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Sympathetic-parasympathetic cardiac autonomic tonus during induction of anesthesia with propofol and fentanyl

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Abstract

Background: Administration of propofol and fentanyl for induction of general anesthesia is often associated with cardiovascular instability. This effect can be caused by changes in the cardiac autonomic tonus induced by the drugs. In the literature there is no consensus regarding the effect of propofol and fentanyl on sympathetic or parasympathetic balance of the heart.
Material and methods: There was performed a randomized prospective study which was approved by the Ethic Committee. Written informed consent was signed by all patients. The study group involved 47 patients scheduled for surgical intervention, anesthetic risk ASA I-II. The analysis of heart rate variability and the changes in cardiac autonomic tonus was performed with Holter ECG at rest, after premedication with fentanyl solution and after induction of general anesthesia with propofol and fentanyl.
Results: After administration of fentanyl in doses of 1.0 mkg/kg for premedication there were not significant changes of heart rate variability and autonomic heart tonus. Administration of propofol 2.5 mg/kg combined with fentanyl 1.0 mkg/kg for induction of general anesthesia leads to significant changes in heart rate variability. There was a considerable reduction of heart rate variability. The LFun (marker of sympathetic heart tonus) has enhanced by 6.8% compared with previous stage (67.1 (95% CI 63.1-71.1) vs 72.0 (95% CI 67.9-76.1) (p=0.004). The HFun (marker of parasympathetic cardiac tonus) has reduced by 19.8% (32.9 (95% CI 28.9-36.8) vs 26.4 (95% CI 20.4-34.3) (p=0.007). After administration of propofol and fentanyl for induction of general anesthesia the LFun/HFun ratio has enhanced by 30.8% (2.7 (95%CI 2.1-3.4) vs 3.9 (95%CI9 2.9-4.8) (p=0.003), signaling an enhanced sympathetic heart tonus.
Conclusions: Administration of fentanyl solution in doses 1.0 mkg/kg for premedication is not associated with significant changes of autonomic tonus of the heart. Administration of propofol 2.5 mg/kg in combination with fentanyl 1.0 mkg/kg for induction of general anesthesia leads to significant enhanced sympathetic cardiac tonus.

Key words: heart rate variability, sympathetic cardiac tonus, parasympathetic cardiac tonus.

Introduction

Heart rate variability (HRV) is a noninvasive electrocardiographic marker which reflects the sympathetic and parasympathetic influences on sinus node of the heart, and in this way can show the ability of the heart to adapt to different physiological situations. HRV expresses the variations of heart rate and duration of RR intervals (intervals between QRS complexes on ECG) when depolarization in the heart is controlled by normal pacemaker. In other words, HRV analysis shows the baseline autonomic function of the heart [1,2,3]. In a healthy heart with normal sympathetic- parasympathetic influences on sinus pacemaker, there will be continuous changes of the sinus cycles. Normal HRV reflects a balanced sympathovagal state of the heart. Gender, age, circadian rhythm, respiratory rate and body position are physiological factors which may influence HRV [4,5,6]. Measurements of HRV are noninvasive, and highly reproducible. They may be performed on the basis of 24 hour Holter recordings or on shorter periods ranging from 0.5 to 5 minutes particularly in the field of dynamic electrocardiography. Most Holter devices manufactured nowadays have HRV analysis programs which are incorporated into their instrument systems [7,8]. Most studies in anesthesia and intensive care which used the HRV for analysis of changes in sympathetic-parasympathetic balance of the heart performed the 5 minutes analysis of HRV [9-15].

In 1996 a Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) defined and established standards of measurement, physiological interpretation and clinical use of HRV. Time domain indices, geometric measures and frequency domain indices constitute nowadays the standard clinically used parameters [16].

Heart rate variability has been used in different clinical settings, including diabetes, arterial hypertension, coronary artery disease, sudden cardiac death, and for the screening of patients with obstructive sleep apnea. Furthermore, the effects of a variety of pharmacological and non-pharmacological interventions on HRV have been studied, such as antiarrhythmic drugs, physical effort and after radiofrequency ablation procedures [2.9]. In the field of Anesthesiology and Intensive Care, HRV analysis was used for assessment of se-

dation and analgesia, risk for development of hypotension after spinal or epidural anesthesia, for assessment of vegetative effects of different hypnotic drugs used in general anesthesia [2,14,15,17,18].

