УДК 616.12-008.313-073.97:615.22
DOI: https://doi.org/10.17816/PAVLOVJ104696

# Изучение электрофизиологических свойств атриовентрикулярного узла в условиях постоянной электрокардиостимуляции под влиянием триметазидина дигидрохлорида

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***АННОТАЦИЯ***

***Введение.*** Двухкамерная электрокардиостимуляция (ЭКС) позволяет сохранить постоянную предсердно-желудочковую синхронизацию. Осуществляется физиологическая последовательность распространения импульса от предсердий к желудочкам с наличием искусственного интервала задержки по аналогии с задержкой распространения возбуждения по атриовентрикулярному (АВ) узлу здорового человека. Интервал задержки формируется таким образом, чтобы минимизировать правожелудочковую стимуляцию. Это сохраняет фракцию выброса левого желудочка, снижает риск развития хронической сердечной недостаточности (ХСН), увеличивает функциональные возможности пациента и снижает риск развития фибрилляции предсердий. С другой стороны, предельное увеличение атриовентрикулярной задержки ведет к развитию пейсмекерного синдрома: ухудшается функция кровообращения, наблюдается одышка, недостаточная толерантность к физической нагрузке, головокружение, синкопальные состояния. Остается до конца неразрешённым вопрос о влиянии постоянной ЭКС на проводимость АВ узла.

***Цель.*** Изучить влияние триметазидина дигидрохлорида на проводимость АВ узла в условиях постоянной ЭКС, определить влияние ЭКС на АВ узел в исследуемый временной период.

***Материалы и методы.*** В исследование включено 86 пациентов. Проведена оценка активности АВ узла путем определения точки Венкебаха антеградно интраоперационно по данным электрокардиограммы, через 24–48 ч после имплантации электрокардиостимулятора, через 6–8 часов, через 7, 14, 21, 90 и 180 дней после приема препарата триметазидина дигидрохлорида и через 7, 14, 21 и 30 дней после его отмены. Для сравнения степени влияния изучаемого препарата на активность АВ узла в зависимости от основной патологии исследуемые пациенты были разделены на три группы: группа 1 — пациенты с синдромом слабости синусового узла (n = 38, 44,2%); группа 2 — пациенты с АВ блокадой 2 степени (n = 25, 29,1%); группа 3 — пациенты с АВ блокадой 3 степени (n = 23, 26,7%).

***Результаты.*** Триметазидина дигидрохлорид улучшает электрофизиологические свойства АВ узла в первой и второй группе исследуемых больных: прибавка в среднем значении точки Венкебаха антеградно в сумме в первой группе составила 3,26% (p = 0,022), во второй группе — 4,68% (p = 0,001). У третей группы пациентов улучшений не отмечено, но стоит указать, что под действием исследуемого препарата на фоне АВ блокады 3 степени у 4-х пациентов из 23 появилось антеградное АВ проведение (p = 0,236).

***Заключение.*** Назначение триметазидина дигидрохлорида оказывает положительное влияние на активность АВ узла уже через 6–8 ч после приема, а своего максимального эффекта препарат достигает спустя 3 недели. ЭКС не оказывала влияние на АВ узел в течение периода наблюдения (6 месяцев).

**Ключевые слова:** *электрокардиостимуляция; брадикардия; триметазидина дигидрохлорид; метаболическая терапия; атриовентрикулярный узел; точка Венкебаха*

**Для цитирования:**
Смирнов В.Н., Староверов И.Н., Гридин А.Н. Изучение электрофизиологических свойств атриовентрикулярного узла в условиях постоянной электрокардиостимуляции под влиянием триметазидина дигидрохлорида // Российский медико-биологический вестник имени академика И.П. Павлова. 2022. Т. 30, № 3. С. 305–312. DOI: https://doi.org/10.17816/PAVLOVJ104696

**Рукопись получена:** 11.03.2022 **Рукопись одобрена:** 28.06.2022 **Опубликована:** 30.09.2022

ЭКО•ВЕКТОР

DOI: https://doi.org/10.17816/PAVLOVJ104696

# Study of Electrophysiological Properties of Atrioventricular Node in Permanent Cardiac Pacing under Influence of Trimetazidine Dihydrochloride

