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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Risk factors for intraoperative variations in blood pressure and cardiac dysrhythmia during thyroid surgery

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SUMMARY

Introduction/Objective Intraoperative variations in blood pressure and/or cardiac dysrhythmias (IOVBP/CD) represent one of the most common causes of morbidity and mortality in surgical patients. The aim of the study was to determine the incidence and risk factors for IOVBP/CD in thyroid surgery patients with comorbidities.

Methods The study included 1,252 euthyroid patients with ASA 2 and ASA 3 status (American Society of Anesthesiologists – physical status classification) who underwent thyroid surgery. The following risk factors were examined: sex, age, body mass index (BMI), ASA status, admission diagnoses, type of operation, duration of surgery, time under general anesthesia, difficult intubation of trachea, and coexisting diseases – hypertension, cardiomyopathy, cardiac arrhythmias, angina pectoris, diabetes mellitus, kidney disease. The following intraoperative events were recorded: hypertension, severe hypertension, hypotension, and cardiac arrhythmias. We used Pearson χ^2 square test, univariate, and multivariate logistic regression for statistical analysis.

Results The majority of patients were female (86.3%). In 903 (72.1%) patients IOVBP/CD were detected. The most common problem was intraoperative hypertension (61.4%). Eight risk factors for IOVBP/CD were registered by univariate analysis: advanced age, ASA 3 status, BMI > 25 kg/m^2, duration of surgery, time under general anesthesia, hypertension, and cardiomyopathy as a coexisting disease. The multivariate regression model identified three independent predictors for IOVBP/CD: age, hypertension, and cardiomyopathy.

Conclusion IOVBP/CD are common in thyroid surgery. The most common is intraoperative hypertension. Older age, hypertension, and cardiomyopathy as a coexisting disease are independent risk factors for IOVBP/CD.

Keywords: thyroidectomy; hypotension; hypertension; arrhythmias, cardiac

INTRODUCTION

Intraoperative variations in blood pressure and/or cardiac dysrhythmias (IOVBP/CD) represent one of the most common causes of morbidity and mortality in surgical patients. According to different reports, the incidences of IOVBP/CD are between 4.9% and 17.5% [1, 2]. However, these studies are methodologically different, and they use different definitions of IOVBP/CD and different ways of recording complications [1–4].

The type of surgery and advanced age were identified as significant risk factors in most studies [5, 6]. Previous studies have mostly observed the occurrence of IOVBP/CD in cardiac or non-cardiac surgery [7, 8]. In the case of non-cardiac surgery, most studies focus on so-called "major" surgery which involves major abdominal, orthopedic and urological surgery. However, there is little data in the literature about the incidence of IOVBP/CD in low risk and intermediate risk surgery. To the best of our knowledge, thyroid surgery, which could be classified as intermediate risk surgery, has been studied rarely [9]. This is why the aim of our study was to determine the incidence and predictors of IOVBP/CD in thyroid surgery patients.

METHODS

This prospective five-year study was conducted at the Center for Endocrine Surgery, University Clinical Center of Serbia, Belgrade, where most patients with thyroid pathology in Serbia are operated on. The study was institutionally approved; signed patient consent was waived as the treatment of patients did not differ from the usual one and no protected health information was collected. Eligible patients were those aged

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18 years and older referred to the University Clinical Center of Serbia for thyroid surgery. A total of 2,559 patients were included in the study. Because of the potential influence on the incidence of IOVBP/CD, we excluded seven patients with a diagnosis of hypothyroidism, 264 patients with hyperthyroidism, and 278 patients with autoimmune thyroid disease. We also excluded 758 patients with ASA 1 status because these were patients without comorbidities. A total of 1,252 euthyroid ASA 2 and ASA 3 patients were included. Our patients had the following admission diagnoses: 1) nodular goiter – 350 (28%); 2) multinodular goiter – 652 (52%); 3) thyroid gland cyst – 9 (0.7%); 4) struma recidivans – 69 (5.5%); 5) papillary carcinoma – 78 (6.2%); 6) medullary carcinoma – 69 (5.5%); 7) Hürthle cell carcinoma – 8 (0.6%); 8) follicular carcinoma – 5 (0.4%); 9) oxyphil lesion – 12 (0.9%).

