International Heart and Vascular Disease Journal • Volume 9, № 31, September 2021
Journal of the Cardioprogress Foundation

DOI 10.24412/2311-1623-2021-31-14-22

Electrical remodeling and heart rhythm disturbances in patients with primary arterial hypertension

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Abstract

Objective. *frequency of heart rhythm disturbances (HRD) and cardiac electrophysiological parameters depending on the presence of left ventricular hypertrophy (LVH) in patients with primary arterial hypertension (AH).*

Materials and methods. *The study included 157 patients (89 men and 68 women) aged from 43 to 65 years (54.2± 6.3 years) with 1–2 grades of AH. All the patients underwent electrocardiography (ECG), blood pressure (BP) monitoring, diagnostic transesophageal electrical stimulation of the heart, echocardiography, and the assessment of heart rate variability (HRV). According to echocardiography, 64 patients (40.8 %) had LVH (group 1), and 93 patients (59.2 %) — had not (group 2).*

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Results. *Various HRD were identified in 68 patients (43.3 %) — in group 1 in 40 patients (62.5 %), and in group 2 in 28 patients (30.1 %). The most common HRD was atrial fibrillation (12.7 %), supraventricular (13.4 %) and ventricular (11.5 %) extrasystoles, the frequency of which was 3–4 times higher in the 1st group compared with the 2nd group. 15 patients (9.6 %) had asymptomatic paroxysmal supraventricular tachycardia and latent sinus node dysfunction. In both groups, patients with HRD, showed greater P-wave dispersion, and the parameters of atrial effective refractory period (aERP) and vagosympathetic balance SDNN were lower compared with patients without HRD.*

Conclusion. *Thus, the presence of LVH in patients with AH was associated with a high incidence of HRD and cardiac electrical remodeling, which should be considered during cardiac risk stratification.*

Keywords: *arterial hypertension, left ventricular hypertrophy, heart rhythm disturbances.*

Conflict of interest: None declared.

Received: 28.12.2020 **Accepted:** 26.05.2021

Introduction

Primary arterial hypertension (AH) and cardiovascular complications associated with it are still one of the main problems of modern medicine despite significant success that has been achieved in the management of these conditions [1,2]. It has been established that left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular morbidity and mortality that can be at least partially explained by the occurrence of heart rhythm disturbances (HRD) [1,3,4]. It has been shown that the frequency of various HRD in patients with AH reaches 96 % that is 10 times higher compared with normotensive people [5,6]. Moreover, early studies emphasized that HRD in patients with LVH and AH are 10 times more common than in patients without LVH [6,7]. According to epidemiological studies, over 70 % of patients with AH have atrial fibrillation (AF), and 35 % of patients have short and asymptomatic paroxysms of AF [4].

Large number of clinical studies has confirmed the exceptional role of cardiac electrical remodeling in patients with AH without severe morphological changes of the myocardium and coronary vessels [5,8,9]. Is has been established that pathogenetic factors involved in the development and progression of AH, such as autonomic nervous system, neurohumoral, hormonal and electrolyte disturbances, can increase cardiac arrhythmogenic potential [10,11]. The relevance of this issue is also associated with the revision of echocardiographic, diagnostic criteria for LVH in the updated international clinical guidelines for the diagnosis and management of AH [1,8]. Thus, over the past two decades, the threshold values of the left ventricular myocardial mass index (LVMI) for the diagnosis of LVH decreased from 134 g/m^2 to 115 g/m^2 in men and to 95 g/m^2 in women [12]. As the result of the increased sensitivity of the criteria for the diagnosis of LVH, the prevalence of LVH in patients with AH on average increased from 35 % to 50 % [6,12].

It is also important to study the association between the frequency of HRD and markers of arrhythmogenic risk in patients with AH depending on the presence of LVH. It is worth noting that not all the studies confirm the correlation between markers of arrhythmogenic risk and the prevalence and severity of HRD in patients with AH [4,7,9], therefore, further investigations are needed to substantiate the role of cardiac electrical remodeling and arrhythmic syndrome as an unfavorable factor in the cardiac risk stratification.

Objective of the study — to assess the frequency of HRD and cardiac electrophysiological parameters depending on the presence of LVH in patients with primary AH.