General anesthesia is usually associated with changes in sympathetic activity that may be due to mechanical ventilation, specific anesthetic drugs effects, the direct circulatory effects they induce, and/or their effects on central or peripheral nervous system. Most anesthetics used nowadays interfere with sympathetic neural outflow and cardiovascular regulation [19-22]. Propofol is a frequently used hypnotic for induction of general anesthesia but it can induce hypotension, particularly when injected rapidly. Many mechanisms have been involved for explanation of propofol induced arterial hypotension, mainly direct depression of myocardium, reduced peripheral vascular resistance caused by direct vasodilatory effect of the drug, reduction of preload and afterload. The studies anyway, showed controversial results, and any of these factors could be imputed for hemodynamic instability after administration of propofol for sedation or for induction of general anesthesia. The observed decrease of peripheral vascular resistance in patients with artificial hearts points to a direct vasodilatating effect of propofol or a decrease in sympathetic vasoconstrictor activity. On the other hand, when propofol was infused in the brachial artery vasodilatation did not occur. Accordingly, other mechanisms must be responsible for the observed vasodilatation during propofol anesthesia [20,23,24].

Most published studies regarding the effects of propofol or fentanyl on heart autonomic tonus were performed with sedative doses of drugs. Administration of propofol for moderate or deep sedation is frequently associated with a significant decrease in mean blood pressure. This hypotensive effect of the drug can be caused by reduction of sympathetic cardiac tonus or disturbances in baroreceptor-mediated cardiac activity [20,25,26,27].

The purpose of this clinical research was to find changes in sympathetic and parasympathetic heart tonus by analyzing HRV after administration of propofol in combination with fentanyl for induction of general anesthesia.

Material and methods

We performed a prospective randomized study to evaluate the changes of vegetative heart tonus after induction of general anesthesia with fentanyl and propofol. The protocol of the study was approved by the Ethic Committee of Nicolae Testemitsanu State University of Medicine and Pharmacy, No 20 of 02.02.2016.

Between March 2017 and September 2017, ASA physical status I-II patients scheduled for elective surgical procedures aged under 60 years (to exclude age-related changes of HRV), and with normal sinus rhythm on ECG were enrolled in the study. We obtained an informed consent from all participants in the study. Patients with diseases that could interfere with vegetative heart tonus (endocrine, neurological, cardiovascular diseases) were excluded from the study. Another exclusion criterion was the presence of more than 20% of artifacts on ECG trace.

In the operating room, the patients were monitored with electrocardiogram (ECG), non-invasive blood pressure, pulse oximetry and capnography. Baseline heart rate, blood pressure and respiratory rate were recorded. During induction of general anesthesia, oxygen was delivered to ensure a SpO_2 above 95%. The patients received 10 ml/kg crystalloid intravenously before induction of anaesthesia.

We attached 10 electrodes on the chest and abdomen of the patients and connected them to Holter monitor (Holter TLC 5000, USA) within 25-30 minutes after admission to surgical room. HRV parameters were analyzed at rest (baseline), after premedication with fentanyl 1.0 mkg/kg and after induction of general anesthesia with propofol 2.5 mg/kg and fentanyl 1.0 mkg/kg (fig. 1). The dose of propofol and fentanyl was given over 30 s, until a loss of consciousness, while the patient was breathing 100% oxygen. The loss of consciousness was defined as a loss of the eyelash reflex and no reaction to subsequent positive-pressure mask ventilation. After administration of propofol and fentanyl and development of bradypnea or apnea, the mask ventilation was initiated in order to ensure a frequency of ventilation of 14-16/min and a tidal volume 7-8 ml/kg, an important requirement for correct registration and analysis of HRV and interpretation of sympathetic-parasympathetic heart tonus.

