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ASSOCIATION OF PLASMA ALDOSTERONE LEVELS IN STAGE II HYPERTENSION PATIENTS WITH INDICATORS OF INSTRUMENTAL RESEARCH METHODS

Abstract. The aim of the study was to determine the associations of plasma aldosterone content in patients with stage II hypertensive disease with the indices of instrumental methods of investigation. A total of 120 patients with stage II hypertensive disease were examined (defined according to the recommendations of the European Society of Hypertension, 2023, as well as the Clinical protocol of primary and specialized medical care for patients with hypertensive disease, 2024) with and without concomitant chronic coronary disease (defined according to invasive coronarography data) and frequent ventricular extrasystole (verified according to Holter electrocardiogram monitoring data). The mean age of the examined patients was $57,3 \pm 0,9$ years. Echocardiography was performed in all patients. Four groups of patients were distinguished (30 in each): the first group – patients with hypertensive disease without concomitant chronic coronary disease and ventricular extrasystole, the second – patients with hypertensive disease and frequent ventricular extrasystole, the third – patients with hypertensive disease and concomitant chronic coronary disease, the fourth – patients with hypertensive disease and concomitant chronic coronary disease and frequent ventricular extrasystole. The aldosterone content in EDTA plasma of blood was determined by enzyme immunoassay using the commercial kit “Aldosterone ELISA” (“DiaMetra”, Italy) in accordance with the manufacturer’s instructions. Statistical analysis of the obtained results was performed using methods of variational statistics with the use of Microsoft Excel (2019) and Statistica 12.0 (Statsoft, USA). Using the method of variational statistics it was found that the plasma aldosterone content in the examined cohort of patients ($n=120$) is in the range of 42,8–285,0 pg/mL, the mean value is $158,1 \pm 55,5$ pg/mL (the median of the index is 152,5 pg/mL, the interquartile range is 116,5 and 204,5 pg/mL). In order to perform analytical comparisons, the aldosterone index was dichotomized according to the median. The rounded value of the median of the marker (153,0 pg/mL) was taken

to distinguish groups with a relatively low (RLL) ($\leq 153,0$ pg/mL) and relatively high content (RHL) ($> 153,0$ pg/mL) of the marker in the general cohort of patients. It was found that a relatively high plasma aldosterone content is associated with a marked increase in cases of chronic coronary disease and cases of verified obstructive chronic coronary disease (occlusion or subocclusion of at least one coronary artery according to coronaroveniculography data). It has been shown that a relatively high plasma aldosterone content is associated with signs of worsening diastolic filling of the left ventricle (an increase in the absolute and relative size of the left atrium and a decrease in the end-diastolic size and end-diastolic volume of the left ventricle) and with an increased frequency of cases of aortic valve calcification.

Keywords: aldosterone, hypertension, echocardiography, chronic coronary disease, premature ventricular contractions, cardiac remodelling

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АСОЦІАЦІЯ ВМІСТУ АЛЬДОСТЕРОНУ В ПЛАЗМІ У ПАЦІЄНТІВ ІЗ ГІПЕРТОНІЧНОЮ ХВОРОБОЮ ІІ СТАДІЇ З ПОКАЗНИКАМИ ІНСТРУМЕНТАЛЬНИХ МЕТОДІВ ДОСЛІДЖЕННЯ

Анотація. Метою роботи було визначити асоціації вмісту альдостерону в плазмі у пацієнтів із гіпертонічною хворобою ІІ стадії із показниками інструментальних методів дослідження. Обстежено 120 пацієнтів із гіпертонічною хворобою ІІ стадії (визначали за рекомендаціями European Society of Hypertension, 2023, а також Клінічним протоколом первинної та спеціалізованої медичної допомоги пацієнтам з гіпертонічною хворобою, 2024) з/та без супутніх хронічної коронарної хвороби (визначеної за даними інвазивної коронар-вен-трикулографії) та частої шлуночкової екстрасистолії (верифікованої за даними холтерівського моніторингу електрокардіограми). Середній вік обстежених хворих становить $57,3 \pm 0,9$ років. Ехокардіографія проведена всім пацієнтам. Виділено чотири групи хворих (по 30 у кожній): перша група – пацієнти із гіпертонічною хворобою без супутніх хронічної коронарної хвороби і шлуночкової екстрасистолії, друга – пацієнти із гіпертонічною хворобою і частою шлуночковою екстрасистолією, третя – пацієнти із гіпертонічною хворобою та супутньою хронічною коронарною хворобою, четверта – пацієнти із гіпертонічною хворобою та супутніми хронічною коронарною хворобою і частою шлуночковою екстрасистолією. Вміст альдостерону в ЕДТА-плазмі крові