Materials and methods

This open clinical trial included 157 patients (89 men and 68 women) aged from 43 to 65 years (mean age 54.2±6.3 years). According to the clinical guidelines "Arterial hypertension in adults" (2020) of the Russian Society of Cardiology [1], 92 patients (58.6 %) had stage I AH and 65 patients (41.4 %) — stage II. According to daily blood pressure level, 74 patients had grade I AH (47.1 %) and 83 patients (52.9 %) — grade II. According to echocardiography, 64 patients (40.8 %) had LVH (group 1), and 93 patients (59.2 %) — had not (group 2). Additionally, 27 patients had type 2 diabetes mellitus (DM) without kidney damage. According to the data of daily blood pressure monitoring in the 1st group the normal dipper pattern was defined in 42 patients

(43.8 %) and in the 2nd group — in 18 patients (29.5 %): χ^2= 3.49 (p= 0.046). It should be noted that all patients received antihypertensive therapy with the achievement of target blood pressure, and the frequency of the prescription of certain classes of antihypertensive medications did not differ significantly between groups.

The study was carried out in accordance with the standards of good clinical practice and the Declaration of Helsinki principles of the World Medical Association. The study protocol was approved by the local Ethical Committee of the Penza Institute for Advanced Medical Studies. Prior to the study written informed consent for participation in the study was waived from all the participants. The study included patients with stable AH of 1–3 grade. The exclusion criteria were: the presence of associated clinical conditions in patients with AH, non-coronary myocardial lesions, valvular heart disease, anemia, and chronic obstructive pulmonary disease.

Structural and functional characteristics of the heart were assessed using Doppler echocardiography on the Acuson X300 apparatus (Siemens-Acuson, Germany) during the sinus rhythm. Left ventricular (LV) end-systolic and end-diastolic volumes, left atrial volume index, LV ejection fraction, cardiac index, LV relative wall thickness and LVMI were calculated. LV diastolic function was assessed by spectral analysis of the diastolic transmitral flow during the sinus rhythm and the maximum speed of rapid and slow LV filling (Ve, Va) and their ratio (Ve / Va), isovolumic relaxation time, and flow deceleration time of rapid LV filling were determined. The criteria for the diagnosis of LVH included: LVMI over 115 g/m^2 in men and over 95 g/m^2 in women [1]. In order to verify the diagnosis some patients underwent various diagnostic imaging methods: chest x-ray, computed tomography and coronary angiography.

Using the method of bifunctional monitoring of ECG and blood pressure for 48 hours (on the Kardiotekhnika-07-AD-3, Russia), we studied daily blood pressure profile, as well as the frequency and possibility of HRD detection, including undocumented ones by conventional ECG at rest that included short episodes and / or asymptomatic paroxysms of tachyarrhythmias and cardiac pauses.

Time and spectral parameters in 5-minute intervals during 24-hour ECG monitoring were analyzed to assess the HRV. The integral indicators of HRV were used: the standard deviation of all normal sinus RR intervals (SDNN) and the ratio of low-frequency and high-frequency power components (LF/HF).

The state of the cardiac conduction system, latent disturbances of heart rhythm and conduction, including "arrhythmogenic readiness" of the atria, were studied by the method of frequent and programmed transesophageal electrical stimulation (TES) of the left atrium using the Astrocard complex (Meditek, Russia). At the same time, the parameters characterizing the state of the cardiac conduction system were determined: sinus node recovery time (SNRT), corrected SNRT (CSNRT), "Wenckebach's point", refractory periods of the atria and atrioventricular junction (RPa, RPav).

The statistical analysis was performed using Statistica 8.0. software. The normality of distribution was assessed using the Shapiro-Wilk test. The significance of differences of the mean values between groups was determined using the Student's t-test. The association between qualitative variables was determined using the Spearman's rank correlation coefficient (R). The Prison χ^2 test was used for the comparison of categorial variables. Data were presented as M± SD. The level of significance was set as p<0.05.

