	133 (86.9)	100 (86.2)	
Age			0.000
≤40 years	11 (7.2)	19 (16.4)	
41–60 years	60 (39.2)	62 (53.4)	
≥61 years	82 (53.6)	35 (30.2)	
BMI			0.006
≤20	8 (5.3)	7 (6.0)	
20.01–25	48 (31.06)	54 (46.6)	
≥25.01	96 (63.2)	55 (47.4)	
ASA status			0.009
I	6 (3.9)	15 (12.9)	
II	97 (63.4)	74 (63.8)	
III	50 (32.37)	27 (23.3)	
Type of operation			0.223
Extirpation	144 (94.7)	107 (93)	
Subtotal	7 (4.6)	4 (3.5)	
Other	1 (0.7)	4 (3.5)	
Preoperative hypertension			0.000
Yes	122 (79.7)	62 (53.4)	
No	31 (20.3)	54 (46.6)	
Duration of surgery, min	42.61 ± 17.38	38.91 ± 16.46	0.042
Duration of anesthesia, min	52.48 ± 18.66	48.00 ± 17.34	0.029

Values are presented as *n* (%) or means ± SD. BMI, body mass index; ASA status, physical status based on American Society of Anesthesiologists classification; IOH, intraoperative hypertension.

patients without IOH (*n* = 122 [79.7%] vs. *n* = 62 [53.4%], *p* = 0.000). In the group with IOH, the duration of anesthesia and the duration of the surgical procedure were significantly longer (*p* = 0.042 and 0.029, respectively). The type of operation did not differ between the observed groups.

No significant differences between the groups were recorded regarding the incidence of preoperative comorbidities: cardiac rhythm disorders, cardiomyopathy, ischemic heart disease, diabetes mellitus, hyperlipoproteinemia, and renal insufficiency (Table 3).

Based on the univariate analysis, the risk factors for the occurrence of IOH were age (OR = 0.467, 95% CI: 0.318–0.685, *p* = 0.000), BMI (OR = 0.633, 95% CI: 0.422–0.950, *p* = 0.027), ASA status (OR = 0.555, 95% CI: 0.357–0.864, *p* = 0.009), duration of anesthesia (OR = 0.986, 95% CI: 0.972–1.000, *p* = 0.049), and preoperative hypertension

**Table 3.** Comorbidities of patients with and without intraoperative hypertension (IOH)

Comorbidities	IOH, <i>n</i> (%)		<i>p</i> value
	with	without	
Preoperative cardiac rhythm disorders	26 (17.0)	28 (24.1)	0.147
Preoperative cardiomyopathy	9 (5.9)	6 (5.2)	0.802
Preoperative ischemic heart disease	17 (11.1)	10 (8.6)	0.501
Preoperative diabetes mellitus	20 (13.1)	9 (7.80)	0.164
Preoperative hyperlipoproteinemia	17 (11.1)	18 (15.5)	0.278
Preoperative renal insufficiency	9 (5.9)	9 (7.8)	0.542

**Table 4.** Uni- and multivariate logistic regression

Variable	Univariate		Multivariate	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age	0.467 (0.318–0.685)	0.000	0.569 (0.360–0.901)	0.016
BMI	0.633 (0.422–0.950)	0.027	0.774 (0.499–1.200)	0.252
ASA status	0.555 (0.357–0.864)	0.009	0.926 (0.555–1.544)	0.768
Duration of anesthesia	0.986 (0.972–1.000)	0.049	0.985 (0.970–1.000)	0.055
Preoperative hypertension	3.428 (2.003–5.865)	0.000	2.080 (1.102–3.925)	0.024

BMI, body mass index; ASA status, physical status based on American Society of Anesthesiologists classification.

(OR = 3.428, 95% CI: 2.003–5.865, *p* = 0.000). Multivariate analysis showed that independent predictors of IOH were a history of hypertension (OR = 2.080, 95% CI: 1.102–3.925, *p* = 0.024) and age (OR = 0.569, 95% CI: 0.360–0.901, *p* = 0.016) (Table 4).

## Discussion

In this study, the 56.9% incidence rate of IOH was similar to the 54.1% reported by Corneci et al. [12] and comparable to the 61.4% in thyroidectomy [14].

The high incidence rate could be due to several factors. Hulter et al. [15] suggested a theory that hypertension associated with pHPT results from either direct or indirect effects of PTH excess. Later studies confirmed this theory [16, 17] because PTH directly stimulates activity of the renin-aldosterone system and thus leads to an increase in blood pressure [18, 19]. Of equal importance, it has been reported that PTH has a secretagogue effect on stress hormones of the adrenal cortex – aldosterone and cortisol – which, at least in part, may explain hypertension in pHPT

[20]. Hypertension could be caused by increased levels of blood calcium, intracellular calcium, and hypomagnesemia. Nilsson et al. [21] reported that acute hypercalcemia caused by calcium infusion in healthy subjects led to dose-dependent disorders of vasodilatory endothelial function and increased SBP [21]. Hypertension secondary to pHPT is still being debated [22]. The 54.1% incidence rate of hypertension in pHPT is within the range of 20–69% reported in various studies [5, 23, 24]. This large variation in reported incidence could be due to variations between different authors due to differences in blood pressure measurement criteria of hypertension and different patient characteristics. IOH during pHPT surgery might be caused by surgical manipulation of the glands, which can lead to PTH insertion into the bloodstream, which might cause an increase in blood pressure. The findings of this study indicate that approximately every other pHPT patient might develop IOH during parathyroidectomy. Because IOH has been marked as an independent risk factor for various perioperative complications, particularly after long procedures [25], it could substantially compromise the treatment outcome.

In this study, the finding that over 79% of patients had previous hypertension is consistent with those of previous studies [26–29]. Hypertension in general is the most common comorbidity in surgical patients – preexisting hypertension is present in over two-thirds of all patients over 60 years of age [27], and the vast majority of these patients were in advanced age in which the prevalence of the disease is more frequent. Prys-Roberts [28] reported that hypertension that exists preoperatively increases the probability of its occurrence during the surgery [28]. In a meta-analysis, Howell et al. [29] reported that patients with hypertension prior to surgery had a 1.31-fold higher risk for the occurrence of cardiovascular complications, compared with normotensive patients. Although hypertension is associated with increased hemodynamic instability in the perioperative period, a direct and independent correlation between preoperative hypertension and perioperative complications is unclear [30]. There are a few studies which show preoperative hypertension is an independent predictor of IOH occurrence [12, 28]. This study is one of them.

The limitations of this study include: (1) the study was neither controlled nor randomized and could hence

lead to preselection bias, (2) the duration and degree of IOH were not sufficiently investigated and the type of antihypertensive drugs the patients used preoperatively were not taken into account, and (3) the literature search and review included only “English and Serbian language” articles, so language bias may exist in our discussion.

## Conclusion

This study showed that advanced age and hypertension as a coexisting disease prior to parathyroid surgery represent independent risk factors for the occurrence of IOH. In these subgroups, we recommend that special attention be paid to them during anesthetic evaluation in order to avoid potential complications, primarily hemodynamic instability.

## Disclosure Statement

The authors report no conflicts of interest.

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