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***ABSTRACT***

***INTRODUCTION:*** Dual-chamber cardiac pacing permits to maintain permanent atrial-ventricular synchronization. Physiological sequence of propagation of the impulse from atria to ventricles is provided with an artificial delay analogous to delay of propagation of excitation through the atrioventricular (AV) node of a heathy individual. The delay interval is formed so that to minimize stimulation of the right ventricle. This preserves the left ventricular ejection fraction, reduces the risk of development of the chronic heart failure (CHF) and of atrial fibrillation, and increases functional abilities of the patient. On the other hand, critical increase in the atrioventricular delay leads to pacemaker syndrome: impairment of circulation function, shortness of breath, reduced tolerance to exercise, dizziness, syncopal state. The question of the influence of the permanent electrical pacing on the AV node conduction remains unsolved.

***AIM:*** To study the effect of trimetazidine dihydrochloride on the AV node conduction in conditions of permanent cardiac pacing, to determine the effect of cardiac pacing on the AV node in the studied time period.

***MATERIALS AND METHODS:*** The study involved 86 patients. The AV node activity was assessed by antegrade intraoperative determination of Wenckebach point on the basis of electrocardiography data in 24–48 hours after pacemaker implantation, in 6–8 hours, 7, 14, 9 and 180 days after intake of trimetazidine dihydrochloride and in 7, 14, 21 and 30 days after its cancellation. To compare the extent of influence of the studied drug on the AV node activity, the patients were divided to three groups depending on the basic pathology: group 1 — patients with the sick sinus node syndrome (n = 38, 44.2%); group 2 — patients with II degree AV block (n = 25, 29.1%); group 3 — patients with III degree AV block (n = 23, 26.7%).

***RESULTS:*** Trimetazidine dihydrochloride improved the electrophysiological properties of the AV node in the first and second groups: increase in the mean value of Wenckebach point antegrade in the first group was in total 3.26% (p = 0.022), in the second group 4.68% (p = 0.001). In the third group of patients no improvement was noted, but it should be said that under the action of this drug, in 4 of 23 patients with III degree AV block, antegrade AV conduction appeared (p = 0.236).

***CONCLUSION:*** Trimetazidine dihydrochloride has a positive effect on the AV node activity as early as in 6–8 hours of intake, which reaches maximum in 3 weeks. Cardiac pacing had no effect on AV node within the follow-up period (6 months).

**Keywords:** *cardiac pacing; bradycardia; trimetazidine dihydrochloride; metabolic therapy; atrioventricular node; Wenckebach point*

**For citation:**
Smirnov VN, Staroverov IN, Gridin AN. Study of Electrophysiological Properties of Atrioventricular Node in Permanent Cardiac Pacing under Influence of Trimetazidine Dihydrochloride. *I.P. Pavlov Russian Medical Biological Herald.* 2022;30(3):305–312. DOI: https://doi.org/10.17816/PAVLOVJ104696

**Received:** 11.03.2022 **Accepted:** 28.06.2022 **Published:** 30.09.2022

ECO•VECTOR

## LIST OF ABBREVIATIONS

AV — atrioventricular
CA — cardiac arrhythmias
CHD — coronary heart disease
CHF — chronic heart failure
CP — cardiac pacing
EPE — electrophysiological examination
IVS — interventricular septum
LV — left ventricle
PICS — postinfarction cardiosclerosis
SSS — sick sinus syndrome
WPA — Wenckebach point, antegrade

## INTRODUCTION

Among numerous cardiac arrhythmias (CA), of special importance cardiac pacing methods had been introduced in clinical practice, the annual mortality rate of patients with acquired complete atrioventricular block exceeded 50% [2, 3]. In chronic bradycardias/conduction disorders, pharmacological antiarrhythmic drugs are in most cases ineffective — a gold standard of treatment is permanent electrical pacing [4–6].

The number of antiarrhythmic devices implanted in the Russian Federation, annually increases by 10% [7], and currently reaches about 50 thousand devices [8]. The majority of devices are dual-chamber pacemakers (in Europe — 60%–70%) [9]. This type of stimulation permits to maintain electrophysiological atrioventricular synchronization: the impulse travels from atria to ventricles along the natural pathway with delay analogous to propagation of excitation through the atrioventricular node (AVN) of a healthy individual. Abnormal activation of ventricles in stimulation of the right ventricle, like in the left bundle branch block, leads to impairment of the function of the left ventricle (LV) and its structural alterations resulting from the electrical and mechanical dyssynchrony of the myocardium [10]. The basis of stimulation of the right ventricle is the reduction of increase in systolic thickening of the interventricular septum (IVS) and increase in diastolic pressure in the cavity of the LV. During contraction of the LV, the mechanical work of IVS may decrease with increase in the load in the area of the free wall of the LV, which leads to its hypertrophy [11].