We noted the incidence and risk factors of the following IOVBP/CD: hypertension, severe hypertension, hypotension, tachycardia, bradycardia, new onset atrial fibrillation/flutter and extrasystole, ventricular and supraventricular, which we define as follows: hypertension – an increase of systolic blood pressure ≥ 20% compared to baseline values within 15 minutes; severe hypertension – blood pressure ≥ 220/120 mmHg; hypotension – a decrease of systolic blood pressure ≥ 20% compared to baseline values within 15 minutes; tachycardia: heart rate ≥ 85 beats per minute for at least five minutes; bradycardia: heart rate ≤ 60 beats per minute for at least five minutes; frequent VES/SVES (premature ventricular and supraventricular contractions) > 6 per minute; new onset atrial fibrillation/flutter [9].

The observed values of blood pressure and heart rate were recorded at least every five minutes using noninvasive measurements and recorded in the list of anesthesia. The treating anesthesiologist was deciding on when to use a certain drug and in which dose, so that the occurrence of these events would not affect the outcome of the surgery. There was no mortality in our study, neither intraoperative nor postoperative. The patients were divided into two groups – the group with IOVBP/CD and the group without it.

The predictive power of 10 variables were studied: age (< or ≥ 50 years), sex, body mass index (BMI) (< or > 25 kg/m^2), ASA status (ASA 2 and ASA 3), admission diagnosis, type of operation (total thyroidectomy vs. others), difficult intubation of the trachea (defined as the inability to visualize the glottis during laryngoscopy, Cormack–Lehane grades 3 and 4), duration of surgery (minutes), time under general anesthesia (minutes) and coexisting diseases. The following coexisting diseases were observed: hypertension, cardiomyopathy (CMP), cardiac arrhythmias (tachycardia, bradycardia, atrial fibrillation/flutter and extrasystoles), angina pectoris, diabetes mellitus (DM) (and therapeutic regimen in patients with DM – insulin, oral hypoglycemic agents, diet), and kidney disease (chronic and terminal renal insufficiency).

The patients who were on chronic antihypertensive, antiarrhythmic therapy (especially on beta blockers) received their therapy preoperatively, including the day of surgery. All surgery was performed during general anesthesia. The patients were pre-medicated 20 minutes prior to surgery (midazolam 0.1 mg/kg and atropine 0.5 mg i.m.). During induction, all the patients received 0.05–0.1 mg of fentanyl and 1.5 mg/kg of propofol. To facilitate intubation, we used 1.1 mg/kg of succinylcholine, and maintained further relaxation with 0.5 mg/kg of rocuronium. Anesthesia was maintained with fentanyl (5 μg/kg) and a mixture of air gases (2 L/min.), oxygen (2 L/min.), and sevoflurane at an appropriate concentration.

For statistical analysis of data we used the statistical software package SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were described using measures of central tendency (mean) and measure of dispersion (standard deviation). We used percentage to describe categorical data. The normality of data distribution was checked by one-sample Kolmogorov–Smirnov test. For statistical analysis of continuous variables, Mann–Whitney U-test was used, depending on the nature of the data. Categorical data were compared using Pearson's χ^2 test. Logistic regression analysis was conducted to evaluate the differences between patients with and without IOVBP/CD in their observed risk factors. Odds ratios and their 95% confidence intervals represented relative risks for each independent risk factor associated with intraoperative incidents. All reported p-values were two-sided. The level of significance was set at 0.05.

RESULTS

Most of our patients were female (86.3%), mean age 56.7 ± 11.5 years. We also converted age into a categorical variable through the use of a receiver operating characteristic curve, and demonstrated the optimal balance of sensitivity and specificity at a cutoff age of ≥ 50 years. Nine hundred and nineteen patients (73.4%) were older than 50 years, most of them had at least one IOVBP/CD (77.9% vs. 22.1%), which was statistically significant (p = 0.000). The average duration of surgery was 69.5 ± 24.1 minutes and the mean time under general anesthesia was 79.4 ± 24.7 minutes. The distributions of other risk factors in our study are shown in Table 1. IOVBP/CDs were registered in 72.1% of the patients, whereas 27.9% of the patients were without IOVBP/CDs. The most common problem was hypertension (61.4%), while severe hypertension occurred in 3.1% and hypotension in 6.5% of the patients. In 27.9% of the patients, different intraoperative cardiac arrhythmias were registered, the most common being tachycardia (18.2%), followed by bradycardia (6.5%), frequent VES/SVES (2.4%), and the least common was atrial fibrillation/flutter (0.7%).