HRV parameters and changes in sympathetic and parasympathetic vegetative heart tonus were analyzed by Holter computerized system. Parameters of HRV and their significance are presented in table 1 and were interpreted according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [16].

Statistical analysis of the results was done in accordance with the statistical program GraphPad Prism 6 (GraphPad Software, San Diego, California, USA). Values of parametric distribution were analyzed by t-pair and repeated measures of ANOVA tests. Values of non-parametric distribution were analyzed by Wilcoxon and Friedman tests. Results are presented in the form of average and 95% confidence interval (for parametric data) and median with interquartile range (IQR – for non-parametric data). Value of $p<0.05$ was

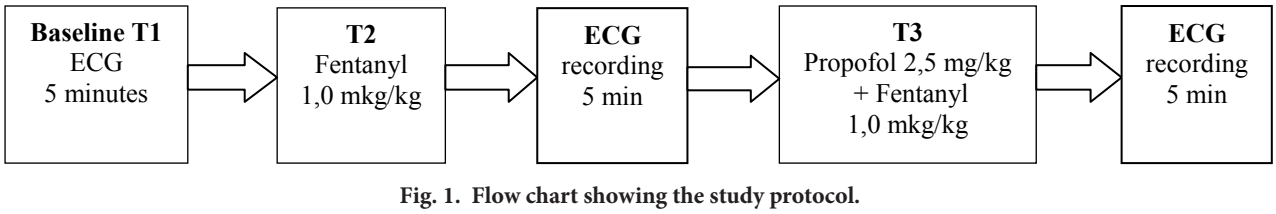

Fig. 1. Flow chart showing the study protocol.

considered statistically significant. The number of patients involved in the study group was determined in order to ensure a study power of 80%, α-error of 5% at a detectable difference of heart tonus between stages of at least 0.5. As well, there was considered a proportion of 10% of patients that couldn't be involved in final analysis for different reasons. Such study group involved 47 patients.

Table 1

Parameters of HRV analyzed by ECG Holte

Parameters of HRV	Significance	Reference values
TP – Total spectral power of HRV (ms^2)	All vegetative influences on the heart (sympathetic, parasympathetic, influences from peripheral and central chemoreceptors, baroreceptors)	3466.0±1018.0
Normalized spectral power of low frequency (**LFun** – *Low Frequency*)	Sympathetic and baroreceptor influences on the heart	54.0 ±4.0
Normalized spectral power of high frequency (**HFun** – *High Frequency)*	Parasympathetic influences on the heart	29.0 ±3.0
LFun/HFun ratio	Sympathetic-parasympathetic heart balance	1.5-2.0

Interpretation and normal ranges are presented according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [16].

Results

The group of patients who benefited from the induction of general anesthesia with propofol and fentanyl comprised 47 patients (26 females and 21 males) at the age of 37.5±11.9 years. Body mass index varied from 16.1 kg/m^2 to 30.0 kg/m^2 with the average 24.6±3.4 kg/m^2. Most patients in the group benefited from the induction of general anesthesia with fentanyl and propofol for laparoscopic cholecystectomy (24 cases – 51.1%), followed by 7 patients with mandible osteosynthesis (14.9%), 4 cases for discectomy (8.5%), 2 cases for syaloadenectomy (4.2%), 2 patients for excision of maxilar cyst (4.2%), 2 cases for scar excision and lip remodeling (4.2%). The other six cases (12.8%) were for different surgical procedures (maxillary osteoplastia, plastia of frontal bone, removal of metallic blade from the arm, resection of cervical cyst, remodeling of ears, and reposition of nasal bones). All patients involved in the study were with minimal anesthetic risk (ASA I-II).

