

I.I. Isayev, I.T. Rasul, M.M. Fataliyeva, R.A. Rzayeva, D.I. Gahramanova¹
Azerbaijan Medical University, Baku, Azerbaijan

¹Azerbaijan State Institute of Advanced Training of Doctors named after A. Aliyev, Baku,
Azerbaijan

DETERMINATION OF VENTRICULAR LATE POTENTIALS IN PERSONS WITH HIGH NORMAL BLOOD PRESSURE

e-mail: mic_amu@mail.ru

Disturbances in the autonomic regulation of the heart are the earliest predictors of complications such as arrhythmia and sudden cardiac death against the background of high normal blood pressure. With the purpose to study the signs of myocardial electrical instability, we registered indicators of high-resolution electrocardiography. According to our results, a statistically significant difference was observed in group with high normal blood pressure for RMS40 and for the TotQRSf/RMS40 index as $p < 0.001$ compared with healthy individuals. Between individuals with high normal blood pressure and patients from group with arterial hypertension there were significant difference for TotQRSf, RMS40 and TotQRSf/RMS40 ($p < 0.001$) and for LAS40 ($p < 0.05$) and statistically significant difference between patients with high normal blood pressure and arterial hypertension for TotQRSf and TotQRSf/RMS40 ($p < 0.001$). Thus, in individuals with high normal blood pressure, electrophysiological heterogeneity is formed in the myocardium due to disturbances in the autonomic regulation of cardiac activity.

Key words: high normal blood pressure, disturbances in the autonomic regulation of the heart, electrical instability of the myocardium, ventricular late potentials, risk of death.

І.І. Ісаєв, І.Т. Расул, М.М. Фаталієва, Р.А. Рзаєва, Д.І. Гахраманова

ВИЯВЛЕННЯ ПІЗНІХ ПОТЕНЦІАЛІВ ШЛУНОЧКІВ У ОСІБ З ВИСОКИМ НОРМАЛЬНИМ АРТЕРІАЛЬНИМ ТИСКОМ

Порушення вегетативної регуляції серця є ранніми предикторами таких ускладнень, як аритмії і раптова серцева смерть на тлі високого нормального артеріального тиску. З метою вивчення ознак електричної нестабільності міокарда реєструвалися показники електрокардіографії високої роздільної здатності. Згідно з отриманими нами результатами, у групі з високим нормальним артеріальним тиском спостерігалася статистично значуща різниця за RMS40 та індексом TotQRSf/RMS40 при $p < 0,001$ порівняно зі здоровими особами. Між особами з високим нормальним артеріальним тиском і пацієнтами з групи з артеріальною гіпертензією спостерігалися статистично значущі відмінності по TotQRSf, RMS40 і TotQRSf/RMS40 ($p < 0,001$) і по LAS40 ($p < 0,05$) і статистично значущі відмінності між пацієнтами з високим/RMS40 ($p < 0,001$). Таким чином, у осіб з високим нормальним артеріальним тиском у міокарді формується електрофізіологічна неоднорідність, що зумовлена порушенням вегетативної регуляції серцевої діяльності.

Ключові слова: високий нормальний артеріальний тиск, порушення вегетативної регуляції серця, електрична нестабільність міокарда, пізні потенціали шлуночків, ризик смерті.

Studies using cardiovascular risk scores, either individually or in combination, have shown that an increase in systolic BP (BPs) to 130–139 or diastolic BP (Bpd) to 85–89 mm Hg is associated with increased cardiovascular risk [6, 10]. The use of high normal blood pressure (HNBP) as an intermediate blood pressure is important because it is associated with a comparable increase in the risk of cardiovascular complications (CVCs) and mortality [12, 13].

Persistent HNBP develops within 5 years into arterial hypertension (AH), which can significantly increase the risk of complications and death. In combination with cardiovascular risk factors (CRF), HNBP is more likely to cause CVCs. In this regard, HNBP is being actively studied by researchers as an independent CRF [3].