Results

Various HRD were found in 68 patients (43.3 %) — in 40 patients (62.5 %) in group 1, and in 28 patients (30.1 %) — in group 2: χ^2=16.20 (p<0.001) according to standard ECG, daily ECG monitoring and electrophysiological study using TES. At the same time LVH was detected in 24 patients (27.0 %) among patients without HRD, and 40 patients (44.9 %) did not have LVH: χ^2=6.25 (p= 0.013). Evaluation of the diastolic transmitral flow revealed the presence of LV diastolic dysfunction caused by impaired active relaxation of the myocardium in 96 patients (61.2 %), including 55 patients (85.9 %) from the 1st group and 41 patients (44, 1 %) from the 2nd group (p<0.000).

Patients from the 1st group had higher duration of AH and the value of LVMI, and glomerular filtration rate (GFR), calculated using the CKD-EPI formula, was lower compared with the 2nd group (table 1). In addition, patients from the 1st group had higher frequency of metabolic disorders compared with the 2nd group — abdominal obesity (χ^2=3.82, p=0.039) and dyslipidemia (χ^2= 4.19, p=0.031). The frequency of various grades of AH, DM, and the value of GFR did not differ significantly between groups (p>0.05).

The most frequent HRD in patients with AH were: atrial fibrillation, ventricular and supraventricular extrasystoles, as well as various paroxysmal supra-

Table 1. **Clinical characteristics of patients from compared groups (M±SD)**

Parameter	Group 1 (n=64)	Group 2 (n=93)	p
Men, n / %	38/ 59.4	51/ 54.8	is
Age, years	56.3±7.2	54.2±6.9	is
The duration of AH, years	7.6±2.3	6.5±2.1	0.015
1 grade AH, n / %	34 / 53.1	40 / 43.0	is
2 grade AH, n / %	30 / 46.9	53 / 57.0	is
Hereditary burden, n / %	39 / 60.9	47 / 50.5	is
LVMI, г/м^2	119.3±12.4	99.5±9.3	<0.001
Heart rhythm and conduction disturbances, n / %	40 / 62.5	26 / 28.0	<0.001
Type 2 DM, n / %	14 / 21.9	13 / 14.0	is
Chronic kidney disease, n / %	15 / 23.4	17 / 18.3	is
GFR, ml/min/1.73 m^2	65.1±6.3	61.5±7.4	0.026
Abdominal obesity, n/%	22 / 34.4	19 / 20.4	0.039
Body mass index, kg/m^2	28.6±4.5	26.8±4.1	0.003
Dyslipidemia, n / %	28 / 43.8	26 / 28.0	0.031
Smoking, n / %	31 / 48.4	41 / 44.1	is

Is — insignificant

Table 2. **Diagnosis and features of heart rhythm disturbances depending on the presence of LVH in patients with AH**

Types of heart rhythm disturbances	The frequency of heart rhythm disturbances, n / %		
	Group 1 (n=64)	Group 2 (n=93)	Total (n=157)
AF:	13 / 20.3	7 / 7.5	20 / 12.7*
Paroxysmal	8 / 11.0	7 / 7.5	15 / 9.6
Persistent	5 / 7.8	–	5 / 3.2
Paroxysmal atrial flutter	3 / 4.7	2 / 2.2	5 / 3.2
Paroxysmal atrioventricular tachycardia	2 / 3.1	–	2 / 1.3
Paroxysmal atrial tachycardia	2 / 3.1	1 / 1.1	3 / 3.0
Paroxysmal ventricular tachycardia	1 / 1.6	–	1 / 0.6
Ventricular premature beats:	13 / 20.3	5 / 5.4	18 / 11.5*
Single	9 / 14.1	5 / 5.4	14 / 8.9
Paired	4 / 6.2	–	4 / 2.6
Over 500 premature beats per day	7 / 10.9	–	7 / 4.5
Supraventricular premature beats:	10 / 15.6	11 / 11.8	21 / 13.4
Single	5 / 7.8	7 / 6.5	12 / 7.6
Paired	5 / 7.8	4 / 3.2	9 / 5.7
Over 700 premature beats per day	6 / 9.4	3 / 3.2	9 / 5.7
Second-degree atrioventricular block	3 / 4.7	2 / 2.2	5 / 3.2
Second-degree sinoatrial block	2 / 3.1	3 / 3.2	5 / 3.2
Latent sinus node weakness	4 / 6.2	6 / 6.5	10 / 6.4
Complete bundle branch block	9 / 14.1	7 / 7.5	26 / 10.9
Wolff-Parkinson-White syndrome	2 / 3.1	–	2 / 1.3
Combined heart rhythm disturbances	11 / 17.2	5 / 5.4	16 / 10.2*