визначали імуноферментним методом з використанням комерційного набору «Альдостерон ІФА» («DiaMetra», Італія) відповідно до інструкції фірми-виробника. Статистичний аналіз отриманих результатів проводили за допомогою методів варіаційної статистики з використанням програми Microsoft Excel (2019) і Statistica 12.0 (Statsoft, USA). З використанням методу варіаційної статистики з'ясовано, що вміст альдостерону в плазмі в обстеженій когорті пацієнтів (n=120) знаходиться у діапазоні 42,8-285,0 пг/мл, середнє значення становить $158,1 \pm 55,5$ пг/мл (медіана показника - 152,5 пг/мл, інтерквартильний розмах – 116,5 і 204,5 пг/мл). Щоб проводити аналітичні порівняння показник альдостерону дихотомізовано за медіаною. Округлене значення медіани маркеру (153,0 пг/мл) взято для виділення груп з відносно низьким (ВНВ) ($\leq 153,0$ пг/мл) і відносно високим вмістом (ВВВ) маркеру ($> 153,0$ пг/мл) в загальній когорті пацієнтів. З'ясовано, що відносно високий вміст альдостерону в плазмі асоційований із значним зростанням випадків хронічної коронарної хвороби і випадків верифікованої обструктивної хронічної коронарної хвороби (оклюзія або субоклюзія хоча б однієї коронарної артерії за даними коронарореніографії). Показано, що відносно високий вміст альдостерону в плазмі асоціюється з ознаками погіршення діастолічного наповнення лівого шлуночка (збільшення абсолютного і відносного розміру лівого передсердя і зменшення кінцево-діастолічного розміру і кінцево-діастолічного об'єму лівого шлуночка) та збільшенням частоти випадків кальцифікації аортального клапану.

Ключові слова: альдостерон, гіпертонічна хвороба, ехокардіографія, хронічна коронарна хвороба, шлуночкова екстрасистолія, ремоделювання серця

Statement of the problem. The role of aldosterone and its pathophysiological action in hypertensive disease (HTN) are well known [1]. Epidemiological data show that, in the general population, a higher concentration of aldosterone is associated with higher blood pressure and a higher risk of developing HTN in the future [2].

Excess aldosterone leads to harmful metabolic and pathophysiological reactions and may cause inflammatory, oxidative, and fibrotic changes in the heart, kidneys, and blood vessels [3]. Increased systemic inflammation and subsequent ventricular fibrosis provide substrates for re-entry, promoting the maintenance of electrical instability of the myocardium [4].

The aim of the study is to determine the associations of plasma aldosterone levels in patients with stage II hypertension with indicators of instrumental research methods.

Research objects and methods. The study involved 120 Stage II HTN patients (defined according to the recommendations of the European Society of Hypertension, 2023 [5], as well as the Clinical Protocol for primary and specialized medical care for patients with HTN, 2024 [6]) with/without a diagnosis of concomitant chronic coronary disease (CCD) (defined according to invasive coronaroveniculography data) and frequent premature ventricular contractions (PVC) (verified according to Holter electrocardiogram monitoring data). The mean age of the examined patients is $57,3 \pm 0,9$

years. Echocardiography (EchoCG) was performed in all patients. 4 clinical groups of patients with HTN were distinguished (30 patients in each): 1-st group – HTN patients without concomitant CCD and PVC, 2-nd group – HTN patients with frequent PVC, 3-rd group – HTN patients with concomitant CCD, and 4-th group – HTN patients with concomitant CCD and frequent PVC. The aldosterone content in EDTA plasma of blood was determined by enzyme immunoassay using the commercial kit “Aldosterone ELISA” (DiaMetra, Italy) in accordance with the manufacturer’s instructions. Statistical analysis of the study results was carried out using variational statistics methods using Microsoft Excel (2019) and Statistica 12.0 (Statsoft, USA).

Presentation of the main material.

Research results and their discussion.