The presence of traditional cardiovascular risk factors and the development of hypertension against the background of asymptomatic HNBP are considered predictors of an unfavorable outcome. It has been shown in a number of studies that intermediate pressure leads to subclinical atherosclerosis, target organ damage and increases cardiovascular disease mortality by 66 % compared to normal BP [8, 14]. However, the impact of risk factors (RF) on the formation of organ damage associated with HNBP has not been studied. Functional disorders in the regulation of cardiac activity by the autonomic nervous system (ANS) are the earliest predictive signs of the development of complications. It has been proven that functional and structural changes occur in parallel in patients with HNBP. In many cases, biopotentials occurring in the myocardium precede structural manifestations, and disturbances in depolarization and repolarization processes are observed in various areas of the myocardium. These changes, without clinical manifestations, act as serious RA of inattentive ventricular tachyarrhythmias and in the early stages are characterized only by delayed electrical activity. Heart rate variability and myocardial electrical instability (MEI) act as indicators of these changes. MEI creates the basis for the development of arrhythmogenic mechanisms and

is manifested by the detection of ventricular late potentials (VLP), one of its markers. These are low-voltage (1–20 mV), high-frequency (40–250 Hz) potentials of fragmented electrical activity recorded at the end of the QRS complex or at the beginning of the ST segment. These potentials, called “late depolarization potentials of the myocardium” and creating arrhythmogenic zones, arise in areas of delayed myocardial conduction [9, 11].

Along with various inflammatory, ischemic and sclerotic processes, ventricular late potentials, which occurs as a result of activation of the sympathetic nervous system and the microre-entry mechanism entering the circulation, is recorded using high-resolution electrocardiography (HR-ECG) [4, 7].

Early diagnosis, correction, and secondary prevention of MEI is possible only by accumulating a large amount of evidence about the electrical processes occurring in the myocardium, but there is no information in the available literature about the role of MEI, especially VLP, in individuals with HNBP, therefore, scientific research in this area can be considered relevant.

The purpose of the study was to assess the indicators of high-resolution electrocardiography in individuals with high normal blood pressure.

Materials and methods. The study collected data from 90 people aged 19–59 years. The participants were divided into the following 3 groups:

- 1) main group – individuals with HNBP (n=30);
- 2) comparison group – individuals with grade I AH (n=30);
- 3) control group – individuals with normal BP (n=30).

Inclusion criteria: normal BPs 120–129 mmHg and/or BPd 80–84 mmHg, HNBP: BPs 130–139 mmHg and/or BPd 85–89 mmHg, AH grade I: BPs 140–159 mmHg and/or BPd 90–99 mmHg. It should be noted that the comparison group was purposefully selected and included individuals with AH grade I who had no complaints from the cardiovascular system before our study, were randomly detected and did not receive any treatment.

Exclusion criteria: any complaints related to cardiovascular system; history of syncope; treated grade I AH; grade II–III AH and its complications; sinus bradycardia, sinus tachycardia; heart block and arrhythmias, cardiac conduction system disorders; disorders of electrolyte metabolism; congenital and acquired heart defects; cardiomyopathies; short PQ interval; ischemic heart disease; history of stroke; oncological diseases; severe anemia; diabetes mellitus; metabolic syndrome; thyroid pathology; peripheral arterial disease; chronic kidney disease.

In a prospective study, the following examinations were performed in an outpatient setting:

- clinical examination and RF assessment;
- ECG recording in 12 standard leads;
- high-resolution ECG (HR-ECG).

In these groups, following international recommendations on AH, various risk factors were assessed using a standardized questionnaire, and anamnesis was also collected. Psychosocial (low socioeconomic status, family/work stress, anxiety, depression, social isolation), behavioral (tobacco use, alcohol intake, unhealthy diet, hypodynamia), demographic (gender, age, occupation) RF were evaluated, and the presence of hereditary predisposition to cardiovascular diseases was determined.

During the physical examination, anthropometric parameters (height, weight, waist circumference (WC)) were determined, and body mass index (BMI) was calculated using the Quetelet's equation. Blood pressure was measured twice in all individuals with an interval of 1–4 weeks in accordance with international guidelines on AH. After a 5-minute rest in a sitting position, it was measured first in both arms using an automatic tonometer Omron M3 Comfort (OMRON, Japan), then in the arm with the higher data, it was measured 3 times with an interval of 1 minute between them, and the average values of the last 2 measurements of BPs and BPd were used [10, 13].