* –significant differences between groups, p<0.05.

ventricular tachycardias (table 2). At the same time AF and ventricular extrasystoles were 3–4 times more common in patients from group 1 compared with group 2. Sinoatrial (SA) and atrioventricular (AV) conduction disturbances often had latent nature and were mainly detected during electrophysiological investigation and did not depend on the presence of LVH. The combination or alternation of different types of HRD were detected in 16 (24.2 %) out of 66 patients, including 11 patients from group 1 and 5 patients from group 2 (17.2 % versus 5, 4 %, p=0.017). Two patients from group 1 were diagnosed with Wolff-Parkinson-White syndrome.

According to LVMI criteria for the diagnosis of LVH (over 125 g/m^2 in men and over 110 g/m^2 in women), we diagnosed LVH in 49 patients (31.2 %), and among them HRD were detected in 40 patients (81.6 %). These findings can indicate that the use of more "stringent" echocardiographic criteria for LVH is associated with a higher detection rate of HRD: 81.6 % versus 62.5 % (p= 0.021).

The analysis of the associations between HRD and LV diastolic dysfunction in patients with AH showed that HRD are more common in patients with LV diastolic relaxation disturbances, especially paroxysmal AF compared with patients with preserved diastolic function: 17.7 % versus 4.9 % (p=0.019). It has also been shown that the frequency of HRD between patients with hypertrophic LV diastolic dysfunction, when it is combined with LVH, compared with isolated LV diastolic dysfunction does not differ significantly: 74.5 versus 68.3 % (p>0.05). It should be noted that ischemic ST segment depression was not found in the examined patients according to ECG monitoring. At the same time, the maximum ST segment depression in the 1st group was significantly higher compared with 2nd group, regardless of the presence of HRD.

We also analyzed the sensitivity of diagnostic methods in HRD detection. Thus, during the control (planned) ECG at rest, HRD were detected in 39 patients (24.8 %), including 22 patients from group 1 and 14 patients from group 2: 34.4 % versus 15.1 % (χ^2= 8.01; p= 0.004). According to 48-hour ECG monitoring, HRD were detected in 34.4 % of cases, including 20.3 % of patients from group 1 and 5.4 % of patients from group 2: χ^2=4.61 (p=0.032). The TES method revealed unstable and / or asymptomatic paroxysmal supraventricular tachycardias, latent sinus node dysfunction and "ischemic" ventricular extrasystoles in 15 patients (9.6 %). In 12 patients (7.6 %) HRD, espe-

Table 3. **The comparison of cardiac electrophysiological parameters between study groups depending on the presence of HRD in patients with AH (M± SD)**

Parameter	Group 1 (n= 64)		Group 2 (n= 93)	
	Patients with HRD (n=24)	Patients without HRD (n=40)	Patients without HRD (n=65)	Patients with HRD (n=28)
HR, beats/min	70.8±4.2	72.3±4.9	68.3±6.5	73.6±5.0
P-wave dispersion, m/s	42.3±7.4	48.1±5.7*	37.8±5.2†	45.1±6.7*
RPa, m/s	272.3±31.6	256.1±25.0*	292.6±23.5†	263.4±22.5*
SNRT, m/s	1006.4±56.0	1288.0±81.2*	987.2±40.4	1169.6±68.5*§
CSNRT, m/s	254.4±35.8	279.4±65.1*	215.6±27.3†	260.7±31.0*§
Wenckebach's point, imp. / min	141.4±17.5	137.0±21.6	152.3±24.1	148.7±20.3
RPav, m/s	324.7±32.5	318.5±40.6	314.5±42.1	313.5±44.7
SDNN, m/s	66.9±14.1	55.7±15.3*	72.0±13.5	64.1±17.4*§
LF/HF, conventional units	1.2±0.3	1.7±0.4*	1.1±0.2	1.4±0.3*§
Maximum ST segment depression, mm	1.2±0.3	1.2±0.4	0.5±0.2†	0.6±0.2§
Detection of ST segment depression, n /%	8 / 33.3	19 / 47.5	12 / 18.5	6 / 21.4§

* — significant differences between parameters depending on the presence of HRD, p<0.05. † — significant differences between groups of patients without HRD: †<0.05; § — significant differences between groups of patients with HRD; §<0.05.

cially paroxysmal supraventricular tachycardias, debuted or reoccurred during a hypertensive crisis.