In patients with ventricular pacing exceeding 50%, the frequency of the recorded cases of heart failure and deaths over a 4$^{th}$ year follow-up period was 25% higher than in the group with ventricular stimulation below 50% [11]. Therefore, the *delay interval must be formed in the way to reduce the percent of the right ventricular stimulation*. This preserves the LV ejection fraction, decreases the risk of development of chronic heart failure (CHF), increases the functional abilities of the patient and decreases the risk of atrial fibrillation. On the other hand, increase in the AV delay above the limit leads to *pacemaker syndrome*: impairment of the function of circulation, shortness of breath, poor tolerance to exercise, dizziness, syncopal conditions.

Many patients to whom a pacemaker is implanted are already having comorbid pathologies: coronary heart disease, (CHD), CHF, arrhythmias. These diseases require intake of drugs that also worsen the AV conduction (β-blockers, antiarrhythmic drugs, etc.).

The question of the influence of the permanent electrical pacing on the antegrade AV conduction remains unsolved.

The **aim** to this study the effect of trimetazidine dihydrochloride on the antegrade atrioventricular conduction in patients with different heart rhythm disorders and disorders in conduction in the permanent electrical pacing in different modes, to study the effect of electrical pacing on the activity of the atrioventricular node in 6-month follow-up period.

## MATERIALS AND METHODS

The study included 86 patients with bradysystolic forms of arrhythmia who were implanted permanent pacemaker systems in conditions of Yaroslavl Regional Clinical Hospital in the period from 2019 to 2021. The research protocol was approved by the Local Ethics Committee of the Yaroslavl State Medical University (protokol No. 41 dated October 22, 2020). The signing of the Informed Consent was carried out according to standard procedures of the Yaroslavl Regional Clinical Hospital before performing any medical interventions.

***Inclusion criteria:***

– age 18 years and older;

– the main disease: sick sinus syndrome (SSS) or II or III degree AV block;

– first implantation of a dual-chamber pacemaker;

– implantation of the right ventricular electrode only into the interventricular septum;

– implantation of the right atrial electrode only into the auricle of the right atrium;

– sinus rhythm recorded at all stages of the study;

– absence of evident cardiac defects and interventions on the open heart in history;

– adherence of patients to the adequate drug therapy;

– the expected follow-up period of 6 months and more.

In result, the study included 28 (32.6%) men and 58 (67.4%) women aged 32 to 94 years, the mean age

74.26 ± 11.47 years. The studied patients had different forms of SSS (38 patients, 38%) and of AV blocks (permanent I degree AV block — 11 patients (11%), transient II degree AV block — 14 patients (14%), permanent III degree AV block — 23 patients (23%)). Most patients had comorbid diseases: essential hypertension — 81 patients (94.2%) (III stage — 80 patients (99.3%), II stage — 1 patient (1.2%)); I stage CHF (by Strazhesko–Vasilenko classification) — 4 patients (4.7%), IIA stage — 46 patients (53.5%), IIB stage — 8 patients (9.3%); CHD — 51 patients (59.3%) including postinfarction cardiosclerosis (PICS) — 17 patients (19.8%); diabetes mellitus — 26 patients (30.2%); nodular goiter — 11 patients (12.8%); chronic kidney disease of different extent of severity — 11 patients (12.8%); chronic cerebrovascular insufficiency with preceding acute cerebrovascular event — 2 patients (2.3%); aortic stenosis — 2 patients (2.3%); mitral insufficiency — 1 patient (1.2%), combined mitral-aortic stenosis — 1 patient (1.2%).

The following ***groups*** of patients were formed:

***group 1*** — patients with SSS (n = 38, 44.2%);

***group 2*** — patients with II degree AV block (n = 25, 29.1%);

***group 3*** — patients with III degree AV block (n = 23, 26.7%).

By the basic clinical and demographic data (mean age and the number of comorbid diseases), except for the gender of the patients, the groups were comparable (Table 1), which enabled further comparative analysis of the results of the study. Gender differences between the groups were neglected due to the absence of any mention of the effect of gender of healthy individuals on the activity of the AV node in the literature.