Using the method of variational statistics it was found that the plasma aldosterone content in the examined cohort of patients ($n=120$) is in the range of 42,8–285,0 pg/mL, the mean value is $158,1 \pm 55,5$ pg/mL (the median of the index is 152,5 pg/mL, the interquartile range is 116,5 and 204,5 pg/mL). To perform analytical comparisons, the aldosterone index was dichotomized according to the median. The rounded value of the median of the marker (153,0 pg/mL) was taken to distinguish groups with a relatively low level (RLL) ($\leq 153,0$ pg/mL) and relatively high level (RHL) ($> 153,0$ pg/mL) of the marker in the general cohort of patients.

In Fig. 1, an analysis of the frequency of registration of concomitant CCD in patients with HTN depending on the plasma aldosterone content is presented, which shows that the RHL of the index was associated with an increase in the frequency of registration of CCD (66,7 %, $n=40$ versus 33,3 %, $n=20$, $p=0,0003$) and, conversely, the RLL of the factor – with a decrease in the frequency of registration of concomitant CCD in patients with HTN.

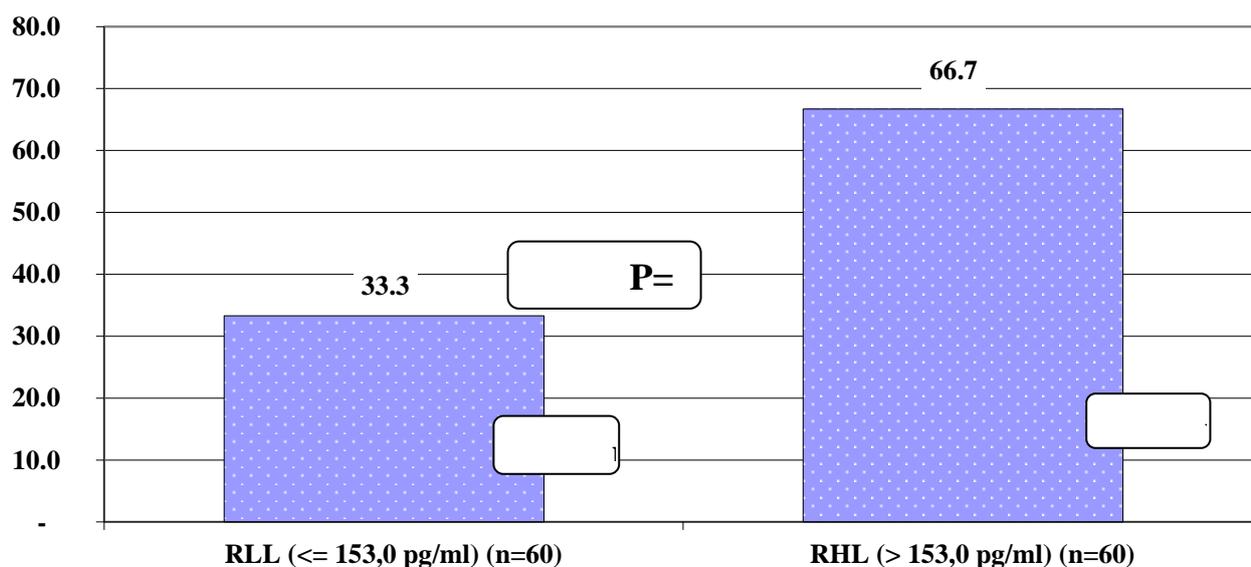


Fig. 1. Frequency of chronic coronary disease in patients with hypertension depending on plasma aldosterone levels (in %).

Notes (here and after): 1. RLL – relatively low and RHL – relatively high plasma aldosterone content, respectively.

2. Statistical difference between groups calculated using the χ^2 test for independent samples.

In Fig. 2, the frequency of verified obstructive CCD (occlusion or subocclusion of at least one coronary artery according to coronaroculography data) in patients with HTN depending on the plasma aldosterone content is analyzed. The obtained results show that the RHL of plasma aldosterone is associated not only with cases of CCD, but also with an increased detection of obstructive CCD in patients with HTN (23,3 %, n=14 versus 56,7 %, n=34, p=0,0002). Thus, our data indicate that an increase in plasma aldosterone content in patients with HTN can be considered not only as a marker of a resistant course of the disease, but also as a marker of clinically significant atherosclerotic vascular lesions, including in the coronary circulation.

