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## CHANGES OF VEGETATIVE HEART TONUS AFTER INDUCTION OF GENERAL ANESTHESIA WITH MIDAZOLAM AND FENTANYL

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### ИЗМЕНЕНИЯ ВЕГЕТАТИВНОЙ РЕГУЛЯЦИИ СЕРДЕЧНОГО РИТМА ПРИ ПРОВЕДЕНИИ ИНДУКЦИИ АНЕСТЕЗИИ МИДАЗОЛАМОМ И ФЕНТАНИЛОМ

**Актуальность темы.** Проведение индукции анестезии мидазоламом в сочетании с фентанилом часто приводит к гемодинамическим нарушениям, которые могут быть вызваны изменениями вегетативной регуляции деятельности сердца. В настоящее время отсутствуют исследования, посвященные изучению влияния индукции анестезии мидазоламом и фентанилом на вегетативную регуляцию сердечной деятельности.

**Целью** данного исследования было установление изменений вегетативной регуляции ритма сердца при индукции анестезии с использованием фентанила и мидазолама.

**Материалы и методы.** Было проведено проспективное рандомизированное исследование, одобренное этическим комитетом Государственного университета медицины и фармации имени Николая Тестемицану. Все участники дали

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письменное информированное согласие. Нами было обследовано 47 больных с риском по ASA I–II, которым планировались хирургические вмешательства. Анализ вариабельности сердечного ритма и изменений вегетативной регуляции сердечной деятельности проводили, основываясь на мониторинговании ЭКГ по Холтеру в исходном состоянии, после премедикации фентанилом, а также после индукции анестезии мидазоламом и фентанилом.

**Результаты исследования.** После проведения премедикации фентанилом в дозе 1,0 мкг/кг не наблюдали значительных изменений показателей вариабельности сердечного ритма и вегетативной регуляции сердечного ритма. Однако после проведения индукции мидазоламом (0,2–0,3 мг/кг) в сочетании с фентанилом (1,5 мкг/кг) наблюдали значительное снижение показателей вариабельности сердечного ритма. LFun (показатель активности симпатического звена вегетативной регуляции сердечного ритма) уменьшился на 24,2 % (с 69,1 (95 % ДИ 65,9–72,3) до 52,4 (95 % ДИ 62,9–70,0),  $p=0,14$ ), а HFun (показатель активности парасимпатического отдела вегетативной регуляции сердечного ритма) достоверно увеличился на 34,9 % (с 30,9 (95 % ДИ 27,6–34,1) до 47,5 (95 % ДИ 30,4–57,4),  $p=0,01$ ). Отношение LFun/HFun после индукции уменьшилось до 1,1 (95 % ДИ 0,6–1,8,  $p=0,02$ ), что свидетельствует о повышении активности парасимпатической нервной системы.

**Выводы.** Проведение премедикации фентанилом в дозе 1,0 мкг/кг не приводит к существенным изменениям вегетативной регуляции сердечного ритма. Проведение индукции анестезии мидазоламом (0,2–0,3 мг/кг) в сочетании с фентанилом (1,5 мкг/кг) сопровождается значительным снижением вариабельности сердечного ритма и повышением тонуса парасимпатической нервной системы.

**Ключевые слова:** вариабельность сердечного ритма, симпатическая и парасимпатическая регуляции сердечного ритма.

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#### CHANGES OF VEGETATIVE HEART TONUS AFTER INDUCTION OF GENERAL ANESTHESIA WITH MIDAZOLAM AND FENTANYL

**Background.** Administration of midazolam and fentanyl for induction of general anesthesia is often associated with cardiovascular instability. This effect can be caused by changes in the cardiac vegetative tonus induced by the drugs. There are no studies which analyzed the changes in vegetative heart tonus during induction of general anesthesia with midazolam and fentanyl.

**The aim of the study** was to establish the changes of vegetative heart tonus in induction of general anesthesia with fentanyl and midazolam.

**Materials 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 ASA I–II. The analysis of heart rate variability and the changes in cardiac vegetative tonus was performed with Holter ECG in baseline, after premedication with fentanyl solution and after induction of general anesthesia with midazolam and fentanyl.

