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Association Between Hyperaldosteronemia and Electrophysiological Myocardial Activity in Heart Failure with Preserved Ejection Fraction

Abstract

Background. Sudden cardiac death, one of the most common types of cardiac death, is most often triggered by ventricular arrhythmia. Plasma aldosterone level has been shown to be an independent risk factor of life-threatening ventricular arrhythmia in patients with left ventricular systolic dysfunction following acute myocardial infarction. Whether either effect also occurs in patients with heart failure and preserved ejection fraction is currently unknown. **Purpose.** The study aims to investigate the relationship between plasma aldosterone level and ventricular arrhythmias in long-term heart failure with preserved ejection fraction. **Methods.** A cross-sectional study included 158 patients (58 men and 100 women, mean age 62.3±7.4 years) with heart failure with preserved ejection fraction (> 50%). Patients had no history of primary aldosteronism and did not use the mineralocorticoid receptor antagonists during the last 6 weeks. Aldosterone plasma level was measured and 24-hour electrocardiographic monitoring was performed. **Results.** According to laboratory results 99 patients (62.7%, 95% confidence interval 55.0-70.0%) had normal (40-160 pg/ml) aldosterone plasma level (nAld) and 59 patients (37.3%, 95% CI 30.0-45.0%) had high (> 160 pg/ml) aldosterone level (hAld). hAld patients more often had QTc prolongation (44.1% versus 18.2%) and ventricular arrhythmias (83.1% vs 61.6%) compared to nAld patients (all *Ps* <0.001). The number of ventricular premature complexes in 24 hours were higher in hAld group (median 214, range 64-758) compared to nAld (median 52, range 16-198, P < 0.003). hAld patients more often occurred bigemy, couple ventricular ectopy and nonsustained ventricular tachycardia (39.0% vs 19.0%, p=0.01). In Cox regression model's high aldosterone plasma level was the independent risk factors of QTc prolongation (odds ratio 1.6, 95% confidence interval 1.1-5.7, p=0.034) and prognostically unfavorable ventricular arrhythmias (odds ratio 1.8, 95% confidence interval 1.2-6.8, p=0.024). **Conclusion.** In long-term HFpEF plasma aldosterone level is significantly related to QTc prolongation as well as ventricular arrhythmias.

Key words: *aldosterone, secondary hyperaldosteronisn, heart failure, preserved ejection fraction, arrhythmias, QT interval, sudden cardiac death*

Conflict of interests

The authors declare no conflict of interests

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AF — atrial fibrillation, ALP — atrial late potentials, CHF — chronic heart failure, CI — confidence interval, ECG — electrocardiography, LA — left atrium, LV — left ventricle, pEF — preserved ejection fraction, QTc — corrected QT interval

Chronic heart failure (CHF) is one of the most prognostically unfavorable diseases of the cardiovascular system. EPOCHA epidemiological studies show that CHF prevalence in Russia has doubled over the past decade and a half: from 4.9% in 1998 to 10.2% in 2014 [1]. The overall mortality of patients with CHF, regardless of etiology, stands at 6% a year, and five-year survival is at most 25–38% [2]. In half of the patients with CHF, death is as a result of multiple organ failure due to refractivity to treatment; other patients die suddenly. The risk of sudden death among patients with CHF is five times higher than in the general population; it is mainly caused by ventricular rhythm disturbances [3, 4].

Various structural and electrophysiological changes in the heart are the reason for prognostically unfavorable rhythm disturbances in CHF. The hyperactivity of the renin-angiotensin-aldosterone system, especially its final effector aldosterone, significantly contributes to the genesis of myocardial remodeling. It was demonstrated that aldosterone level in plasma is an independent risk factor for life-threatening ventricular arrhythmias in patients with systolic dysfunction of the left ventricle after acute myocardial infarction [5, 6]. It is unclear whether aldosterone has the same effect in patients with heart failure and preserved ejection fraction (pEF). The role of excessive aldosterone activity in the development and progression of atrial fibrillation has also been reported. However, the relationship between hyperaldosteronism and atrial electrical instability in individuals with CHF-pEF has not been studied [7, 8].