The comparative analysis of cardiac electrophysiological parameters showed that SA and AV conduction disturbances are often observed in patients with LVH. In addition, SNRT and CSNRT parameters differed significantly between patients with and without HRD (Table 3). The parameters of anterograde AV-conduction — "Wenckebach's point" and RPa significantly differed between the groups of patients without HRD. It is also remarkable that during the electrophysiological study the values of CSNRT in 10 patients, and the "Wenckebach's point" parameters in 5 patients were "pathological": over 525 m/s and below 110 impulses/min, respectively. The P wave dispersion and RPa that serve as markers of atrial electrical instability, differed significantly between groups of patients with and without HRD. The P wave dispersion in patients without HRD from the 1st group were significantly higher compared with 2nd group (on average by 10.6%; p= 0.013), and the RPa value was significantly lower (on average by 7.5%; p= 0.029).

The spectral parameters of HRV also significantly differed between groups, depending on the presence of HRD. In patients with HRD from group 1 compared with group 2 the SDNN parameter was lower by 13.1% on average (p=0.017), and the LF/HF ratio was higher by 17.7% on average (p<0.001). Difference between groups of patients without HRD was not significant (p>0.05).

Correlation analysis of the HRD development in patients with AH revealed the main correlates that can serve as morphofunctional and electrophysiological markers of arrhythmogenic risk (table 4). It has been shown that the presence of HRD directly correlates with the age of patients, the duration of the disease, LVMI, the maximum LA volume, the P wave dispersion, daily variability of systolic blood pressure (SBP), the LF/HF index and vice versa — with the RPa, Ve/Va and SDNN parameters.

Table 4. **Correlates of heart rhythm disturbances in patients with AH**

Independent variables	Dependent variable — heart rhythm disturbance		
	R	t	p
Men	0.127	1.595	0.113
Age, years	0.321	4.219	< 0.001
The duration of AH, years	0.198	2.509	0.013
P-wave dispersion, m/s	0.190	2.412	0.017
RPa, m/s	– 0.215	– 2.739	0.007
CSNRT, m/s	0.129	1.622	0.107
SDNN, m/s	– 0.192	– 2.433	0.016
LF/HF	0.222	2.839	0.005
LVMI, g/m^2	0.207	0.628	0.01
Left atrial volume index, ml/m^2	0.189	2.399	0.017
LV EF, %	– 0.118	– 1.481	0.141
Ve / Va	– 0.169	– 2.134	0.034
Systolic blood pressure variability, mmHg	0.185	2.348	0.02

Thus, despite the changes in echocardiographic diagnostic criteria for LVH, morphofunctional cardiac remodeling remains a reliable predictor of cardiovascular complications, including the development of prognostically unfavorable cardiac arrhythmias.

Discussion

It is known that morphofunctional cardiac remodeling that leads to transmembrane ion channels impairment is one of the trigger factors of arrhythmogenesis in patients with AH [7, 10, 12]. Therefore, LV diastolic dysfunction, size and function of LV as well as LVH are seem to be the main risk factors of HRD in patients

with AH [11, 13]. AH proved to be strong and independent risk factor for the development of supraventricular and ventricular HRD, the presence and severity of which adversely affects morbidity and mortality, as well as the quality of life of these patients [4, 5, 10]. It has also been proven that the pathogenetic mechanisms of AH development and progression, such as electrolyte disturbances, sympathetic hyperactivity, labile hypertension and episodes of transient myocardial ischemia, contribute to the increase of the cardiac proarrhythmic potential in patients with LVH [4, 11, 14].