**Results of the research.** After administration of fentanyl in doses of 1.0 mkg/kg for premedication there were not significant changes of heart rate variability and vegetative heart tonus. Administration of midazolam 0.2–0.3 mg/kg combined with fentanyl 1.5 mkg/kg for induction of general anesthesia leads to significant changes of HRV. There was a significant reduction of heart rate variability. The LFun (marker of sympathetic heart tonus) reduced by 24.2% (69.1 (95% CI 65.9–72.3) vs

52.4 (95% CI 62.9–70.0) ( $p=0.14$ ), meantime the HFun (marker of parasympathetic cardiac tonus) enhanced by 34.9% (30.9 (95% CI 27.6–34.1) vs 47.5 (95% CI 30.4–57.4) ( $p=0.01$ ). After administration of midazolam and fentanyl for induction of general anesthesia the LFun/HFun ratio was 1.1 (95% CI 0.6–1.8) ( $p=0.02$ ), signaling the enhanced parasympathetic heart tonus.

**Conclusions.** Administration of fentanyl solution in doses 1.0 mkg/kg for premedication is not associated with semnificative changes of vegetative tonus of the heart. Administration of midazolam 0.2–0.3 mg/kg in combination with fentanyl 1.5 mkg/kg for induction of general anesthesia leads to significant decrease of heart rate variability and enhanced parasympathetic cardiac tonus.

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

## Introduction

Midazolam is a hypnotic agent used for sedation as well as for induction of general anesthesia, and its intravenous administration is frequently associated with blood pressure and heart rate changes. Midazolam acts via GABAA receptors which have an important role in regulation of vegetative nervous system [1; 2]. Fentanyl is an opioid used in combination with other hypnotic agents for induction of general anesthesia.

The sympathetic and parasympathetic influences on the sinus node in the heart are manifested by cyclic changes of the RR interval on the ECG, a phenomenon known as heart rate variability (HRV). HRV is a widely used method to asses changes in vegetative tonus of the heart in different medical fields [3–5]. In anesthesia and intensive care, HRV was used for assessment of changes in cardiac heart vegetative tonus during spinal and epidural anesthesia, during endotracheal intubation, inhalational anesthesia, pain assessment [6; 7]. Some recent studies have demonstrated the efficacy of HRV analysis for risk assessment of cardiovascular (hemodynamic) instability during induction of anesthesia in abdominal surgery or spinal anesthesia for caesarian section [8–10].

In most of the studies that used HRV for interpretation of changes in the vegetative tonus, midazolam was used for sedation.

This study tested the hypothesis that the induction of general anesthesia with midazolam and fentanyl reduces the cardiac sympathetic vegetative tonus and enhances the cardiac parasympathetic tonus. The study hypothesis started from the clinical observation that the combination of midazolam and fentanyl for induction of anesthesia frequently is associated with development of arterial hypotension and sinus bradycardia.

## Materials and methods

We performed a prospective randomized study to evaluate the changes of vegetative heart tonus after induction of general anesthesia with fentanyl and midazolam. The protocol of study was approved by the Ethic Committee of the State University of Medicine and Pharmacy “Nicolae Testemițanu”, Chișinău.

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.

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 midazolam 0.2–0.3 mg/kg and Fentanyl 1.5 mkg/kg. After administration of midazolam 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. During induction of general anesthesia, oxygen was delivered to ensure a SpO<sub>2</sub> above 95%.

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* [14].

Statistical analysis of the results was done with the statistical program GraphPad Prism 6 (GraphPad Software, San Diego, California, SUA). Values with parametric distribution were analyzed by t-pair and repeated measures ANOVA tests. Values with non-parametric distribution were analyzed by Wilcoxon and Friedman tests. Results are presented in 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 considered statistically significant. The number of patients involved in the study group was determined in order to ensure a study power of 80%,  $\alpha$ -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.