Patients with IOVBP/CD were significantly older, more often had a BMI > 25 kg/m^2 and were ASA 3. There was no statistically significant difference in frequency of IOVBP/CD between male and female patients. Significantly higher number of patients in the group with IOVBP/CD had a history of hypertension. There was no significant difference in the frequency of previous diagnosis of cardiac arrhythmias and angina pectoris between the two groups, while the CMP was more often recorded in the group with IOVBP/CD. There were no differences in relation to

Table 1. Distribution of risk factors

Risk factor	n (%)
Age (mean ± SD)	56.86 ± 11.42
Sex: male/female	171 (13.7%) / 1081 (86.3%)
BMI > 25 kg/m²	823 (65.7%)
ASA 2 / ASA 3	1004 80.2%) / 248 (19.8%)
Type of surgery: total thyroidectomy / others	959 (76.6%) / 293 (23.4%)
Difficult intubation	153 (12.2%)
Coexisting disease	
Hypertension	832 (66.5%)
Cardiac arrhythmias	85 (6.8%)
Bradycardia	2 (0.2%)
Tachycardia	24 (1.9%)
Atrial fibrillation / flutter	36 (2.9%)
Frequent VES/SVES*	23 (1.8%)
Angina pectoris	62 (5%)
Cardiomyopathy	98 (7.8%)
Diabetes mellitus / insulin dependent	149 (11.9%) / 44 (3.5%)
Kidney disease	22 (1.8%)

* > 6 premature ventricular or supraventricular contractions/minute;
BMI – body mass index; ASA – American Society of Anesthesiologists

Table 2. Incidence of risk factors among patients with and without IOVBP/CD

Risk factor	IOVBP/CD		p
	Yes	No	
Sex (female)	780 (86.4%)	301 (86.2%)	0.951
BMI > 25 kg/m²	619 (68.5%)	204 (58.5%)	0.001*
ASA 2 ASA 3	708 (78.5%) 194 (21.5%)	296 (84.8%) 53 (15.2%)	0.012*
Age (mean ± SD)	58.3 ± 11.1	53.2 ± 11.4	0.000*
Admission diagnosis (multinodular goiter)	482 (53.4%)	152 (43.6%)	0.167
Hypertension	643 (71.2%)	189 (54.2%)	0.000*
Cardiac arrhythmias	63 (7.0%)	22 (6.3%)	0.671
Bradycardia Tachycardia Atrial fibrillation/flutter Frequent VES/SVES**	2 (3.2%) 14 (22.2%) 31 (49.2%) 16 (25.4%)	0 (0%) 10 (45.5%) 5 (22.7%) 7 (31.8%)	0.601
Angina pectoris	50 (5.5%)	12 (3.4%)	0.125
Cardiomyopathy	84 (9.3%)	14 (4.0%)	0.002*
Diabetes mellitus	117 (13%)	32 (9.2%)	0.064
Insulin-dependent diabetes mellitus	36 (30.8%)	8 (25%)	0.672
Kidney disease	16 (1.8%)	6 (1.7%)	0.949
Difficult intubation of trachea	119 (12.1%)	44 (12.6%)	0.297
Type of surgery (total thyroidectomy)	702 (77.7%)	257 (73.6%)	0.103
Duration of surgery (minutes)	70.4 ± 23.9	67 ± 24.4	0.008*
TUGA (minutes)	80.3 ± 24.3	76.9 ± 25.5	0.006*

BMI – body mass index; ASA – American Society of Anesthesiologists; CMP – Cardiomyopathy; DM – diabetes mellitus; TUGA – time under general anesthesia;
*statistically significant $p < 0.05$;
**> 6 premature ventricular or supraventricular contractions/minute

admission diagnosis, type of surgery and the incidence of difficult intubation, while the duration of surgery and the time under general anesthesia were statistically significantly longer in patients with IOVBP/CD (Table 2).