The heterogeneity in the results among various studies can be explained by differences in baseline covariates, such as age, gender, coronary insufficiency, DM, systolic dysfunction, etc. Thus, S. Chatterjee et al. (2014) performed the meta-analysis of 10 randomized clinical trials that assessed the relationship between LVH and sustained cardiac arrhythmias in over 27 thousand patients with AH, and found that supraventricular tachycardias in patients with LVH were detected in 11.1% of cases and in patients without LVH — in 1.1% of cases ($p<0.001$), and ventricular arrhythmias — in 5.5 and 1.2% of cases, respectively ($p<0.001$). It has also been shown that the risk of ventricular tachycardia/ventricular fibrillation is 2.8 times higher in patients with hypertensive LVH compared with patients without LVH. However, R. Sultana et al. (2010) showed that various HRD were diagnosed in 90% of cases according to the data of daily ECG monitoring among 500 patients with AH, and they also revealed that the frequency of HRD was higher in women compared with men [6]. It has been shown that the presence of hypertensive LVH also contributes to the progression and the course of existing HRD. Thus, according to data of Ö. Erküner et al. (2018), AF progression, the transformation of paroxysmal AF into persistent and / or permanent form, during 12-months follow-up was observed more often in patients with LVH compared with patients without LVH: 23.3% versus 8.8% ($p= 0.011$) [15].

In patients with AH without complications, various HRD were identified in 43.3% of cases, including 62.5% of patients with LVH and 30.1% of patients without LVH. Paroxysmal supraventricular tachycardias and extrasystoles were prevalent in this category of patients. This can be explained by relatively low LVMI criteria for the diagnosis of LVH compared with previous studies. Therefore, hypertensive LVH is detected relatively more often, when at the same time LVH-associated HRD are rarer. This fact highlights the importance of LVH preventive diagnosis to ensure effective prophylaxis of cardiovascular complications.

Despite the existence of large evidence base according to many clinical studies, paroxysmal tachycardia and heart block associated with systemic AH are still not considered as risk factors in cardiovascular risk stratification [1, 4, 7]. It is known that various biomarkers of myocardial damage, echocardiographic parameters and electrophysiological criteria, such as: P-wave signal averaging, dispersion of the QT interval, HRV, late ventricular potentials, heart rate turbulence, etc., are used to identify electrical instability of the myocardium and the risk of sudden cardiac death in patients with AH. [2, 10].

We have shown that RPa value of less than 240 m/s correlates with the occurrence of paroxysmal AF in patients with AH even without LVH. In addition, an inverse correlation between LV diastolic dysfunction, the Ve/Va index, and the development of paroxysmal supraventricular tachycardias, AF, and atrial extrasystoles was found. This indicates a close relationship between markers of electrical and morphofunctional cardiac remodeling and their role in the occurrence of HRD.

Thus, the results of this study demonstrate that cardiac conduction disturbances and electrical instability of the myocardium are the leading cardiac syndromes in patients with AH, even in those with benign disease course, and/or asymptomatic/ubclinical cardiac lesions. Based on this, the presence of HRD should be considered as a risk factor during cardiac risk stratification in patients with AH, since it has been proven that the occurrence of HRD, including life-threatening tachycardias, can cause cardiovascular complications, including sudden cardiac death.

Conclusion

HRD in patients with benign primary AH are diagnosed in 43.4% of cases, including 62.5% of patients with LVH, and 30.1% of patients without LVH ($p<0.001$). At the same time 18.5% of patients have latent HRD that can be detected only using 24-hour ECG monitoring and/or transesophageal electrical stimulation test.

Revealed correlation between morphofunctional remodeling (presence of LVH and/or LV diastolic dysfunction) with markers of electrical myocardial instability indicates that the new diagnostic criteria for LVMI, which are over 110 g/m^2 in men and over 95 g/m^2 in women, are highly prognostically valuable.

The detection of HRD correlates with the value of LVMI, the presence of LV diastolic dysfunction and

reduced HRV. Electrophysiological parameters of the cardiac conduction system in patients with uncomplicated AH indicate electrical remodeling of the myocardium in patients with and without LVH.

Conflict of interest: None declared.

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