### Results and discussions

The study group consisted of 47 patients (27 females and 20 males), aged (38.0±12.0) years. The mean body mass index was (24.5±3.3) kg/m<sup>2</sup> (it ranged between 16.7 and 29.7 kg/m<sup>2</sup>). Patients were scheduled for different types of surgery: 18 (38.3%) patients for laparoscopic cholecystectomy, 12 (25.5%) patients — for discectomy, 9 (19.1%)

Table 1

HRV parameters measured in frequency domain and their significance

Parameters of HRV	Spectral frequency, Hz	Significance	Normal values
TP — <i>Total Power</i> (ms <sup>2</sup> )	0.1–0.4	All vegetative influences on the heart (sympathetic, parasympathetic, influences from chemoreceptors and baroreceptors)	3466.0±1018.0
Spectral power of normalized low frequency power (LFun)	—	Sympathetic and baroreceptor influences on the heart	54.0±4.0
Spectral power of normalized high frequency power (HFun)	—	Parasympathetic influences on the heart	29.0±3.0
LFun/HFun ratio	—	Sympathetic–parasympathetic balance of the heart	1.5–2.0

**Changes of HRV parameters in different stages of induction of general anesthesia with midazolam and fentanyl**

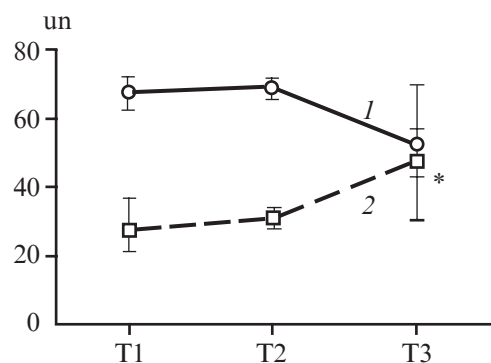
HRV parameters	Baseline (T1)	After premedication (T2)	After induction (T3)	p
TP*, ms <sup>2</sup>	924.2 (404.2–1913.0)	829.1 (438.5–2395.0)	209.1 (68.8–566.9)	0.0001
LFun	67.7 (62.9–72.5)	69.1 (65.9–72.3)	52.4 (42.9–70.0)	0.12
HFun	27.4 (21.4–37.0)	30.9 (27.6–34.1)	47.5 (30.4–57.4)	0.01
LFun/HFun	3.1 (2.4–3.8)	2.8 (2.2–3.4)	1.1 (0.6–1.8)	0.03

*Note.* \* — statistical analysis was performed with repeated measures ANOVA and Friedman test. Values are presented as average and 95% confidence interval for parameters with parametric distribution and median with interquartile range (IQR), range for parameters with non-parametric distribution.

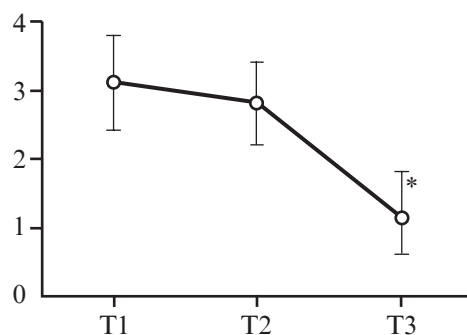
patients — for mandible osteosynthesis, 3 patients (6.4%) — for sinusotomy, 3 patients (6.3%) — for syaladenectomy, one patient (4.2%) — for rhinoplasty and one patient (4.2%) — for appendectomy.

The baseline values of HRV parameters (TP, LFun, HFun and LFun/HFun) are presented in the Table 2. It can be observed that the baseline value of LFun/HFun was  $3,1 \pm 0,3$ , indicating enhanced tonus of sympathetic nervous system.

After administration of fentanyl 1.0 mg/kg for premedication the spectral power of LFun and HFun increased while spectral power of TP and LFun/HFun ratio decreased. It is worth mention that the spectral power of HRV parameters after premedication was not significantly different from the baseline values (Fig. 1, Fig. 2).