After administration of fentanyl solution for premedication purposes there were no attested significant changes of HRV parameters when compared with baseline values (tab. 2). Total spectral power of HRV has reduced by 12.6% compared with baseline (1400.0 ms^2 (CI 95%1069.0-1731.0) vs 1223.0 ms^2 (CI 95% 949.4-1496.0), (p=0.2). The LFun – marker of sympathetic cardiac tonus – has increased by 0.4% (66.8 (CI 62.6-70.9) vs 67.1 (CI 95% 63.1-71.1), (p=0.8). On the other hand, HFun – marker of parasympathetic cardiac tonus – has reduced, although this reduction is statistically insignificant compared with baseline value. The spectral power of HFun has reduced by 0.9% (33.2 (95% CI 29.0-37.4) vs 32.9 (95% CI 28.9-36.8), (p=0.8), (fig. 2). The LFun/HFun ratio didn't change significantly and was 2.7±0.3 both, in baseline and after administration of fentanyl for premedication (fig. 3). So, after administration of fentanyl 1.0 mkg/kg for premedication there were not attested significant changes in autonomic heart tonus, and the HRV parameters show the presence of enhanced sympathetic tonus of the heart in patients involved in the study.

Significant changes of HRV were attested after administration of propofol 2.5 mg/kg and fentanyl 1.0 mkg/kg for the induction of general anesthesia (tab. 3). The total spectral power of HRV has reduced by 70.4% (1223.0 ms^2 (95% CI 949.4-1496.0) vs 362.1ms^2 (95% CI 257.3-466.9), (p=0.0001). There was noted a significant reduction of spectral power of HFun – marker of heart parasympathetic vegetative tonus. The spectral power of HFun has reduced by 19.8% (32.9 (95% CI 28.9-36.8) vs 26.4 (95% CI 20.4-34.3), (p=0.007). The reduction of the power of HFun is a proof of the cardiac vagolitic effect of propofol given in doses for the induction of general anesthesia. On the other hand, there was registered enhanced spectral power of LFun, such marking an enhanced sympathetic heart tonus and baroreceptor influences on the sinus node of the heart. The spectral power of LFun has enhanced by 6.8% compared with previous stage (T2) (67.1 (95% CI 63.1-71.1) vs 72.0 (95% CI 67.9-76.1), (p=0.004), (fig. 2). The ratio LFun/HFun has enhanced by 30.8% (2.7 (95%CI 2.1-3.4) vs 3.9 (95%CI9 2.9-4.8), (p=0.003) after administration of fentanyl and propofol (fig. 3). Both, significantly enhanced LFun and LFun/HFun ratio in patient who received propofol 2.5 mg/kg and fentanyl 1.0 mkg/kg for the induction of general anesthesia proved the presence of enhanced sympathetic heart tonus and the cardiac sympathomimetic effects of propofol.

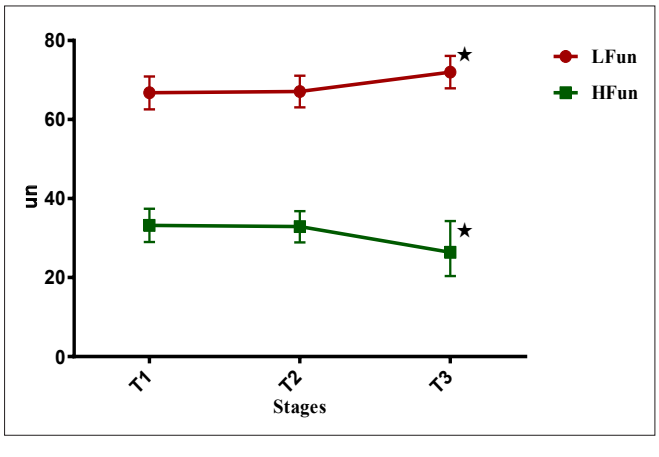

Fig. 2. Changes of LFun and HFun during anesthesia induction with propofol and fentanyl (*p<0.05). Values are presented as mean with 95% confidence intervals (error bars).

