

Authors' opinions

Assessment of frequency components of ECG waveform variability: Are there prospects for research into cardiac regulation processes?

Anton R. Kiselev, Maksim O. Zhuravlev, Anastasia E. Runnova

National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia

Received 20 May 2024, Revised 18 September 2024, Accepted 15 October 2024

© 2024, Russian Open Medical Journal

Abstract: This brief review discusses the potential and prospects of using the electrocardiogram (ECG) signal directly for frequency analysis to study the processes of cardiac regulation. The advantage of the ECG signal over the generally accepted frequency analysis of the RR series is its higher sampling rate: 1000 samples per second (sps) for ECG signal vs. 4 sps for RR series. This may be important, first of all, when analyzing the interaction of cardiac regulation processes with other periodic processes in the body, such as the activity of neural circuits in the brain.

Keywords: ECG waveform variability, P-QRS-T waveform, spectral analysis, regulatory processes.

Cite as Kiselev AR, Zhuravlev MO, Runnova AO. Assessment of frequency components of ECG waveform variability: Are there prospects for research into cardiac regulation processes? *Russian Open Medical Journal* 2024; 13: e0412.

Correspondence to Anton R. Kiselev. Email: antonkis@list.ru.

Assessment of five characteristic waves (P, Q, R, S and T waves) on the electrocardiogram (ECG) during one heartbeat was a routine practice in clinical cardiology for many decades [1, 2]. However, various factors (patient's motion artifacts, power line interference, baseline drift due to breathing, etc.) affect the ECG waveform, which often complicates the detection of the above waves [3, 4]. Many authors developed methods to improve the quality of identification and evaluation of P, Q, R, S and T waves on the ECG [5-8].

In addition to the conventional analysis of each of the characteristic ECG waves separately, periodic processes extracted from the ECG signal also deserve attention. In particular, heart rate variability (HRV) is the most extensively studied phenomenon already employed in both research and clinical practice [9, 10]. HRV analysis is based on the determination of the RR series (the time elapsed between two consecutive R waves on the ECG). For many years, the study of the autonomic regulation of the cardiovascular system was traditionally based on the analysis of HRV using the RR series [9]. The frequency components of HRV characterize various processes of cardiac regulation (mainly, chronotropic control of the heart). Traditionally, several frequency components of HRV are distinguished. High-frequency (0.15-0.4 Hz) oscillations are caused by vagal activity and respiratory influences on the heart rate [9]. Low-frequency (0.04-0.15 Hz) oscillations are believed to reflect the baroreflex function [11-13] and, to a lesser extent, sympathetic and vagal activity [14, 15]. Very low-frequency (0.003-0.04 Hz) oscillations are generated by humoral and local factors, as well as sympathetic activity influencing the heart rate [10]. Of course, scientists have mixed opinions about the nature of these frequency components of HRV, so the debate continues. Nevertheless, indicators based on

quantitative assessments of these components show certain promise for clinical practice [9, 11, 16-20].

However, the limitations of the HRV analysis by RR series become obvious if we turn, for example, to the analysis of a type of arrhythmia, known as atrial fibrillation, frequently encountered in cardiology practice [21], when the main heart rhythm is chaotic and the informativeness of conventional HRV analysis for studying the processes of autonomic regulation is questionable. However, it is well known that atrial fibrillation and its lifetime prognosis are to a certain extent associated with autonomic influences [22-24]. Therefore, the search for alternative approaches to assessing the processes of cardiac regulation in these patients is very relevant.

Despite many years of global experience in using RR series to calculate various HRV parameters (including frequency), a certain feature of this approach deserving a proper attention is a rather low sampling rate of classical RR series used for HRV analysis: usually, 4 samples per second (sps). This may limit the ability to use the RR series to study their relationship with higher frequency processes in the human body, such as those based on electroencephalograms (EEG). The high sampling rate of the ECG signal (in our case, 1000 sps) provides more opportunities to study their relationship with the frequency components of the EEG. The question remains how well the frequency components in the P-QRS-T waveform variability below the baseline heart rate can be compared with the known frequency measures used in conventional HRV analysis.