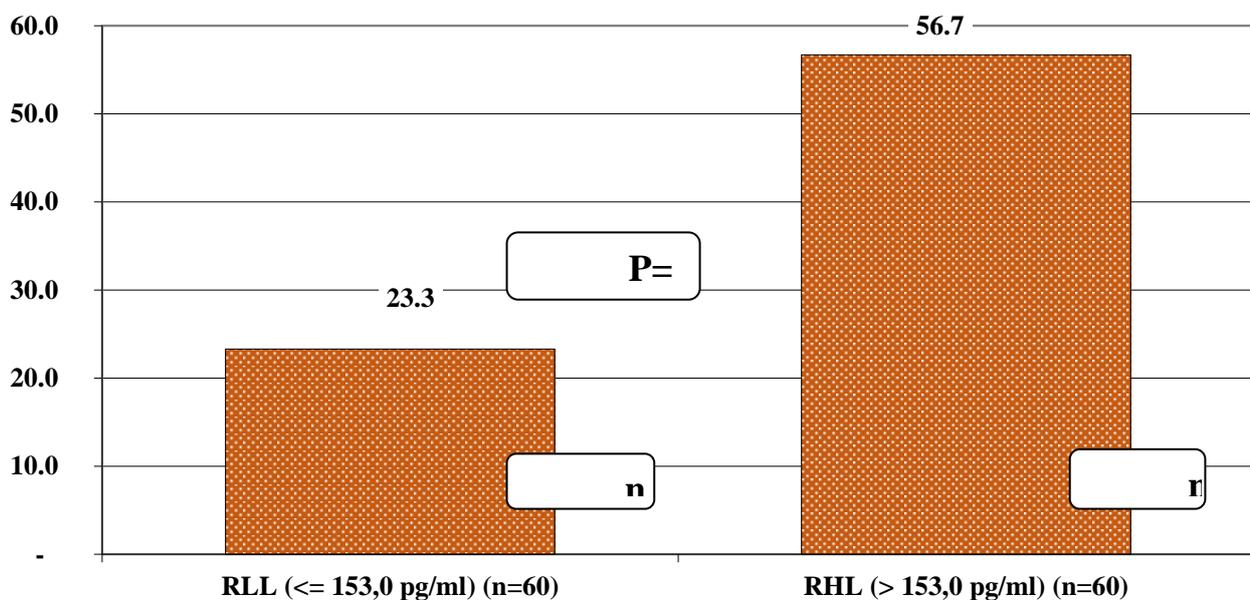


Fig. 2. Frequency of registration of cases of obstructive chronic coronary disease in patients with hypertension depending on the content of aldosterone in plasma (in %).

In Fig. 3, an analysis of the pattern of anatomical lesions of the coronary bed in patients with HTN and concomitant CCD is presented, which showed only a trend towards more severe changes in patients with RHL compared to RLL of plasma aldosterone, which was primarily determined by an increased frequency of registration of multivessel lesions (occlusion or subocclusion of 3 or more coronary arteries) (37,5 % versus 25,0 %, p=0,33).