HR-ECG registration was performed using a 12-channel “ECGlab” device in X, Y, Z bipolar orthogonal leads according to the Simpson method analogous to the standard ECG V1–V6 unipolar chest leads. According to the instructions, during the examination, in X lead (chest electrodes V5, V6), the electrodes were placed symmetrically in the right and left IV intercostal space along the lin. axillaris media. In Y lead (chest electrodes V3, V4), the V3 electrode was placed under the clavicle along the lin. medioclavicularis sin., and the V4 electrode was placed in the V intercostal space along the lin. medioclavicularis sin. In Z lead (chest electrodes V1, V2), the electrode V2 was in its place as in the standard 12-channel ECG, and the V1 electrode was placed opposite the V3 electrode on the left edge of the spine from behind.

The following parameters of the HR-ECG are determined:

- TotQRSf, ms – duration of the filtered QRS complex;

– LAS40, ms (Under 40 μ V) – duration of the last part of the filtered QRS complex with amplitude less than 40 μ V;

– RMS40, μ V – root mean square voltage of the last 40 ms of the filtered QRS complex.

The values of the analyzed indicators were calculated by an automatic algorithm. The following values were considered criteria for the presence of high normal blood pressure VLP: TotQRSf >114ms; RMS40 <20 μ V; LAS40 >38 ms. If the values of two or three of these indicators differ from the norm, the presence of VLP is confirmed.

In order to characterize the group of units according to the purpose of the research, their mean value (M), its standard error (m) and the variation interval (min-max) were determined. The absolute numbers and its share (%) of the occurrence of quality signs were calculated. To assess the statistical significance of the difference between the indicators, the Mann-Whitney U-test (non-parametric method) was used for groups independent of each other. The statistical significance of the difference between the occurrence of quality signs was determined using non-parametric methods – Pearson's χ^2 criterion or Fisher's exact test. The difference between the indicators was considered statistically significant if $p < 0.05$. Statistical processing of the data was performed in the Microsoft Office Excel spreadsheet using the MedCalc 22.009 statistical software package.

Results of the study and their discussion. The data obtained during the study demonstrated some features of the HR-ECG indicators in the examined patients. Table 1 presents the HR-ECG parameters analyzed in all three groups of subjects under observation in a comparative manner.

Table 1

Values of HR-ECG indicators in individuals with various levels of BP

	Main group	Comparison group	Control group
TotQRSf, ms	93.7 \pm 3.30 [^] (67.0–129.0)	110.6 \pm 2.67** (85.0–136.0)	86.4 \pm 5.29 (53.0–142.0)
RMS40, μ V	43.8 \pm 2.37**	38.7 \pm 1.84**	64.7 \pm 4.34 (40.0–129.0)
LAS40, ms	38.9 \pm 2.72 (17.0–62.0)	42.6 \pm 1.53* (28.0–67.0)	35.1 \pm 1.62 (26.0–60.0)
TotQRSf/RMS40	2.21 \pm 0.06** [^] (1.64–2.77)	2.97 \pm 0.1** (1.88–4.23)	1.35 \pm 0.03 (1.02–1.7)

Note: * $p < 0.05$, compared to healthy individuals, ** $p < 0.001$, compared to healthy individuals, [^] $p < 0.001$, compared to AH group.

Thus, in the group with HNBP, the value of the TotORSf indicator increased by 8.4 %, the LAS40 value increased by an average of 11.0 %, and the RMS40 indicator decreased by 32.3 % compared to the control group. TotQRSf/RMS40 increased by 63.0 % compared to healthy people. A statistically significant difference was observed between the respective groups for RMS40 and for the TotQRSf/RMS40 index as $p < 0.001$.

In patients with grade I AH, the value of the TotQRSf index tended to increase by 28.0 %, the LAS40 value by an average of 21.4 %, and the RMS40 index tended to decrease by 40.2 % compared to the control group. TotQRSf/RMS40 increased by 119.3 % compared to healthy subjects. A statistically significant difference was observed between the groups for TotQRSf, RMS40 and TotQRSf/RMS40 ($p < 0.001$) and for LAS40 ($p < 0.05$).

In the HNBP group, the value of the TotQRSf index was 15.3 % lower, LAS40 was 9.0 % lower on average, TotQRSf/RMS40 was 25.6 % lower, and RMS40 was 13.2 % higher compared to the AH group. A statistically significant difference was observed between these two groups for TotQRSf and TotQRSf/RMS40 ($p < 0.001$).

Patients with high normal blood pressure are vulnerable group that requires special attention due to latent pathological processes which remain clinically undetected for a long time. In recent years, the authors have studied various indicators of cardiac activity that can help in the early diagnosis of complications in people with high normal blood pressure [8, 10].