In this regard, the purpose of this study was to assess the relationship between plasma aldosterone level and the electrophysiological characteristic of the myocardium in patients with CHF-pEF.

Materials and Methods

This study was conducted in accordance with international GCP standards (Good Clinical Practice). The study protocol and informed consent form for patients were approved by the Commission on Bioethics at M. Gorky Donetsk National Medical University (minutes of meeting No. 2 from April 22, 2016). Prior to enrollment in the study, all participants gave written informed consent.

The cross-sectional study included 158 patients (58 men and 100 women, mean age 62.3 ± 7.4 years) with stable CHF-pEF, functional class I–III. Diagnosis of CHF-pEF was confirmed based on symptoms and signs of CHF, increased N-terminal pro-B-type natriuretic peptide (NT-proBNP), left ventricular (LV) EF > 50%, and at least one of the following criteria: 1) relevant structural changes of the heart (LV hypertrophy and/or increased volume of the left atrium (LA)); 2) LV diastolic dysfunction according to echocardiography. All patients involved in the study received drug treatment of their underlying diseases in accordance with current recommendations.

The following diseases and conditions were exclusion criteria: taking antagonists of mineralocorticoid receptors six weeks before blood sampling to determine the level of aldosterone; primary hyperaldosteronism; other conditions, except CHF, that are associated with secondary hyperaldosteronism (portal hypertension, cirrhosis, edema syndrome, parenchymal renal lesions, history of renal artery stenosis); acute coronary syndrome and stroke in the previous three months; arterial hypertension (systolic blood pressure ≥ 160 mm Hg); concomitant diseases at the decompensation stage; oncological diseases; pregnancy; alcohol and drug abuse.

Transthoracic echocardiography was performed in M-mode, 2D and Doppler mode using the Aplio MX SSA-780 A cardiac ultrasound system (Toshiba Medical Systems Corporation, Japan) with the patient lying on the left side or back. Examinations were carried out in the left parasternal position along the long and short axes, and in the apical four- and two-chamber views.

LV volume indexed to body surface area, end-diastolic and end-systolic volumes, LVEF, and LV posterior wall thickness and thickness of the interventricular septum in diastole, relative thickness of LV walls and LV myocardial mass index were evaluated. LV hypertrophy was diagnosed with LV myocardial mass index ≥ 115 g/m² in men and ≥ 95 g/m² in women.

LV diastolic function was assessed using pulsed Doppler study of transmitral blood flow and tissue Doppler study of diastolic LV base elevation. The following parameters were determined: maximum rates of early diastolic filling (E) and systolic filling of atria (A), septal and lateral velocity of the mitral valve annulus (e'), indexed volume of the left atrium and maximum rate of tricuspid regurgitation. A patient was diagnosed with LV diastolic dysfunction if he/she had at least three of following symptoms:

- velocity of mitral valve annulus e' (septal e' < 7 cm/s and lateral e' < 10 cm/sec);
- ratio of mitral flow velocity E to the average mitral annulus velocity E/e'_{av} (>14);
- left atrial volume index (>34 ml/sq. m);
- maximum tricuspid regurgitation rate (> 2.8 m/s).

All patients underwent 24-hour ECG monitoring using the Kardiotekhnika 04-3P system (INCART, Russia) with registration of three modified leads close to V_4, V_6 and III standard. Heart rate (HR), corrected QT interval (QTc), the presence of rhythm disturbances, conduction and ischemically significant changes in the ST segment were evaluated. Ischemic changes in the ST segment were considered to be its horizontal or oblique decrease by 1 mm or more, at least 80 ms from the J point, and lasting at least 1 min. The minimum time interval between two episodes of ST depression was considered to be 1 min. During monitoring, patients maintained standard physical activity. They also kept a diary where they recorded the actions performed in the course of the study and changes in their state. Diary data were compared with the recorded ECG.