**Table 1.** Clinical and Demographic Characteristics of Study Groups of Patients

| Parameters | Group 1 | Group 2 | Group 3 | p |
|---|---|---|---|---|
| n | 38 | 25 | 23 | |
| Mean age, years, M ± SD | 71.50 ± 9.03 | 73.28 ± 7.37 | 79.04 ± 8.99 | > 0.05 |
| Many men, n (%) | 15 (39.5) | 8 (32.0) | 6 (26.1) | < 0.05 |
| Number of comorbid diseases per one patient, n, M ± SD | 3.5 ± 0.9 | 3.5 ± 1.0 | 3.5 ± 0.9 | > 0.05 |

All the patients underwent surgical treatment — implantation of a permanent electrical pacemaker (EP). Dual-chamber pacemakers were used with passive and active electrodes with the "atrial" electrode placed in the auricle of the right atrium and the "ventricular" electrode of the right ventricle placed in the area of the middle third of IVS. The operations were performed under local anesthesia in the x-ray operating room. Also, all the patients were administered the drug under study — trimetazidine dihydrochloride — at a dose 80 mg orally once a day in the morning.

Electrophysiological properties of the conducting system of the heart and the activity of the AV node were evaluated by determination of Wenckebach point antegrade (WPA) intraoperatively (in testing the EP system), in 24–48 hours after EP implantation, in 6–8 hours after intake of trimetazidine dihydrochloride, in 7, 14, 9 and 180 days after intake of trimetazidine dihydrochloride and in 7, 14, 21 and 30 days after its cancellation (to evaluate the extent of antegrade AV node conduction, it was required in testing to set EP to AAI mode and to gradually increase the frequency of stimulation until escape of the first "ventricular" complexes).

A special aspect of the research was to study the effect of permanent electrical pacing on the electrophysiological properties of the AV node *separately from the influence of metabolic therapy* in the studied time period. It is just for this reason that in each patient WPA was determined before EP implantation and after implantation, but before use of metabolic therapy and in 30 days after its cancellation, when the effect of the drug was completely neutralized. Another important task was evaluation of the extent of the influence of trimetazidine dihydrochloride on AV conduction depending on the duration of its intake and of the period after its cancellation.

Statistic processing of results of the study was performed using MedCalc 12.5.0.0 (MedCalc Software bvba, 2013), Microsoft Office Excel 2007 program. With the normal distribution of the variables, the results were presented as arithmetic means and standard deviation (M ± SD) with the indication of 95% confidence interval (CI). With the distributions of variables different from normal, the values were presented as median (Me) and interquartile range ($25^{th}$ and $75^{th}$ percentiles). Student's t-test was used to compare groups with normal distribution of variables, for distribution different from normal, non-parametric Wilcoxon test and $\chi 2$ Pearson test were used. In testing statistical hypotheses, the critical level of statistical significance was taken 0.05.

DOI: https://doi.org/10.17816/PAVLOVJ104696

## RESULTS

It was demonstrated that in the *first group* EP system had the following effect on WPA: on admission, the mean value of WPA in all the patients was 113.16/minute (Table 2), and in 24–48 hours after implantation of EP system — 113.03/minute (reduction by 0.11%, p = 0.161). In 6–8 hours after administration of trimetazidine dihydrochloride, the mean WPA value per minute increased by 2.05% (from 113.03 to 115.39), in 7 days — by 0.12% (from 115.39 to 115.53), in 14 days — by 1.12% (from 115.53 to 116.84), in 21 days — by 0.11% (from 116.84 to 116.97), in 30, 90, 180 days — without changes. In 7 days after cancellation of the drug, the mean WPA decreased by 0.34% (from 116.71 до 116.31), in 14 days — by 1.92% (from 116.31 to 114.08), in 21 days — by 1.15% (from 114.08 to 112.77), in 30 days — by 0.24% (from 112.77 to 112.50).