To determine the effect of each variable on the occurrence of IOVBP/CD, the logistic regression model was used (Table 3). Univariate logistic regression analysis revealed a statistically significant difference between patients with and without IOVBP/CD in their age, ASA status, BMI, duration of surgery, and the time under general anesthesia, as well as previous hypertension and CMP. Multivariate analysis showed that independent predictors for IOVBP/CD were age, hypertension, and cardiomyopathy.

DISCUSSION

The results of our study indicate a high incidence of IOVBP/CD in euthyroid patients undergoing thyroid gland surgery (72.1%). Röhrig et al. [2] registered IOVBP/CD in 17.5% of patients, but they studied all types of non-cardiac surgery, including urgent surgery. It was shown that the occurrence of IOVBP/CD was affected by age, male gender, ASA status, previous cardiac disease and type of surgery. Sanborn et al. [4] found the incidence of IOVBP/CD in 6.5% of patients. The authors define intraoperative hypertension as systolic blood pressure of more than 195 mmHg, with the explanation that if they used lower values, almost two thirds of patients would have intraoperative hypertension. It was shown that independent predictors were urgent surgery, age over 70 years, and ASA 3. Both studies registered IOVBP/CD automatically by using computerized machine-readable record sheets, in contrast to our study where data were recorded manually.

To indicate the importance of methods of data recording, the study of Benson et al. [3] compared manual with automatic recording of blood pressure (BP). On a sample of 16,019 patients, it has been shown that much more adverse events were detected automatically than manually (18.7% vs. 5.7%). Both ways of recording data have their advantages and drawbacks. The main complaint to the automatically recorded values of blood pressure is the frequent occurrence of artifacts which significantly affect the validity of the data, while the manual mode is criticized for subjectivity.

The explanation for such a high incidence of IOVBP/CD in our study can be viewed from several aspects: selection of patients who were included in the study (excluded ASA 1, thyroid surgery only), institution where the study was carried out (university clinical center – tertiary institution), criteria for defining IOVBP/CD (significantly different among studies), and the method of recording data (in our study manual). Our study included only patients with ASA 2 and ASA 3 status, patients who had coexisting diseases and in which perioperative complications are most commonly reported.

Although preoperative cardiology management has significantly advanced in recent years, we are still not able to exactly predict the individual risk. One of the most commonly used models for cardiovascular risk prediction is Lee's Revised Cardiac Risk Index (RCRI); a patient is at risk if he/she has two or more risk factors (ischemic heart disease, congestive heart failure, cerebrovascular disease,

Table 3. Logistic regression for IOVBP/CD

Parameters	IOVBP/CD			
	Univariate		Multivariate	
	OR (95% CI OR)	p	OR (95% CI OR)	p
ASA	0.808 (0.684–0.955)	0.012*	1.026 (0.853–1.233)	0.788
Age≥ 50 yr	0.962 (0.951–0.972)	0.000	0.971 (0.959–0.983)	0.000*
Sex	0.989 (0.691–1.416)	0.951		
BMI	0.645 (0.500–0.833)	0.001*	0.945 (0.809–1.104)	0.475
Admission diagnosis	1.019 (0 992–1.046)	0.168		
Hypertension	0.478 (0.370–0.616)	0.000*	0.628 (0.474–0.832)	0.001*
Cardiac arrhythmias	0.897 (0.543–1.482)	0.671		
Type of cardiac arrhythmias	0.955 (0.809–1.127)	0.584		
Angina pectoris	0.607 (0.320–1.155)	0.128		
Cardiomyopathy	0.407 (0.228–0.728)	0.002*	0.529 (0.282–0.993)	0.047*
Diabetes mellitus	0.678 (0.449–1.024)	0.065		
Therapy for diabetes mellitus	1.197 (0.522–2.747)	0.671		
Kidney disease	0.970 (0.376–2.499)	0.949		
Type of kidney disease	0.975 (0.664–1.433)	0.899		
Type of surgery	1.033 (0.992–1.075)	0.113		
Difficult intubation	1.180 (0.864–1.611)	0.298		
Duration of surgery (min.)	0.994 (0.988–0.999)	0.027*	0.991 (0.966–1.017)	0.486
TUGA (min.)	0.810 (0.694–0.945)	0.007*	1.004 (0.979–1.029)	0.759

ASA – American Society of Anesthesiologists; BMI – body mass index; TUGA – time under general anesthesia;
*statistically significant $p < 0.05$

diabetes mellitus treated with insulin, renal failure, and high-risk surgery) [10]. Boersma et al. [11] demonstrated a substantial improvement of Lee's index predictive power by adding type of surgery, age, and ECG findings.