Analysis of atrial late potentials (ALP) was performed using the Result-2 software module (INCART, Russia). The duration of the filtered P-wave (FiP) and RMS amplitude of its last 20 ms (RMS-20) were evaluated. FiP > 125 ms and RMS-20 < 3.5 μV were considered as criteria for pathological ECG. The presence of both criteria indicated the presence of ALP.

NT-proBNP level was determined using a quantitative immunological test on a Cardiac Reader apparatus (Roche, Germany) using standard kits (Roche Diagnostics). Method sensitivity is 60 pg/ml, quantification range is 60–3,000 pg/ml. The NT-proBNP threshold for CHF diagnosis verification was considered 125 pg/ml.

Serum aldosterone level was determined by enzyme immunoassay using a Multiskan photometer (Thermo Electron, Germany) and DRG test systems (Germany). Blood was sampled in the morning, in fasting state, after a 30-minute rest lying, 2–3 hours after waking up (between 8.00 and 11.00). Hormone level 40–160 pg/ml was considered as the reference value.

Statistical analysis of results was performed on a personal computer using MedStat and Statistica 6.0 software. Arithmetic mean and standard deviation ($m \pm \sigma$) were used to describe parametric features; median and interquartile ranges were used for nonparametric features (Me (IQR)). To compare two samples of continuous variables subject to the normal distribution law, paired and unpaired Student's t-tests were used, while the Wilcoxon test was used for other distribution than normal distribution. To compare qualitative parameters, we used contingency table analysis with the χ^2 criterion. A 95% confidence interval (CI) for parameters was indicated. The relationship between parameters was established using univariate and multivariate regression analyses. Differences were considered significant at $p < 0.05$.

Results and Discussion

Based on the results of measuring blood aldosterone level, all patients were divided into two groups: group 1 included 99 patients (62.7 (95% CI 55.0–70.0)%) with hormone level within normal range; group 2 included 59 patients (37.3 (95% CI 30.0–45.0)%) with hyperaldosteronism. The average aldosterone level in group 1 was 124.2 ± 18.6 pg/ml, in group 2 — 208.6 ± 16.8 pg/ml ($p < 0.0001$). Patients with hyperaldosteronism were younger, had a higher functional class of CHF, were more

likely to suffer from obesity, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, were more likely to have a history of myocardial infarction and impaired renal function (Table 1; this publication contains data from work that was started and published earlier [9]).

Results of daily ECG monitoring revealed that mean HR, number of supraventricular extrasystoles, conduction disturbance episodes, frequency and severity of ischemically significant ST-segment changes did not differ significantly between these groups (Table 2).

Table 1. *Clinical and demographic characteristics of patients*

Parameter	1st group, (n=99)	2nd group, (n=59)	P
Age, years	65,02±7,1	57,75±7,5*	<0,0001
Male	35 (35,4%)	23 (39,0%)	0,775
NYHA class:			
I	10 (10,1%)	4 (6,8%)	0,674
II	56 (56,6%)	18 (30,5%) *	<0,0001
III	33 (33,3%)	37 (62,7%)*	<0,0001
Arterial hypertension	99 (100%)	59 (100%)	1
History of myocardial infarction	41 (41,4%)	35 (59,3%)*	0,044
Atrial fibrillation	17 (17,2%)	20 (33,9%)*	0,027
including permanent form	8 (8,1%)	11 (18,6%)	0,085
Smoking	23 (23,2%)	8 (13,6%)	0,203
Chronic obstructive pulmonary disease	7 (7,1%)	16 (27,1%)*	0,001
Diabetes mellitus	19 (19,2%)	23 (39,0%)*	0,011
Obesity	29 (29,3%)	38 (64,4%)*	<0,0001
Overweight	35 (35,4%)	17 (28,8%)	0,503
Decreased glomerular filtration rate	50 (50,5%)	52 (88,1%)*	<0,0001
History of stroke or transient ischemic attack	13 (13,1%)	7 (11,9%)	0,989

Note: * — differences are significant compared to the 1st group (p <0,05); continuous data are given as the mean and standard deviation (M ± SD); categorical data are presented as the absolute number of patients and their percentage of the patients total number in the group