In other words, *trimetazidine dihydrochloride started to produce a positive effect on WPA already in 6–8 hours after intake, and reached the maximal effect after 3 weeks of taking*; further intake did not have any additional effect on the activity of AV node either in 90, or in 180 days. The total increase in the mean WPA from the moment of 24–48 hours after EP implantation to the 180th day of taking the drug was 3.26% (p = 0.022). After cancellation of the drug, the mean WPA value decreased already in the first week and reached the minimal value on the 30$^{th}$ day of cancellation (112.50, p = 0.019). In 30 days after cancellation of trimetazidine dihydrochloride, the mean WPA value decreased below the initial level: from 113.16 on admission to 112.50 in 30 days after cancellation (reduction by 0.58%, p = 0.066).

**Table 2.** Comparative Data of Wenckebach Point (Antegrade) of Patients of the First and Second Groups

| Time of Electrophysiological Study | | Mean Value of Wenckebach Point, min$^{-1}$ | |
|---|---|---|---|
| | | Group 1 | Group 2 |
| n | | 38 | 25 |
| Intraoperatively | | 113.16 | 53.20 |
| 24–48 hours after pacemaker implantation | | 113.03 | 54.60 |
| Period of intake of trimetazidine dihydrochloride | 6–8 hours | 115.39 | 56.12 |
| | 7 days | 115.53 | 56.92 |
| | 14 days | 116.84 | 57.00 |
| | 21 days | 116.97 | 57.28 |
| | 30 days | 116.97 | 57.28 |
| | 90 days | 116.97 | 57.28 |
| | 180 days | 116.71 | 57.28 |
| Period after cancellation of trimetazidine dihydrochloride | 7 days | 116.31 | 57.08 |
| | 14 days | 114.08 | 56.00 |
| | 21 days | 112.77 | 54.48 |
| | 30 days | 112.50 | 52.24 |

In patients of the *second group*, the EP system influenced the WPA in the following way: intraoperative mean WPA value was 53.20/minute, in 24–48 hours after EP implantation — 54.60/minute (increase by 2.56%, p = 0.065), in 6–8 hours after intake of trimetazidine dihydrochloride it increased by 2.71% (from 54.60 to 56.12), in 7 days — by 1.41% (from 56.12 to 56.92), in 14 days — by 0,14% (from 56.92 to 57.00), in 21 days — by 0.49% (from 57.00 to 57.28), in 30, 90, 180 days — without changes. In 7 days after cancellation of the drug, the mean WPA value decreased by 0.35% (from 57.28 to 57.08), in 14 days — by 1.89% (from 57.08 to 56.00), in 21 days — by 2.71% (from 56.00 to 54.48), in 30 days — by 4.11% (from 54.48 to 52.24).

Thus, trimetazidine dihydrochloride started to produce a positive effect on WPA already in 6–8 hours after the first intake and reached the maximal effect after 3 weeks of intake, but further intake, like in the first group, did not have any additional effect on the activity of the AV node either in 90, or 180 days. The total increase in the mean WPA from the moment of 24–48 hours after EP implantation to the 180th day of taking the preparation made 4.68% (p = 0.002). After cancellation of the drug, already in the first week, reduction of the mean WPA value was recorded which reached the minimal level on the 30$^{th}$ day of cancellation of the drug (52.24, p = 0.0002). In 30 days after cancellation of trimetazidine dihydrochloride, the mean WPA value decreased below the initial value: intraoperatively, WPA was 53.20/minute, and in 30 days after cancellation of the drug — 52.24/minute (reduction by 1.8%, p = 0.109).

In patients of the *third group*, the following results were recorded. In 2 patients, *in 21 days* of trimetazidine

dihydrochloride intake, *antegrade AV conduction was recorded*. In both patients, WPA was 65 per minute. Further observation revealed no dynamics. After cancellation of the drug, in one of these patients AV block again developed on the 7th day, in the other — on the 14th day. In another two patients, antegrade AV conduction was recorded on the *30th day* of taking trimetazidine dihydrochloride. In both patients, WPA was 70/minute, in further intake of the drug, no dynamics was observed. After cancellation of the drug, in one of these patients AV block developed on the 7th day, in the other — on the 14th day. In the rest of patients, intake of the drug did not influence antegrade AV conduction.