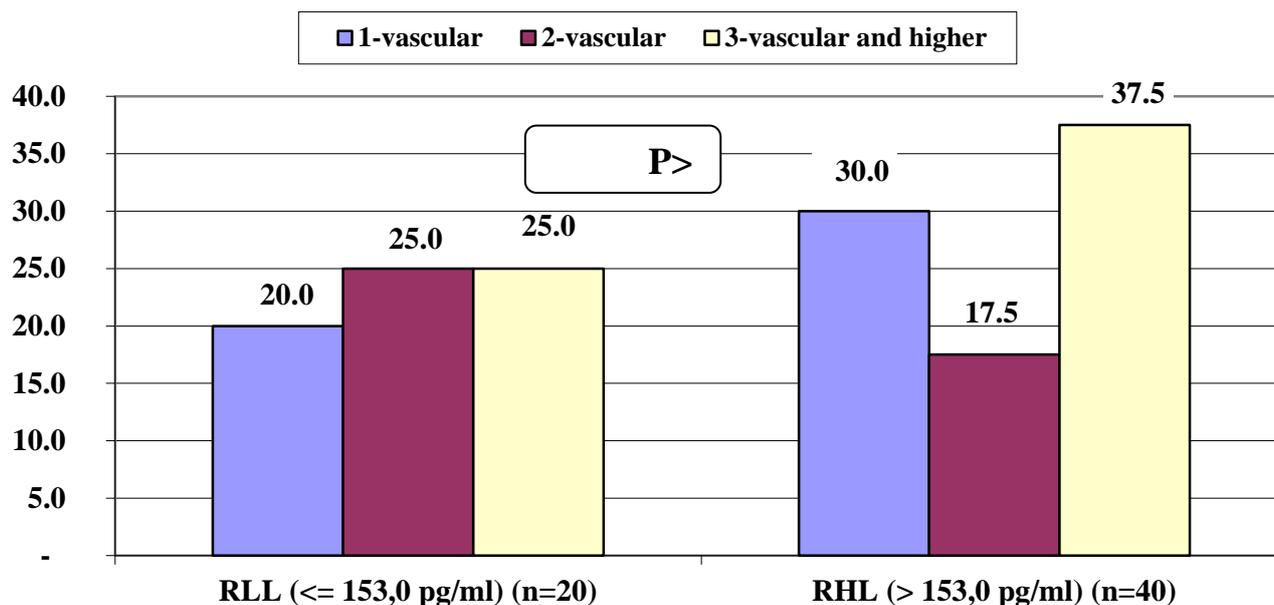


Fig. 3. Frequency of registration of single-, double- and multi-vessel coronary lesions depending on the content of aldosterone in plasma (in %).

In Table 1, the results of the analysis of EchoCG indices depending on plasma aldosterone content are shown. As can be seen from the table, the RHL of the marker is associated with a decrease in the end-diastolic size (EDS) and end-diastolic volume (EDV) of the left ventricle (LV) (50 mm versus 52 mm, $p=0,03$ and 123 versus 130 mL, $p=0,03$, respectively), an increase in the anteroposterior size of the left atrium (LA) (42 versus 40 mm, $p=0,04$), and a decrease in the ratio of aortic diameter to LA (0,82 versus 0,86, $p=0,04$), respectively. There is also a clear trend in patients with RHL of aldosterone towards a decrease in stroke volume (74 versus 78 mL, $p=0,06$) and a decrease in the LA to EDS ratio (0,76 versus 0,78, $p=0,08$), which indicates an increase in the relative size of the LA in these patients.

Table 1

Echocardiographic parameters in patients with hypertension depending on plasma aldosterone content (in pg/ml)

Echocardiography indicators	RLL (<=153 pg/ml) (n=60)	RHL (>153 pg/ml) (n=60)	P
LVEDD, mm	52 (49; 54)	50 (47; 52)	0,03
LVESD, mm	35 (33; 37)	35 (32; 36)	0,49
LVEDV, ml	130 (119; 140)	123 (112; 132)	0,03
LVESV, ml	51 (44; 58)	50 (43; 56)	0,47
SV, ml	78 (70; 82)	74 (67; 78)	0,06
LA AP, mm	40 (38; 43)	42 (39; 44)	0,04
LA AP /LVEDD	0,78 (0,75; 0,82)	0,76 (0,71; 0,80)	0,08
PWTd, mm	12 (11; 12)	12 (11; 12)	0,30

Echocardiography indicators	RLL (≤ 153 pg/ml) (n=60)	RHL (>153 pg/ml) (n=60)	P
IVSTd, mm	12 (12; 13)	12 (12; 13)	0,87
LVMI, g/m ²	120 (115; 136)	118 (115; 132)	0,40
RWT, conditional units	0,46 (0,43; 0,50)	0,46 (0,43; 0,48)	0,67
Ao, mm	34 (32; 36)	34 (32; 37)	0,60
Ao /LA AP	0,86 (0,78; 0,94)	0,82 (0,75; 0,91)	0,04
RV AP, mm	26 (26; 27)	26 (25; 27)	0,54
RV AP /LVEDD	0,50 (0,48; 0,55)	0,51 (0,47; 0,54)	0,97
LVEF, %	61 (56; 64)	58 (56; 63)	0,38
E/A	0,89 (0,75; 1,10)	0,83 (0,74; 1,05)	0,57