However, the most important reason for such large variations in the frequency of IOVBP/CD between different studies is the method of defining intraoperative problems, especially hypertension. Studies differ in the type of blood pressure which is observed, systolic or mean arterial BP; which change of value of BP is considered significant, relative to the patient's baseline blood pressure or below/above a certain absolute threshold. Minimum length of duration of the changes of BP, interval, and the method of measurement (invasive or noninvasive) also differ among studies [1, 2, 4, 7, 8, 12, 13, 14]. Our previous study showed that independent predictors for intraoperative hypertension were older age, BMI 25 kg/m^2, and hypertension as a coexisting disease [15]. Also, our recently published study that examined the prevalence of hypertension and risk factors for its occurrence in patients undergoing parathyroidectomy found intraoperative hypertension in 56.9% of patients and also showed that independent predictors were older age and history of hypertension [16].

More than two thirds of surgical patients and nearly 80% of cardiac patients have hypertension as a coexisting disease [12]. History of hypertension, especially nontreated, increases the risk for intraoperative complications [17]. In our study, 66.5% of patients had hypertension as a coexisting disease, while intraoperative hypertension was registered in 61.4% of patients. Most of the patients who had hypertension as a coexisting disease also had intraoperative hypertension (76.3%), which implies that if a patient had a previous history of hypertension, he or she has a greater likelihood of having intraoperative hypertension.

Demonstrating the effect of defining the value of BP, and having in mind the influence of intraoperative hypotension on the development of postoperative complications and the importance in predicting adverse outcome, one study found 140 different definitions of intraoperative hypotension, resulting that the incidence of intraoperative hypotension varies between 5% and 99% [18]. In our study, hypotension occurred in 6.5% of patients.

Also, there is little available data about the incidence and risk factors of IOVBP/CD in thyroid surgery. In our previous study [9], in which we examined the occurrence of IOVBP/CD in 200 patients who underwent thyroidectomy, IOVBP/CD was recorded in 38% of patients. IOVBP/CDs were defined in the same way as in this study, but the majority of patients (49%) had ASA 1 status (without comorbidity).

Our study showed that independent predictors for the occurrence of IOVBP/CD were age, previous hypertension, and cardiomyopathy. Some other studies have also confirmed the influence of older age on the occurrence of both intraoperative complications and postoperative morbidity and mortality [1, 2, 5, 19]. There is an increasing number of persons older than 65, and these are precisely the patients who most often require surgical treatment. It was shown that age, per se, did not affect the occurrence of postoperative complications, and that, complications in patients older than 70 years should not be expected unless there are comorbidities [20]. Similar results were found in studies which examined the impact of age on the occurrence of postoperative complications in thyroid surgery. Passler et al. [21] have shown no difference in morbidity or mortality between patients aged ≥ 75 years and younger patients, while Mekel et al. [22] demonstrated that the age of ≥ 80 years is associated with higher morbidity after

thyroid surgery, although not independently. Monk et al. [23] demonstrated higher one-year mortality in patients older than 65 years in contrast to younger populations (10.2% vs. 5.5%, respectively) and comorbidity as the most powerful predictive factor.

Our study showed that although the duration of surgery and time under general anesthesia were significantly longer in patients with intraoperative events, they were not selected as predictors. Reich et al. [13] also showed that intraoperative tachycardia and hypertension more often occured in operations of longer duration and that they were associated with negative postoperative outcomes. Other studies have also confirmed the influence of the duration of surgery on the occurrence of IOVBP/CD [5, 14]. It has also been shown that with every extension of the duration of anesthesia there is an increased risk of complications – for every 60 minutes of anesthesia, the risk of having a complication increases by 18% to 36% [20].

We were not able to confirm diabetes mellitus and renal failure as predictors for IOVBP/CD. The study by Kheterpal et al. [5] also found that diabetes mellitus and renal failure were not predictors for IOVBP/CD, with the explanation that the reason for such a result is probably better preoperative management, as well as standardization of treatment of these patients. Our previous studies confirmed the importance of adequate preoperative preparation of diabetic patients, for the prevention and reduction of intra and postoperative complications [24]. Accordingly, all our patients with diabetes mellitus were well prepared for surgery, they had serum glucose level and glycosylated hemoglobin in the range of normal values, which probably contributed to the fact that this comorbidity did not show up as an important risk factor for IOVBP/CD.