## DISCUSSION

In two of the three studied groups, namely, *in the groups of patients with SSS and II degree AV block, trimetazidine dihydrochloride had a positive effect on the antegrade AV conduction*: increase in the mean WPA value from the moment of 24–48 hours after implantation of EP system to the 180th day of taking the drug was 3.26% ($p = 0.022$) in the first group and 4.68% ($p = 0.001$) in the second. In both groups, the permanent electrical cardiac stimulation did not have any effect on the activity of the AV node. The mean WPA value in the first group was 113.16/minute intraoperatively, in 24–48 hours after the ECS implantation — 113.03/minute, reduction by 0.11% ($p = 0.162$). In the second group, the mean WPA value on admission was 53.20/minute and 54.60/minute in 24–48 hours after ECS implantation (increase by 2.56%, but at the level of tendency — $p = 0.065$). In the first group, reduction of the mean WPA value by 3.82% ($p = 0.019$) on the 30th day after cancellation of the drug was noted in comparison with 180th day period of taking the drug, which corresponds to the initial figures before drug intake ($p = 0.236$). In the second group, reduction of WPA by 8.8% ($p = 0.0002$) was recorded on the 30th day of cancellation of the drug compared to the 180-day period of taking the drug, which corresponds to the initial figures before the drug intake ($p = 0.235$).

To note, *the maximal effect of metabolic therapy in the first and second groups was achieved after 3 weeks of taking the drug*, further intake did not demonstrate any additional influence on WPA until the 180th day.

In the third group (patients with permanent III degree AV block), trimetazidine dihydrochloride did not produce any influence on the antegrade AV conduction. It should be noted that in 4 patients of this group, despite the existence of the permanent III degree block, antegrade AV conduction still appeared (was recorded on the 21st and 30th day of the drug intake), although because of insufficient statistical power it is impossible to speak about statistical significance of the result ($p = 0.236$).

Thus, it can be concluded that the maximal effect of trimetazidine dihydrochloride manifests in patients with SSS and II degree AV block *after 3 weeks of intake* and persists throughout the entire follow-up period, and in 30 days after cancelation returns to the initial level. So, *to maintain the positive effect, permanent intake of trimetazidine dihydrochloride is required*. In patients with III degree AV block, no statistically significant positive effect was achieved.

We think that the positive effect of trimetazidine dihydrochloride is associated with prevention of reduction of the intracellular concentration of adenosine triphosphate through preservation of energetic metabolism of cells (including cells of the conducting system of the heart) in hypoxic conditions, since the preparation provides normal functioning of the membrane ion channels, transmembrane transmission of potassium and sodium ions, and preserves cell homeostasis.

In patients with angina pectoris, trimetazidine dihydrochloride increases the coronary reserve thus slowing down the onset of exercise-related ischemia, and maintains the normal blood flow through the coronary arteries including those supplying the AV node. Resting on the improvement of electrophysiological parameters in patients with bradycardia of ischemic and non-ischemic genesis, we think it reasonable to use trimetazidine dihydrochloride in this category of patients. To note, the influence of trimetazidine dihydrochloride on the electrophysiological properties in permanent electrical cardiac stimulation has not been studied before in the international and Russian literature.

## CONCLUSION

Trimetazidine dihydrochloride demonstrated a positive effect on the activity of the atrioventricular node in patients with sick sinus node syndrome and II degree AV block already in 6–8 hours after its intake with the maximal effect in 3 weeks of continuous intake. To maintain this positive effect, permanent intake of the drug is required.

In patients with III degree atrioventricular lock, treatment with trimetazidine dihydrochloride did not produce a statistically significant effect on the antegrade atrioventricular conduction.

To note, the system of electrical cardiac stimulation did not produce any unfavorable effect on the atrioventricular node during the follow-up period.

## ADDITIONAL INFORMATION

**Funding.** This study was not supported by any external sources of funding.
**Conflict of interests.** The authors declare no conflicts of interests.
**Contribution of the authors:** *V. N. Smirnov* — collection and processing of material, statistical processing, writing the text; *I. N. Staroverov* — research

concept and design, statistical processing, editing; *A. N. Gridin* — collection and processing of material, concept and research design, editing. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

**Финансирование.** Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

**Конфликт интересов.** Авторы заявляют об отсутствии конфликта интересов.
**Вклад авторов:** *Смирнов В. Н.* — сбор и обработка материала, статистическая обработка, написание текста; *Староверов И. Н.* — концепция и дизайн исследования, статистическая обработка, редактирование; *Гридин А. Н.* — сбор и обработка материала, концепция и дизайн исследования, редактирование. Авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

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