It is known that periodic processes modulating the main heart rate and forming frequency peaks in the conventional spectral analysis of HRV will form additional peaks near the peak of the main heart rate in the ECG spectrum. If we denote the main heart rate as f_{hr} , and the frequency of the periodic process modulating it

as f_m , then the frequencies of additional peaks in the ECG spectrum will be determined as $f_{hr} \pm n f_m$, where n is a positive integer (see figures in [25]). Of course, oscillations of the actual main heart rate are not harmonic, as are the periodic processes modulating them. Therefore, the frequency-modulated signal of cardiac activity has a complex spectrum.

We hypothesize that regulatory processes (sympathetic, parasympathetic, baroreflex and respiratory), previously studied on the basis of HRV, form frequency responses in the ECG spectrum. The influence of these regulatory processes on the ECG spectrum is possible not only due to the features of the spectral analysis, as described in [25], but also due to the modulating effect on the components of the P-QRS-T waveform.

Besides that, other periodic processes extracted from the ECG signal and associated with other waves (except for R waves) also seem promising. For example, according to some authors, the PP series (the time elapsed between two consecutive P waves on the ECG) exhibits an advantage for its noteworthy ability to identify the onset of paroxysmal atrial fibrillation and to reveal additional information regarding the variability of the RR series [26]. Direct frequency estimates of the P wave are also studied and used to detect fragmentation in atrial conduction, which is a recognized indicator of the onset of paroxysmal atrial fibrillation [27, 28]. The spectral content of the normal P wave is below 20 Hz [29], but higher frequency components (20, 30, 40, 60, and 80 Hz to 150 Hz) may be seen in fragmented P waves [30-32].

The periodicity of ventricular repolarization oscillations, manifested in changes of the T wave vector, appears to be in the same frequency range as the low-frequency oscillations detected during muscle sympathetic nerve activity (MSNA) [33] and spontaneous fluctuations of beat-to-beat RR intervals [15, 34]. It is known that the T wave is caused by transmural voltage gradient across the ventricular myocardium, which develops as a result of the difference in the repolarization time of myocardial cell layers with different action potential durations (APD) [35]. There are data for patients with heart failure that the rhythmic patterns of APD in myocardial cells are coherent with an oscillation frequency of 0.1 Hz of arterial pressure [36]. The relationship between low-frequency (about 0.1 Hz) oscillations with APD and HRV is confirmed by the results of other studies as well [37]. There is an opinion that 0.1 Hz oscillatory patterns in APD reflect the influence of sympathetic activity on the myocardium [38, 39]. However, this hypothesis has many limitations [40] and requires further research to clarify the detailed mechanisms.

There are publications on developing approaches to identifying arrhythmic events based on frequency analysis of various components of the P-QRS-T waveform, including the QRS complex [41-44]. Noteworthy progress applicable to clinical practice has been made in this field.

The multifrequency oscillatory mode is a key biophysical feature of the cardiovascular system, provided by the presence of several different oscillatory processes (heart rhythm, baroreflex regulation, respiratory effects, vasomotion, etc.) [45, 46]. In the cardiovascular system, even under conditions of stability, various spontaneous oscillations of parameters of its functioning occur. Their mechanism of formation is very complex and is characterized by the presence of many oscillatory processes at different frequencies, which are subject to the modulating effects of external factors [47-49]. Previously, we and other authors have demonstrated that the presence of various oscillatory processes in

the cardiovascular system activity somehow related to its multilevel regulation leads to their interaction with each other, up to both phase and frequency synchronization and complete synchronization [46, 48, 50, 51]. The emergence of synchronization is one of the key mechanisms of self-organization in various body systems. Nevertheless, we recognize that the results demonstrating such synchronization are ambiguous and far from explaining the observed phenomena. Also, the analysis of phase and frequency synchronization only on certain frequency components arbitrarily identified by researchers does not provide an explanation of the structure of interactions between regulatory mechanisms.