It is known that the incidence of difficult intubation of the trachea is higher in thyroid surgery compared to other types of surgery. The incidence of difficult intubation in our previous studies, which included more than 2,000 patients who underwent thyroid surgery, were 5.5% and 6.81%, respectively [25, 26], while Adnet et al. [27] and Amathieu et al. [28] reported even higher incidence (8% and 11.1%, respectively). In this study, difficult intubation was registered in 12.2% of patients. Difficult intubation, especially if it takes a long time, increases the risk of various complications, including cardiovascular. We expected that such a high incidence of difficult intubation would significantly contribute to occurrence of IOVBP/CD. However, difficult intubation was not a risk factor for IOVBP/CD. The reason for that is probably the good practice of the experienced anesthesiological team in our center, who successfully solve difficult intubations on a daily basis.

Although only 7.8% of our patients had cardiomyopathy, CMP was an independent predictor for IOVBP/CD. Other studies also showed similar results [1, 8].

A potential limitation of our study is that we have not examined the impact of these events on the postoperative outcome. However, since the aim of our study was to determine the incidence and risk factors of IOVBP/CD, and not their impact on postoperative outcome, we believe that this is a topic for a future study.

CONCLUSION

Because of the large number of patients with cardiovascular comorbidities, the incidence of intraoperative variations in blood pressure and/or occurrence of cardiac dysrhythmias is high, even in thyroid surgery – which is considered an intermediate-risk surgery. Our study showed that older age, hypertension, and cardiomyopathy as a coexisting disease are independent risk factors for IOVBP/CD. Patients with these risk factors constitute a group in which anesthesiologists should pay special attention to the manner of preparing and maintaining anesthesia, in order to minimize significant variations of intraoperative blood pressure values and/or the occurrence of cardiac dysrhythmias.

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Фактори ризика за појаву интраоперативних варијација вредности крвног притиска и срчаних дисритмија током тиреоидне хирургије

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САЖЕТАК

Увод/Циљ Интраоперативне варијације крвног притиска и/или срчане дисритмије (ИВКП/СД) један су од најчешћих узрочника морбидитета и морталитета хируршких болесника. Циљ студије је био да испита учесталост и факторе ризика за појаву ИВКП/СД у тиреоидној хирургији код болесника са коморбидитетима.

Методе Испитивање је обухватило 1252 еутиреоидна болесника *ASA* 2 и *ASA* 3 статуса подвргнутих тиреоидној хирургији. Испитиван је утицај следећих фактора ризика: пол, старост, индекс телесне масе (ИТМ), *ASA* статус, пријемна дијагноза, тип операције, трајање операције, трајање анестезије, отежана интубација трахеје, као и коморбидитети: хипертензија, кардиомиопатија, срчане аритмије, ангина пекторис, дијабетес мелитус, болести бубрега. Регистровани су интраоперативно: хипертензија, хипертензивна криза, хипотензија и срчане аритмије. Коришћен је Пирсонов χ2-тест, униваријантна и мултиваријантна регресиона анализа за статистичку обраду података.

Резултати Већину болесника су чиниле жене (86,3%). ИВКП/СД су регистровани код 903 (72,1%) болесника. Најчешћи поремећај је била интраоперативна хипертензија – 61,4%. Униваријантном анализом је регистровано седам фактора ризика за појаву ИВКП/СД: године живота, *ASA* 3 статус, ИТМ > 25 kg/m^2, трајање хирургије, трајање анестезије, хипертензија и кардиомиопатија као коморбидитет. Мултиваријантном регресионом анализом издвојила су се три независна предиктора појаве ИВКП/СД: године старости, хипертензија и кардиомиопатија.

Закључак ИВКП/СД су честе у тиреоидној хирургији. Најчешћа је интраоперативна хипертензија. Старије животно доба, хипертензија и кардиомиопатија као коегзистирајуће болести су независни фактори ризика за појаву ИВКП/СД.

Кључне речи: тиреоидектомија; хипотензија; хипертензија; срчане аритмије