*Fig. 1.* Changes of spectral power of LFun and HFun in different stages of induction of general anesthesia with midazolam and fentanyl. Error bars represent 95% confidence interval: 1 — LFun; 2 — HFun; \* —  $p < 0,05$



*Fig. 2.* Changes of LFun/HFun ratio in different stages of induction of general anesthesia with midazolam and fentanyl. Error bars represent the 95% confidence interval: \* —  $p < 0,05$

The spectral power of TP after administration of fentanyl decreased by 10.3%: 829.1 ms<sup>2</sup> (QR 438.5–2395.0 ms<sup>2</sup>) vs 924.2 ms<sup>2</sup> (QR 404.2–1913.0), p=0.16. The marker of sympathetic vegetative tonus LFun increased by 2.0%: 69.1 (95% CI 65.9–72.3) vs 67.7 (95% CI 62.9–72.5), p=0.4, and the most important parameter of parasympathetic heart tonus — HFun — increased by 11.3%: 30.9 (95% CI 27.6–34.1) vs 27.4 (95% CI 21.4–37.0), p=0.4. The ratio LFun/HFun decreased by 9.7%, but non-significantly: 2.8 (95% CI 2.2–3.4) vs 3.1 (95% CI 2.4–3.8), p=0.4. The value of ratio LFun/HFun after premedication was 2.8 which indicates increased cardiac sympathetic tonus (Fig. 2).

The most pronounced changes of HRV parameters were observed after induction of anesthesia. The spectral power of TP, LFun and the LFun/HFun ratio decreased while the spectral power of HFun increased (Table 2) as compared with those after premedication. The spectral power of TP decreased by 74.8% (209.8 ms<sup>2</sup> (QR 68.8–566.9 ms<sup>2</sup>) vs 829.1 ms<sup>2</sup> (QR 438.5–2395.0 ms<sup>2</sup>), p=0.03. The LFun decreased by 24.2%, but statistically non-significantly (52.4 (95% CI 62.9–70.0) vs 69.1 (95% CI 65.9–72.3 ms<sup>2</sup>), p=0.14. The spectral power of HFun increased by 34.9% (47.5 (95% CI 30.4–37.4) vs 30.9 (95% CI 27.6–34.1), p=0.01. As a result, the value of LFun/HFun ratio decreased by 60.7% (1.1 (95% CI 0.6–1.8) vs 2.8 (95% CI 2.2–3.4), p=0.02. The value of ratio LFun/HFun after induction was 1.1 which indicates enhanced cardiac parasympathetic tonus (Fig. 1, Fig. 2).

After induction of general anesthesia the structure of patient group in function of vegetative heart tonus has changed. If in baseline 48.9% of patients presented enhanced sympathetic tonus of the heart, 40.4% — enhanced parasympathetic tonus and 10.6% — normal vegetative tonus of the heart, after administration of fentanyl for premedication there was attested a reduction of proportion of patients with enhanced sympathetic cardiac tonus to 44.7% as well as a reduction of proportion of patients with enhanced parasympathetic heart tonus to 36.2%. At the same time, there was an increase in the proportion of patients with normal vegetative heart tonus to 19.1%. After administration of midazolam and fentanyl the proportion of patients with enhanced sympathetic heart tonus has reduced to 38.2%, as well as there was a reduction of the proportion of patients with normal vegetative heart tonus to 8.5%. There is worth mention the fact that in this stage was a remarkable increased proportion of patients with enhanced parasympathetic heart tonus, which represented more than half from the study group (53.1%) (Fig. 3).

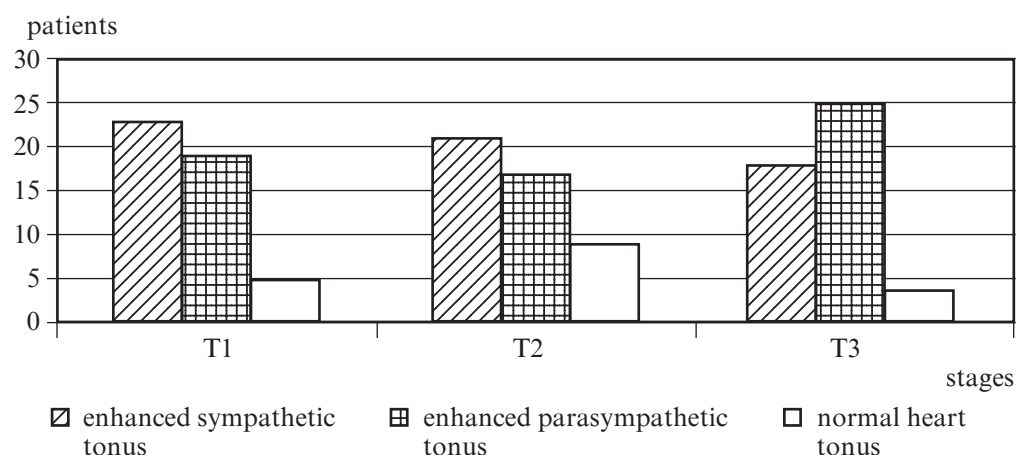


Fig. 3. Structure of the group in function of vegetative heart tonus in different stages of induction of general anesthesia with midazolam and fentanyl