So, Chen X et al., studying relationship between various categories of blood pressure, subtypes of hypertension, and development of cardiovascular disease, concluded that participants with high-normal BP showed greater wall thickness and left ventricular mass index, larger left ventricle size and larger left atrial size when compared with the optimal-normal BP group. The authors also noted that individuals with high-normal BP had a higher risk of cardiovascular diseases than those with optimal-normal BP [3].

It is known that normal blood vessel structure and function are critical for normal cardiovascular physiology. However, intermediate pressure may negatively affect vascular structure and function. For example, decreased coronary flow reserve and increased aortic stiffness are observed more often in patients

with intermediate pressure compared with those with optimal BP. Coronary atherosclerosis is also more pronounced in these patients, and their coronary flow reserve is impaired. In addition, uncorrected prehypertension is associated with accelerated structural stiffening of large and medium-sized arteries and progressive vascular injury, which may be more pronounced in middle-aged and elderly individuals. We did not study arterial stiffness, but this may be a topic for further researches [14].

Modern advances in neuroscience recognize heart rate variability (HRV) as a reliable indicator for objectively assessing stress, physical and mental health. HRV is considered to have a complex structure consisting of oscillations of several overlapping frequencies that are interrelated in a nonlinear manner. The oscillations are associated with the activity of homeostatic reflexes that help maintain allostatic balance and adapt to environmental demands [2].

There is a large array of scientific data on the proportional increase in sympathetic activity and vagal inhibition during intermediate AH. Prolonged sympathicotonia causes MEI, which, in turn, leads to impaired depolarization and the subsequent formation of VLP [5].

It has been established that sympathetic effects are more activated in men than in women [2]. Since the main group was dominated by men, the high values of the indicators characterizing sympathetic activity on the ECG can be explained by this. According to a number of researchers, excess body weight is an independent predictor of the increase in these values. There is scientific evidence of disturbances in the autonomic regulation of cardiac activity in individuals with high BMI [12, 13]. In the comparison group with hypertension, which participated in our study, the BMI was higher than in the others, and the values of the indicators under consideration were significantly higher in this regard.

Jeong J et al., in their study assessed the clinical utility of high-resolution electrocardiography (signal-averaged electrocardiography, SA-ECG) as a method for risk stratification of fatal arrhythmic event in patients at risk of SCD without specific structural heart disease. According to their results, out of 581 patients, 145 patients with positive SA-ECG showed a higher frequency of major arrhythmic event compared with patients with negative SA-ECG (21.4 % vs. 6.7 %, OR 3.816 [95 % CI 2.208–6.597], $p < 0.001$). Moreover, patients with hereditary arrhythmia had a higher frequency of late potential compared with patients with non-hereditary arrhythmia (51.0 % vs. 19.3 %, $p < 0.001$). The obtained results confirm the usefulness and informativeness of high-resolution electrocardiography, as well as its choice for our study [7].

In our study a positive correlation was observed between the values of the HR-ECG indicators and high anthropometric measurements, unhealthy habits, hypodynamia, and a presence of a relevant family history.

Kaya Y et al., revealed that significant improvement in blood pressure, insulin, insulin resistance were found with DASH (Dietary Approaches to Stop Hypertension) diet and exercise in persons with prehypertension [8]. This provides further evidence of the importance of correcting all risk factors, including unhealthy diet and lifestyle, to prevent the development of serious cardiovascular complications in individuals with HNBP and grade I AH.

According to the 2015 European Society of Cardiology guidelines, a HR-ECG is included in the minimum screening of relatives of victims of sudden cardiac death [1]. The hereditary predisposition to cardiovascular diseases, especially the occurrence of premature death in the family, was found to be high (>60 %) in all three groups. This, in turn, influenced the results.

As can be seen, in our study, the presence of different RF in the participants of the HNBP and AH groups led to the development of MEI in them, and as a manifestation of this, changes in the values of the HR-ECG indicators were determined compared to the control group.

Conclusions

1. A statistically significant difference was observed in group with HNBP for RMS40 and for the TotQRSf/RMS40 index as $p < 0.001$ compared with healthy individuals.
2. Between individuals with HNBP and patients from group with AH there was significant difference for TotQRSf, RMS40 and TotQRSf/RMS40 ($p < 0.001$) and for LAS40 ($p < 0.05$).
3. There are statistically significant difference between patients with HNBP and AH for TotQRSf and TotQRSf/RMS40 ($p < 0.001$).