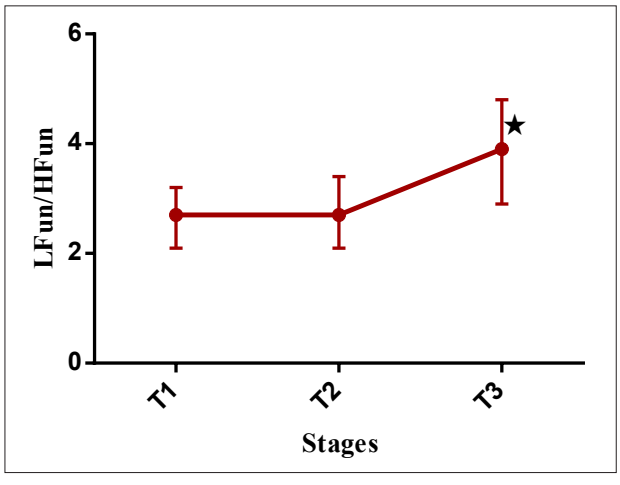

Fig. 3. Changes of sympathetic-parasympathetic heart tonus during general anesthesia induction with propofol and fentanyl (*p<0.05). Values are presented as mean with 95% confidence intervals (error bars).

Table 2

Changes of HRV parameters at rest, after premedication and induction of general anesthesia with propofol and fentanyl (Repeated measures ANOVA and Friedman's test*)

HRV parameters	T1	T2	T3	p
TP (ms²) *	1400.0 (1069.0-1731.0)	1223.0 (949.4-1496.0)	362.1 (257.3-466.9)	0.0001
LFun	66.8 (62.6-70.9)	67.1 (63.1-71.1)	72.0 (67.9-76.1)	0.09
HFun	33.2 (29.0-37.4)	32.9 (28.9-36.8)	26.4 (20.4-34.3)	0.04
LFun/ HFun	2.7 (2.1-3.2)	2.7 (2.1-3.4)	3.9 (2.9-4.8)	0.02

*Values are presented as mean and 95% confidence interval for parameters with normal distribution and median with intercvartilic range for values with non-parametric distribution.

If in baseline, 38.3% of patients presented enhanced sympathetic cardiac tonus, 38.3% – enhanced parasympathetic cardiac tonus and 23.4% – cardiac eutonia, after administration of fentanyl 1.0 mkg/kg for premedication there was detected an enhanced proportion of patients with increased sympathetic tonus of the heart (42.5%). The rate of patients with enhanced parasympathetic heart tonus didn't change and was attested in 18 patients (38.3%), exactly as in baseline. Meantime, the rate of patients with cardiac eutonia has decreased to 19.1%. After administration of propofol 2.5 mg/kg and fentanyl 1.0 mkg/kg for the induction of general anesthesia there was attested a significant increase in the proportion of patients with enhanced sympathetic tonus of the heart (51.1%) and reduction in the proportion of patients with enhanced parasympathetic tonus of the heart (27.7%), (fig. 4).

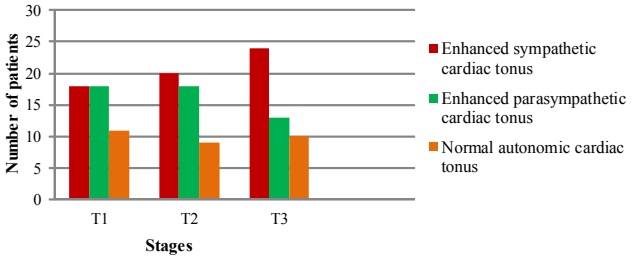

Fig. 4. Structure of the group in function of autonomic heart tonus at rest, after premedication and induction of general anesthesia with propofol and fentanyl.

Discussion

Many factors control perfusion in the peripheral tissues. From these should be mentioned cardiac output, fraction of ejection, stroke volume, microcirculation and vascular tone. Most of these factors are modulated by the autonomic nervous system. Disturbances in cardiac autonomic tonus can lead to adverse cardiovascular events. For anesthesiologists these aspects can be important during perioperative period, especially during the induction of anaesthesia, patient's positioning, episodes of blood loss and surgical stimulation, when cardiovascular instability can be life threatening [9,11,12].