Thus, there are prerequisites for changing the attitude to the use of frequency analysis of the ECG signal per se for studying the processes of cardiac regulation and their interaction with other periodic processes in the body. We believe that the methods used to extract the heart rate from the ECG signal, based on the standard, nearly geometric extraction of the RR series, entail the loss of a significant share of the information contained in the remaining components of the P-QRS-T waveform. Higher sampling rate of the ECG signal can be of decisive importance when using current modeling technologies for data analysis, including nonlinear network approaches, to the tasks of studying the dynamics of the cardiovascular system. This approach is widespread in interdisciplinary sciences for studying biological systems. For example, at present, it is quite habitual to recognize the network-based nature of the dynamics of interacting spatial areas of neural complexes in the cerebral cortex [52].

Conclusion

The potential advantages of using frequency analysis of the native ECG signal over the generally accepted analysis of HRV by RR series, given its higher sampling rate, can be important not only for the tasks of studying the cardiac regulation processes, but also to a greater extent for the analysis of their interaction with other periodic processes in the body, such as the activity of neural circuits in the brain.

Funding

This work was supported by the Russian Science Foundation (Project No. 24-24-00333).

Conflicts of Interest

The authors have no conflicts of interest to disclose.

References

1. Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ, Hancock EW, et al. Recommendations for the standardization and interpretation of the electrocardiogram: Part I: The electrocardiogram and its technology. A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol* 2007; 49(10): 1109-1127. <https://doi.org/10.1016/j.jacc.2007.01.024>.
2. Mason JW, Hancock EW, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. Recommendations for the standardization and interpretation of the electrocardiogram: Part II: Electrocardiography diagnostic statement list. A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the

- Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol* 2007; 49(10): 1128-1135. <https://doi.org/10.1016/j.jacc.2007.01.025>.
3. Zhang F, Lian Y. QRS detection based on multiscale mathematical morphology for wearable ECG devices in body area networks. *IEEE Trans Biomed Circuits Syst* 2009; 3(4): 220-228. <https://doi.org/10.1109/TBCAS.2009.2020093>.
 4. Chen CL, Chuang CT. A QRS detection and R point recognition method for wearable single-lead ECG devices. *Sensors (Basel)* 2017; 17(9): 1969. <https://doi.org/10.3390/s17091969>.
 5. Hossain B, Bashar SK, Walkey AJ, McManus DD, Chon KH. An accurate QRS complex and P wave detection in ECG signals using complete ensemble empirical mode decomposition approach. *IEEE Access* 2019; 7: 128869-128880. <https://doi.org/10.1109/access.2019.2939943>.
 6. Bae TW, Kwon KK, Kim KH. Electrocardiogram fiducial point detector using a bilateral filter and symmetrical point-filter structure. *Int J Environ Res Public Health* 2021; 18(20): 10792. <https://doi.org/10.3390/ijerph182010792>.
 7. Madona P, Basti RI, Zain MM. PQRST wave detection on ECG signals. *Gac Sanit* 2021; 35 Suppl 2: S364-S369. <https://doi.org/10.1016/j.gaceta.2021.10.052>.
 8. Liu J, Jin Y, Liu Y, Li Z, Qin C, Chen X, et al. A novel P-QRS-T wave localization method in ECG signals based on hybrid neural networks. *Comput Biol Med* 2022; 150: 106110. <https://doi.org/10.1016/j.combiomed.2022.106110>.
 9. Malik M, Bigger TJ, Camm JA, Kleiger RE, Malliani A, Moss AJ, et al. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 1996; 17: 354-381. <https://doi.org/10.1093/oxfordjournals.eurhearti.a014868>.
 10. Cygankiewicz I, Zareba W. Heart rate variability. *Handb Clin Neurol* 2013; 117: 379-393. <https://doi.org/10.1016/B978-0-444-53491-0.00031-6>.
 11. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998; 351(9101): 478-484. [https://doi.org/10.1016/s0140-6736\(97\)11144-8](https://doi.org/10.1016/s0140-6736(97)11144-8).
 12. Moak JP, Goldstein DS, Eldadah BA, Saleem A, Holmes C, Pechnik S, Sharabi Y. Supine low-frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Heart Rhythm* 2007; 4(12): 1523-1529. <https://doi.org/10.1016/j.hrthm.2007.07.019>.
 13. Baumert M, Lambert GW, Dawood T, Lambert EA, Esler MD, McGrane M, et al. Short-term heart rate variability and cardiac norepinephrine spillover in patients with depression and panic disorder. *Am J Physiol Heart Circ Physiol* 2009; 297(2): H674-H679. <https://doi.org/10.1152/aipheart.00236.2009>.
 14. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. *Science* 1981; 213(4504): 220-222. <https://doi.org/10.1126/science.6166045>.
 15. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986; 59(2): 178-193. <https://doi.org/10.1161/01.res.59.2.178>.
 16. Brinza C, Floria M, Covic A, Burlacu A. Measuring heart rate variability in patients admitted with ST-elevation myocardial infarction for the prediction of subsequent cardiovascular events: A systematic review. *Medicina (Kaunas)* 2021; 57(10): 1021. <https://doi.org/10.3390/medicina57101021>.
 17. Nayak SK, Pradhan B, Mohanty B, Sivaraman J, Ray SS, Wawrzyniak J, et al. A review of methods and applications for a heart rate variability analysis. *Algorithms* 2023; 16(9): 433. <https://doi.org/10.3390/a16090433>.
 18. Shiryayeva TP, Fedotov DM, Gribanov AV, Krainova IN, Bagretsov SF, Premina OS. Features of the relationship between postural balance indicators and heart rate variability in elderly women with falls syndrome. *Russ Open Med J* 2024; 13: e0102. <https://doi.org/10.15275/rusomj.2024.0102>.