Heart activity is controlled by influences of sympathetic and parasympathetic vegetative nervous system on the sinus node. These influences are manifested by cyclic changes of RR interval on ECG. The modern Holter devices are equipped with computerized system for analysis of HRV and can appreciate the changes in heart vegetative tonus. There is generally accepted that the LFun/HFun ratio represents the sympathetic-parasympathetic balance of the heart, the LFun represents the sympathetic and baroreceptors influences on the heart and the HFun represents the parasympathetic tonus of the heart [3–5].

There are several studies that estimated the effects of midazolam on the vegetative regulation of the heart using HRV analysis. But in most studies midazolam was used for sedation [1; 11–13]. The comparison of these results with ours is not reliable as we administered higher doses of midazolam (0.2–0.3 mg/kg) and it was administered in combination with fentanyl (1.5 mkg/kg). In a recent study Nishiyama T. (2018), demonstrated that administration of midazolam 0.06 mg/kg in combination with 0.5 mg of atropine reduced sympathetic tonus [1].

In another study performed by Tsugayasu R. (2010), sedation with midazolam 0.01 mg/kg decreased cardiac sympathetic tonus without significant effect on cardiac parasympathetic tonus [11]. Smith A. and col. [12] showed that premedication with midazolam 2.5 mg in combination with differential doses of fentanyl (50 mkg, 75 mkg, 100 mkg and 150 mkg) didn't change significantly the cardiac sympathetic and parasympathetic tonus, and a boost in sympathetic cardiac tonus was observed immediately before respiratory depression. The final conclusion was that midazolam for sedation in combination with fentanyl didn't change the sympathetic-parasympathetic balance of the heart and the enhanced cardiac sympathetic tonus mostly is caused by changes in respiratory pattern similar to sleep apnea. Contrary to this study, Dogan I. demonstrated that sedation with midazolam 0.05 mg/kg for transesophageal echocardiography significantly reduced cardiac sympathetic tonus and significantly increased parasympathetic tonus [13].

These results are different from our findings, as in our study the midazolam in combination with fentanyl enhanced the cardiac parasympathetic tonus without significant changes in the cardiac sympathetic tonus. In our study value of LFun/HFun after induction of general anesthesia with midazolam and fentanyl decreased to 1.1 which signifies an enhanced cardiac parasympathetic tonus. This decrease could be attributed to the effects of midazolam, as premedication with fentanyl didn't significantly change LFun/HFun ratio. Benzodiazepines can influence autonomic neuro-cardiac regulation, probably through their interaction with the GABAA receptor complex in the brain [2].

### Conclusions

Premedication with fentanyl didn't change significantly the heart vegetative balance but induction of general anesthesia with midazolam and fentanyl enhanced cardiac parasympathetic tonus.

**Ключові слова:** варіабельність серцевого ритму, симпатична і парасимпатична регуляції серцевого ритму.

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## ТЕХНОЛОГІЯ НИЗЬКОЧАСТОТНОЇ П'ЄЗОТРОМБОЕЛАСТОГРАФІЇ У МОНІТОРИНГУ ПРОТИТРОМБОТИЧНОЇ ТЕРАПІЇ

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## ТЕХНОЛОГИЯ НИЗКОЧАСТОТНОЙ ПЬЕЗОТРОМБОЭЛАСТОГРАФИИ В МОНИТОРИНГЕ ПРОТИВОТРОМБОТИЧЕСКОЙ ТЕРАПИИ

Представлена информация о новой технологии оценки гемостатического потенциала цельной крови в процессе коагуляции — низкочастотной пьезотромбоэластографии, позволяющей проводить интегративную оценку его ха-

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