Table 2. *The results of electrocardiogram daily monitoring*

Parameter	1st group, (n=99)	2nd group, (n=59)	P
The mean heart rate, beats per min	75,6±8,2	76,9±6,4	0,16
Daily number of supraventricular extrasystoles	152 (43; 246)	174 (67; 312) *	0,09
Daily number of ventricular extrasystoles	52 (16; 198)	214 (64; 758) *	<0,0001
Prognostically unfavorable ventricular arrhythmias, n (%)	19 (19,2%)	23 (39,0%) *	0,01
Daily number of sinus pauses	3,5 (2,0; 5,0)	4,0 (2,0; 5,5)	0,20
Total duration of sinus pauses, sec	7,6 (6,6; 10,2)	6,8 (4,9; 11,0)	0,44
Daily number of atrioventricular block episodes	2,0 (2,0; 3,5)	2,0 (1,5; 3,5)	0,6
Total duration of atrioventricular block episodes, sec	3,6 (2,8; 4,9)	4,0 (2,5; 4,8)	0,2
ST segment ischemical changes, n (%)	43 (43,4%)	24 (40,7%)	0,8
Total duration of ST segment depression, min	16,8 (6,3; 26,6)	19,4 (8,7; 36,5)	0,08
QTc prolongation, n (%)	18 (18,2%)	26 (44,1%) *	<0,0001
The presence of late atrial potentials, n (%)	14 (14,1%)	18 (30,5%) *	0,023

Note: * — differences are significant compared to the 1st group (p <0,05); continuous data are given as the median and interquartile intervals (Me (IQR) or as the mean and standard deviation (M ± SD); categorical data are presented as the absolute number of patients and their percentage of the patients total number in the group

Average daily number of premature ventricular complexes was higher in the hyperaldosteronism group (214 (IQR: 64–758) compared with the normal aldosterone group (52 (IQR: 16–198), p < 0.0001). Prognostically unfavorable ventricular arrhythmias were more often registered in patients in group 2 (ventricular extrasystole of high gradations, episodes of unstable ventricular tachycardia — 39% vs. 19%, p = 0.01, χ^2 = 6.44). In addition, patients in group 2 more often had a longer QTc interval compared with group 1 (44.1% vs. 18.2%, <0.0001, χ^2 = 11.07).

The frequency of concomitant atrial fibrillation (AF) was significantly higher among patients with hyperaldosteronism than in patients with normal blood aldosterone level (33.9% vs. 17.2%, respectively, p = 0.027, χ^2 = 4.87). ALP were more often registered in patients of group 2 (30.5% vs. 14.1%, p = 0.023, χ^2 = 5.16).

To find the relationship between plasma aldosterone level and bioelectric parameters of the myocardium, the odds ratio was calculated. All four parameters, i.e., the presence of prognostically unfavorable ventricular rhythm disturbances, ALP, AF and prolonged QTc, demonstrated a relationship with hyperaldosteronism during univariate analysis (Table 3).

After adjusting for gender, age, CHF severity and concomitant pathology, high blood aldosterone was closely associated with the presence of adverse ventricular rhythm disturbances and a prolonged QT interval. The relationship with AF and ALP was lost in the multivariate model (Table 4).

The results of our study showed that in patients with CHF-pEF, high blood aldosterone was closely associated with the deterioration in the electrophysiological properties of the myocardium and was associated with an increased risk of ventricular rhythm disturbances.

Consequences of excessive aldosterone production and activation of mineralocorticoid receptors in relation to the development of serious rhythm disturbances are often underestimated. Nevertheless, the role of aldosterone in the development of electrical instability of the myocardium is obvious and significant.

In 1999, Canadian physicians described a clinical case of the onset of primary aldosteronism in the form of sudden death caused by ventricular fibrillation in a 37-year-old previously apparently healthy woman [10]. After successful cardioversion, severe persistent hypokalemia (1.4 mmol/l) was especially noteworthy. Further examinations revealed increased serum aldosterone and, during imaging, a nodular lesion in the right adrenal gland. This was the first case report of adrenal adenoma manifestation with sudden cardiac death.