HRV has gained importance in recent years as a technique employed to explore the autonomic nervous system. This method is widely used for studying physiology of arrhythmogenesis [1,6]. Frequency domain (power spectral density) analysis describes the periodic oscillations of the heart rate signal decomposed at different frequencies and amplitudes, and provides information on the amount of their relative intensity (termed variance or power) in the heart's sinus rhythm [2,16]. The HRV analysis may quantitatively and rapidly appreciate the balance of cardiac sympathetic and parasympathetic activities, as well as their effects on cardiovascular system. This method is also useful for evaluation of changes in autonomic cardiac tonus after administration of anesthetic drugs in anesthesia [2,9].

The interpretation of HRV (LF, HF, LF/HF ratio) is to some degree still controversial. Nevertheless, interpretation of HF is more certain than that of LF. Based on many studies it is considered that LF reflects (at least in part) the sympathetic activity of the autonomic nervous system. Another parameter of HRV is HF which reflects the cardiac parasympathetic activity, and the LFun/HFun ratio which reflects the sympathetic/parasympathetic influences on the heart [16,28,29].

Propofol is a hypnotic agent widely used in anesthesia because of its favorable recovery profile and low incidence of side effects. However, induction of general anesthesia with propofol is often associated with a significant decrease in arterial blood pressure and heart rate. The hypotensive effect of propofol has been attributed to many factors. Mostly, reduction in arterial pressure after administration of propofol is caused by low systemic vascular resistance or cardiac

output, impaired baroreflex mechanisms, and depression of myocardial contractility. Inhibition of the sympathetic nervous system and reduced sympathetic cardiac tonus may explain all propofol-induced hemodynamic changes during anesthesia and was proposed as a mechanism of hypotensive effect of the drug, but the precise mechanism by which this may occur is still unknown [20,23,26]. Although there is general agreement that induction of anesthesia with propofol is associated with a reduction in HRV, there are some conflicting data regarding the effects of propofol on cardiac sympathetic or parasympathetic tone [25-33].

The present study aimed to investigate the changes in the HRV in patients with minimal anesthetic risk undergoing the induction of general anesthesia with a combination of propofol and fentanyl.

In the literature there are studies which analyzed the changes in cardiac autonomic tonus during general anesthesia with propofol but it is difficult to compare the results between them due to different anesthesia management, doses and combination of drugs, respiratory pattern, and method for HRV assessment. More than that, it was confirmed by some studies that the changes in sympathetic-parasympathetic cardiac balance are different when there is administration of drug in sedative doses or doses for the induction of general anesthesia [27-31].

In our study administration of fentanyl 1.0 mkg/kg for premedication didn't change significantly the HRV parameters when compared to baseline values. In both time points (T1 and T2) the LFun/HFun ratio showed an enhanced sympathetic tonus of the heart. The values of LFun and HFun after fentanyl administration didn't change significantly in our study. A representative study that examined the cardiac vegetative effects of fentanyl by analysis of HRV is the study conducted and published by Vettorello M. et al. [22]. HRV as a measure of sympathovagal balance was prospectively analyzed in 11 subjects during spontaneous and paced breathing at 20 breaths/min both before and after fentanyl 1.0 mkg/kg administration. Conclusion of this study was that low-dose fentanyl administration in healthy volunteers decreases sympathetic cardiac tonus with a trend toward vagal activation of the heart. Anyway, the number of subjects involved is too small for a relevant conclusion. In another study, fentanyl was administered intravenously for premedication in doses of 3.0 mkg/kg. The analysis of HRV showed that HRV and LFun decreased, but not HFun, indicating a greater reduction of cardiac sympathetic activity [30]. To compare these results with our study is difficult as the doses of fentanyl given for premedication in our research are twice smaller. But, the general conclusion is that fentanyl tends to enhance parasympathetic cardiac tonus and decrease the sympathetic one.