 19. Kiselev AR, Posnenkova OM, Karavaev AS, Shvartz VA, Novikov MY, Gridnev VI. Frequency-domain features and low-frequency synchronization of photoplethysmographic waveform variability and heart rate variability with increasing severity of cardiovascular diseases. *Biomedicines* 2024; 12(9): 2088. <https://doi.org/10.3390/biomedicines12092088>.
 20. Tomasi J, Zai CC, Pouget JG, Tiwari AK, Kennedy JL. Heart rate variability: Evaluating a potential biomarker of anxiety disorders. *Psychophysiology* 2024; 61(2): e14481. <https://doi.org/10.1111/psyp.14481>.
 21. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: Population-based estimates. *Am J Cardiol* 1998; 82(8A): 2N-9N. [https://doi.org/10.1016/s0002-9149\(98\)00583-9](https://doi.org/10.1016/s0002-9149(98)00583-9).
 22. Wasmund SL, Li JM, Page RL, Joglar JA, Kowal RC, Smith ML, Hamdan MH. Effect of atrial fibrillation and an irregular ventricular response on sympathetic nerve activity in human subjects. *Circulation* 2003; 107(15): 2011-2015. <https://doi.org/10.1161/01.CIR.0000064900.76674.CC>.
 23. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: Pathophysiology and therapy. *Circ Res* 2014; 114(9): 1500-1515. <https://doi.org/10.1161/CIRCRESAHA.114.303772>.
 24. Vandenberk B, Haemers P, Morillo C. The autonomic nervous system in atrial fibrillation-pathophysiology and non-invasive assessment. *Front Cardiovasc Med* 2024; 10: 1327387. <https://doi.org/10.3389/fcvm.2023.1327387>.
 25. Prokhorov MD, Karavaev AS, Ishbulatov YM, Ponomarenko VI, Kiselev AR, Kurths J. Interbeat interval variability versus frequency modulation of heart rate. *Phys Rev E* 2021; 103: 042404. <https://doi.org/10.1103/PhysRevE.103.042404>.
 26. Martínez A, Alcaraz R, Rieta JJ. Study on the P-wave feature time course as early predictors of paroxysmal atrial fibrillation. *Physiol Meas* 2012; 33(12): 1959-1974. <https://doi.org/10.1088/0967-3334/33/12/1959>.
 27. Dilaveris PE, Gialafos JE. P-wave dispersion: A novel predictor of paroxysmal atrial fibrillation. *Ann Noninvasive Electrocardiol* 2001; 6(2): 159-165. <https://doi.org/10.1111/j.1542-474x.2001.tb00101.x>.
 28. Platonov PG. Atrial conduction and atrial fibrillation: What can we learn from surface ECG? *Cardiol J* 2008; 15(5): 402-407. <https://pubmed.ncbi.nlm.nih.gov/18810714>.
 29. Yamada T, Fukunami M, Ohmori M, Kumagai K, Sakai A, Kondoh N, Minamoto T, Hoki N. Characteristics of frequency content of atrial signal-averaged electrocardiograms during sinus rhythm in patients with paroxysmal atrial fibrillation. *J Am Coll Cardiol* 1992; 19(3): 559-563. [https://doi.org/10.1016/s0735-1097\(10\)80273-6](https://doi.org/10.1016/s0735-1097(10)80273-6).
 30. Stafford PJ, Robinson D, Vincent R. Optimal analysis of the signal averaged P wave in patients with paroxysmal atrial fibrillation. *Br Heart J* 1995; 74(4): 413-418. <https://doi.org/10.1136/hrt.74.4.413>.
 31. Hiraki T, Ikeda H, Ohga M, Hamada T, Kubara I, Yoshida T, et al. Frequency- and time-domain analysis of P wave in patients with paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol* 1998; 21(1 Pt 1): 56-64. <https://doi.org/10.1111/j.1540-8159.1998.tb01061.x>.
 32. Alcaraz R, Martínez A, Rieta JJ. The P wave time-frequency variability reflects atrial conduction defects before paroxysmal atrial fibrillation. *Ann Noninvasive Electrocardiol* 2015; 20(5): 433-445. <https://doi.org/10.1111/anec.12240>.
 33. Furlan R, Porta A, Costa F, Tank J, Baker L, Schiavi R, et al. Oscillatory patterns in sympathetic neural discharge and cardiovascular variables