Later, in 2009, Israeli clinicians described the onset of adrenocortical carcinoma with ventricular fibrillation [11]. In this case, arrhythmia was caused by severe hypokalemia associated with a malignant aldosterone-secreting tumor.

Table 3. *The relationship between hyperaldosteronemia and bioelectrical parameters of the heart (univariate regression analysis)*

Parameters	Odds ratio (OR) (95% confidence interval (CI))
Prognostically unfavorable ventricular arrhythmias	2,69 (1,30-5,55)
QTc prolongation	3,55 (1,72-7,32)
Late atrial potentials	2,66 (1,21-5,88)
Atrial fibrillation	2,47 (1,16-5,24)

Table 4. *The relationship between hyperaldosteronemia and bioelectrical parameters of the heart (multivariate regression analysis)*

Parameters	Odds ratio (OR) (95% confidence interval (CI))
Prognostically unfavorable ventricular arrhythmias	1,8 (1,2-6,8)
QTc prolongation	1,6 (1,1-5,7)
Late atrial potentials	1,5 (0,9-5,8)
Atrial fibrillation	1,3 (0,9-5,2)

Unexplained persistent hypokalemia after successful resuscitation of the patient, coupled with arterial hypertension, prompted the physicians to examine adrenal glands; adrenocortical cancer was detected. In recent years, such cases are increasingly described in the literature [12].

In the OPERA study, higher blood aldosterone levels in patients with acute myocardial infarction, even within the physiological range, were associated with increased risk of ventricular and supraventricular rhythm disturbances, along with increased risk of recurrent infarction, stroke, CHF and death [6]. Similar data were obtained in similar studies [5]. Improved survival in connection with the use of mineralocortioid receptor antagonists demonstrated in the RALES, EPHESUS, EMPHASIS-HF studies was largely achieved by reducing the risk of sudden cardiac death usually caused by ventricular rhythm disturbances [4].

Today, aldosterone is undoubtedly the most important mediator of the electrical remodeling of the myocardium [13]. Proarrhythmogenic mechanisms of the effect of aldosterone on electrophysiological processes are realized through numerous genomic and non-genomic effects of this hormone: induction of oxidative stress [14], dysfunction of ion channels of cardiomyocytes as a result of overproduction of nuclear factor kB (NF-kB) [15] and calcium overload [16], increased tone of the sympathetic nervous system, decreased heart rate variability, impaired baroreceptor function, changes in electrolyte homeostasis [17].

Structural changes in the myocardium also contribute to the realization of the proarrhythmogenic potential of aldosterone. Stimulation of intense collagen production by aldosterone leads to the disruption of electrical uniformity of the ventricular myocardium, longer conduction time between cardiomyocytes, and creates a morphological substrate for ventricular rhythm disturbances [18].

Some authors report the role of aldosterone in the development of atrial electrical instability. This theory is confirmed by studies conducted by Milliez P. et al. (2005), that demonstrated a multifold increase in the risk of AF in individuals with primary hyperaldosteronism, as well as experimental models of AF [8, 19]. Several studies note that blood aldosterone level increases during AF paroxysm and returns to normal after the restoration of sinus rhythm [20, 21]. Our study revealed no significant relationship between blood aldosterone level and atrial electrical instability in patients with CHF-pEF. Although patients with hyperaldosteronism were more likely to have AF and/or ALP compared to individuals with normal plasma hormone concentrations, the relationship between these parameters was lost in the multivariate model. One of the reasons for such results may be the measurement of blood aldosterone level outside the AF episode when neurohormonal activation is less pronounced.

Conclusions

The role of aldosterone in the induction of electrophysiological disorders in the ventricular myocardium is clear today. Hyperaldosteronism in individuals with CHF-pEF leads to a prolonged QT interval, increased ventricular ectopic activity and can be a reason for the high incidence of sudden cardiac death in this category of patients. Further studies will help determine the advisability of including plasma aldosterone evaluation in the comprehensive assessment of the risk of death in patients with CHF-pEF.

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