Thus, in individuals with HNBP, electrophysiological heterogeneity and zones of delayed depolarization are formed in the myocardium due to disturbances in the autonomic regulation of cardiac activity. This, in turn, creates the basis for the occurrence of ventricular tachyarrhythmias against the background of a persistent and long-term increase in the indicators of sympathetic activity of the HR-ECG. The detection of a tendency to the formation of VLP in individuals with HNBP in our study indicates that

the use of HR-ECG in the diagnosis and prediction of fatal arrhythmias is simple, non-invasive and accessible.

References

1. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *European Heart Journal*. 2015; 36: 2793-2867.
2. Calderón-García A, Álvarez-Gallardo E, Belinchón-deMiguel P, Clemente-Suárez VJ. Gender differences in autonomic and psychological stress responses among educators: a heart rate variability and psychological assessment study. *Front. Psychol*. 2024; 15. doi.org/10.3389/fpsyg.2024.1422709.
3. Chen X, Barywani SB, Hansson PO, Rosengren A, Thunström E, Zhong Y, et al. High-normal blood pressure conferred higher risk of cardiovascular disease in a random population sample of 50-year-old men: A 21-year follow-up. *Medicine (Baltimore)*. 2020 Apr;99(17):e19895. doi: 10.1097/MD.00000000000019895.
4. Guaragnella C, Rizzi M, Giorgio A. Marginal Component Analysis of ECG Signals for Beat-to-Beat Detection of Ventricular Late Potentials. *Electronics*. 2019; 8(9):1000. <https://doi.org/10.3390/electronics8091000>.
5. Indumathy J, Pal GK, Pal P, Ananthanarayanan PH, Parija SC, Balachander J, et al. Association of sympathovagal imbalance with obesity indices, and abnormal metabolic biomarkers and cardiovascular parameters. *Obes Res Clin Pract*. 2015 Jan-Feb;9(1):55-66. doi: 10.1016/j.orcp.2014.01.007.
6. Isgandar M, Gurbanov Y, Huseynova N, Mirzazade V. Assessment of cardiovascular risk in type 2 diabetes mellitus with intermediate-range blood pressure. *Azerbaijan Medical Journal*. 2023; 2: 68–72. <https://doi.org/10.34921/amj.2023.2.010>.
7. Jeong J, Choi JI, Kim YG, Choi YY, Min KJ, Roh SY, et al. Late ventricular potential for risk prediction of sudden cardiac death risk: a valuable tool or an unnecessary step? *European Heart Journal*. 2022; 43 (Issue Supplement_2): ehac544.399. doi.org/10.1093/eurheartj/ehac544.399.
8. Kaya Y, Yaman M, Kaya A, Karataş A, Günaydın ZY, Bayramoğlu A, et al. Effects Of Life Style Modifications On Echocardiographic And Biochemical Parameters In Prehypertensive Patients. *Van Med J*. 2016; 23(4): 338-347. doi: 10.5505/vtd.2016.77487.
9. Mirzazade VA, Isayev II, Fataliyeva MM. Features of the bioelectric stability of the myocardium in children of different ages with type 1 diabetes mellitus. *Journal of Metabolism*, 2020; 4 (17): 14-23.
10. Nugroho P, Andrew H, Kohar K, Noor CA, Sutramento AL. Comparison between the world health organization (WHO) and international society of hypertension (ISH) guidelines for hypertension. *Ann Med*. 2022 Dec;54(1):837-845. doi: 10.1080/07853890.2022.2044510.
11. Sultanova LB, Isayev II, Novruzov IH, Mustafayeva AI, Fataliyeva MM. Assessment of late ventricular potentials in young school-age children with type 1 diabetes mellitus. *Modern achievements of Azerbaijani medicine*. 2022; 2: 63-67.
12. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020 Jun;75(6):1334-1357. doi: 10.1161/HYPERTENSIONAHA.120.15026.
13. World Health Organization. Guideline for the pharmacological treatment of hypertension in adults. Geneva: World Health Organization; 2021
14. Zhao L, Meng X, Zhang QY, Dong XQ, Zhou XL. A narrative review of prehypertension and the cardiovascular system: effects and potential pathogenic mechanisms. *Ann Transl Med*. 2021 Jan;9(2):170. doi: 10.21037/atm-20-5482.

Стаття надійшла 15.02.2024 р.