- during orthostatic stimulus. *Circulation* 2000; 101: 886-892. <https://doi.org/10.1161/01.cir.101.8.886>.
34. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991; 84: 482-492. <https://doi.org/10.1161/01.cir.84.2.482>.
 35. Antzelevitch C. Cellular basis for the repolarization waves of the ECG. *Ann N Y Acad Sci* 2006; 1080: 268-281. <https://doi.org/10.1196/annals.1380.021>.
 36. Hanson B, Child N, Van Duijvenboden S, Orini M, Chen Z, Coronel R, et al. Oscillatory behavior of ventricular action potential duration in heart failure patients at respiratory rate and low frequency. *Front Physiol* 2014; 5: 414. <https://doi.org/10.3389/fphys.2014.00414>.
 37. Duijvenboden SV, Porter B, Pueyo E, Sampedro-Puente DA, Fernandez-Bes J, Sidhu B, et al. Complex interaction between low-frequency APD oscillations and beat-to-beat APD variability in humans is governed by the sympathetic nervous system. *Front Physiol* 2019; 10: 1582. <https://doi.org/10.3389/fphys.2019.01582>.
 38. Rizas KD, Nieminen T, Barthel P, Zurn CS, Kahonen M, Viik J, et al. Sympathetic activity-associated periodic repolarization dynamics predict mortality following myocardial infarction. *J Clin Invest* 2014; 124: 1770-1780. <https://doi.org/10.1172/JCI70085>.
 39. Rizas KD, Hamm W, Kaab S, Schmidt G, Bauer A. Periodic repolarisation dynamics: A natural probe of the ventricular response to sympathetic activation. *Arrhythm Electrophysiol Rev* 2016; 5: 31-36. <https://doi.org/10.15420/aer.2015.30.2>.
 40. Ang R, Marina N. Low-frequency oscillations in cardiac sympathetic neuronal activity. *Front Physiol* 2020; 11: 236. <https://doi.org/10.3389/fphys.2020.00236>.
 41. de Chazal P, O'Dwyer M, Reilly RB. Automatic classification of heartbeats using ECG morphology and heartbeat interval features. *IEEE Trans Biomed Eng* 2004; 51(7): 1196-206. <https://doi.org/10.1109/TBME.2004.827359>.
 42. Lin CH, Du YC, Chen YF, Chen TS. Multiple ECG beats recognition in the frequency domain using grey relational analysis. *Conf Proc IEEE Eng Med Biol Soc* 2006; 2006: 2154-2158. <https://doi.org/10.1109/IEMBS.2006.260019>.
 43. Lin CH. Frequency-domain features for ECG beat discrimination using grey relational analysis-based classifier. *Computers & Mathematics with Applications* 2008; 55(4): 680-690. <https://doi.org/10.1016/j.camwa.2007.04.035>.
 44. Singh AK, Krishnan S. ECG signal feature extraction trends in methods and applications. *Biomed Eng Online* 2023; 22(1): 22. <https://doi.org/10.1186/s12938-023-01075-1>.
 45. Accurso V, Shamsuzzaman AS, Somers VK. Rhythms, rhymes, and reasons--spectral oscillations in neural cardiovascular control. *Auton Neurosci* 2001; 90(1-2): 41-46. [https://doi.org/10.1016/S1566-0702\(01\)00266-1](https://doi.org/10.1016/S1566-0702(01)00266-1).
 46. Kiselev AR, Gridnev VI. Oscillatory processes in vegetative regulation of cardiovascular system. *Saratov Journal of Medical Scientific Research* 2011; 7(1): 34-39. <https://www.elibrary.ru/item.asp?id=16909949>.
 47. Glass L. Synchronization and rhythmic processes in physiology. *Nature* 2001; 410(6825): 277-284. <https://doi.org/10.1038/35065745>.
 48. Prokhorov MD, Ponomarenko VI, Gridnev VI, Bodrov MB, Bespyatov AB. Synchronization between main rhythmic processes in the human cardiovascular system. *Phys Rev E Stat Nonlin Soft Matter Phys* 2003; 68(4 Pt 1): 041913. <https://doi.org/10.1103/PhysRevE.68.041913>.
 49. Lecacheur M, Ammerlaan DJM, Dierickx P. Circadian rhythms in cardiovascular (dys)function: approaches for future therapeutics. *npj Cardiovasc Health* 2024; 1: 21. <https://doi.org/10.1038/s44325-024-00024-8>.
 50. Karavaev AS, Prokhorov MD, Ponomarenko VI, Kiselev AR, Gridnev VI, Ruban EI, Bezruchko BP. Synchronization of low-frequency oscillations in the human cardiovascular system. *Chaos* 2009; 19: 033112. <https://doi.org/10.1063/1.3187794>.
 51. Kiselev AR, Karavaev AS, Gridnev VI, Prokhorov MD, Ponomarenko VI, Borovkova EI, et al. Method of estimation of synchronization strength between low-frequency oscillations in heart rate variability and photoplethysmographic waveform variability. *Russ Open Med J* 2016; 5: e0101. <https://doi.org/10.15275/rusomj.2016.0101>.
 52. De Domenico M, Sasai S, Arenas A. Mapping multiplex hubs in human functional brain networks. *Frontiers in Neuroscience* 2016; 10: 326. <https://doi.org/10.3389/fnins.2016.00326>.

Authors:

Anton R. Kiselev – MD, DSc, Professor, Head of Coordinating Center for Fundamental Research, National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia. <http://orcid.org/0000-0003-3967-3950>.

Maksim O. Zhuravlev – PhD, Senior Researcher, Coordinating Center for Fundamental Research, National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia. <https://orcid.org/0000-0002-8620-1609>.

Anastasia E. Runnova – DSc, Leading Researcher, Coordinating Center for Fundamental Research, National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia. <https://orcid.org/0000-0002-2102-164X>.