Most studies which analyzed the cardiac vegetative changes after administration of propofol for sedation purposes show also conflicting results. Tarvainen M. et al. analyzed changes of autonomic cardiac tonus in 9 healthy males, at the age of 18-29 years. In this study, propofol was given intravenously using target control infusion aiming at pseudo steady-state plasma concentrations at 10 min intervals starting from 1.0 μg/ml and followed by 0.25-0.5 μg/ml increases until loss of consciousness was reached. The results showed that there is an overall increase in HRV and especially in HF component [24]. So, propofol in small doses has a vagotonic effect on the heart. In another research authors studied the difference in the effects of midazolam and propofol on the cardiac nervous system during combined spinal and epidural anesthesia. The study showed that propofol given in sedative doses during combined spinal epidural anesthesia produced little changes in LF and HF, and such doses do not influence the cardiac vegetative balance [27]. In a study conducted by Tsugayasu R. et al. propofol was infused using a target controlled infusion pump at an initial target effect-site concentration of 0.7g/mL [25]. The final result and conclusion in this study are similar to ours as in the same way after administration of propofol LFun/HFun ratio enhanced thus showing an increased sympathetic cardiac tonus. Exactly as in our study, the LFun increased and HFun decreased proving the vagolitic effect of propofol. As only 7 subjects were enrolled in the study, the validity of the results obtained could be limited. Win N. et al. studied the effect of propofol sedation on vegetative cardiac balance by analysis of HRV in 30 dental implantation patients (ASA I physical status, age 30-62). Propofol was infused at an initial target effect-site concentration of 1 g/ml. The results of this study demonstrated that intravenous conscious sedations with propofol induced significantly decreases in TP, LF, HF and LFun/HFun ratio, indicating predominance of parasympathetic activity during sedation [26]. So, most studies which used propofol in sedative doses showed the predominant vagotonic effect of it on the heart. These results are different from our results, but in our study the dose of propofol administered for the induction of general anesthesia was higher and it was combined with fentanyl.

One representative study which examined the changes in cardiac balance by analysis of HRV after administration of propofol for the induction of general anesthesia was published in 2017 [23]. In this prospective observational study, consecutive adult patients undergoing surgeries for supratentorial tumour (study group) and brachial plexus injury (control group) were recruited. Electrocardiogram was recorded for 5 min at three time points – before propofol induction, at propofol concentration of 2.0μg/ml and at propofol concentration of 4.0 g/ml. We will compare the results obtained in the control group. In brachial plexus group the sympathovagal balance, assessed by LFun/HFun ratio significantly increased at propofol concentration of 4μg/ml and was due to low HF power. Total power of HRV decreased at 4μg/ml. These results are similar to our findings as in our study administration of propofol reduces total power of HRV more than by 70% and the HFun reduced by 19.8%, thus proving the vagolitic effect of propofol. Riznyk L. et al. in a research on one hundred patients proved the fact that fentanyl-based induction of general anesthesia with propofol increases the ratio of LFun/HFun [30]. Their results suggest that induction of anesthesia with propofol reduces the cardiac parasympathetic tone more than sympathetic tone. This result is similar to that obtained in our research, even if

the doses of fentanyl were higher. Three other studies proved these results [31-33]. Kanaya N. et al. [31] and Hamada Y. et al. [32] using a maximum-entropy method for HRV assessment, confirmed that anesthesia with propofol caused reduction in HFun power but not in LFun power, indicating that induction of anesthesia with propofol might reduce a cardiac parasympathetic tone more than sympathetic tone. In another study forty patients were randomly allocated to the propofol group and the midazolam-propofol group co-induction. Propofol was administered at 2.5 mg/kg in the propofol group. The result revealed a greater decrease of the HFun as compared with that of the LFun in both groups, resulting in an increase of the LFun/HFun ratio.

Our report showed that HRV analysis is a noninvasive method that is applicable to the assessment of changes in sympathovagal regulation that are associated with hemodynamic changes during the induction of general anesthesia. Our findings imply that administration of propofol and fentanyl for the induction of general anesthesia enhances the dominance of sympathetic nervous system on the heart. This finding should be considered during general anesthesia, especially in patients at risk of cardiovascular complications.

Conclusions

Administration of fentanyl 1.0 mkg/kg for premedication during general anesthesia is not associated with significant changes in the autonomic cardiac tonus.

Administration of propofol 2.5 mg/kg and fentanyl 1.0 mkg/kg for the induction of general anesthesia is associated with a significant enhancement of sympathetic cardiac tonus and reduction of vagal influences on the heart.

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