Notes: 1. RLL and RHL – relatively low and relatively high aldosterone levels in plasma, LVEDD and LVESD – left ventricular end-diastolic and end-systolic diameters; LVEDV and LVESV – left ventricular end-diastolic and end-systolic volumes of the left ventricle, respectively; SV – stroke volume; LA AP diameter – anteroposterior diameter of the left atrium; PWTd – posterior wall thickness of the left ventricle in diastole; IVSTd – interventricular septal thickness in diastole; LVMI – left ventricular mass index; RWT – relative wall thickness of the left ventricle; Ao diameter – aortic root diameter; RV AP diameter – anteroposterior diameter of the right ventricle; global LVEF (Simpson’s method) – global left ventricular ejection fraction calculated by the biplane Simpson’s method; E/A ratio – ratio of early (E) to late (A) transmitral flow velocity of the anterior mitral leaflet.

2. Intergroup significance of the results between quantitative variables was calculated using the H. B. Mann – D. R. Whitney U test.

Our data indicate that an increase in aldosterone content in patients with HTN is associated with signs of worsening diastolic filling and relaxation of the LV, which is determined primarily by an increase in the absolute and relative size of the LA and a decrease in the EDS and EDV of the LV.

In Fig. 4, an analysis of structural-geometric remodeling of the LV in the general sample of patients depending on plasma aldosterone content is presented. It demonstrates that in both groups concentric LV hypertrophy (LVH) substantially predominated (78,3 % (n=47) and 86,7 % (n=52), p=0,23). Eccentric LVH was recorded in 21,7 % (n=13) and 13,3 % (n=8), respectively, p=0,23. Other variants of LV remodeling were not identified in the examined cohort of patients. The obtained data indicate the absence of a definite dependence of aldosterone content on the type of structural-functional remodeling of the LV.

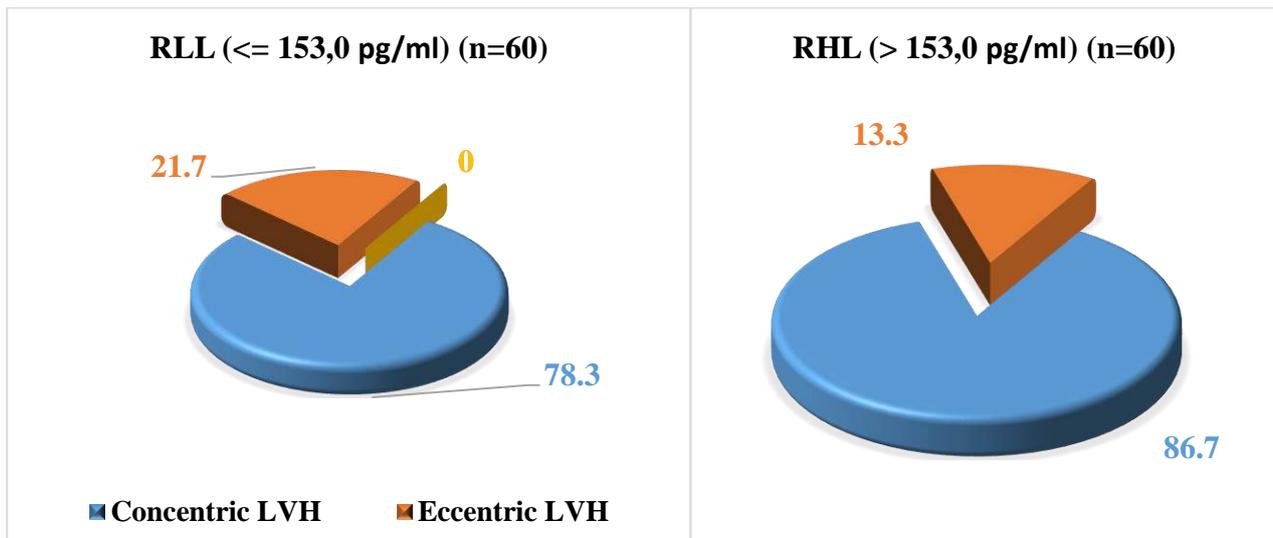


Fig. 4. Frequency of registration of different types of structural and geometric remodeling of the left ventricle depending on the content of aldosterone in plasma (in %).

Notes: 1. LVH – left ventricular hypertrophy, RLL and RHL – relatively low and relatively high aldosterone levels in plasma.

2. The intergroup reliability of the difference % was calculated using the χ^2 criterion for independent samples: $p=0.23$.

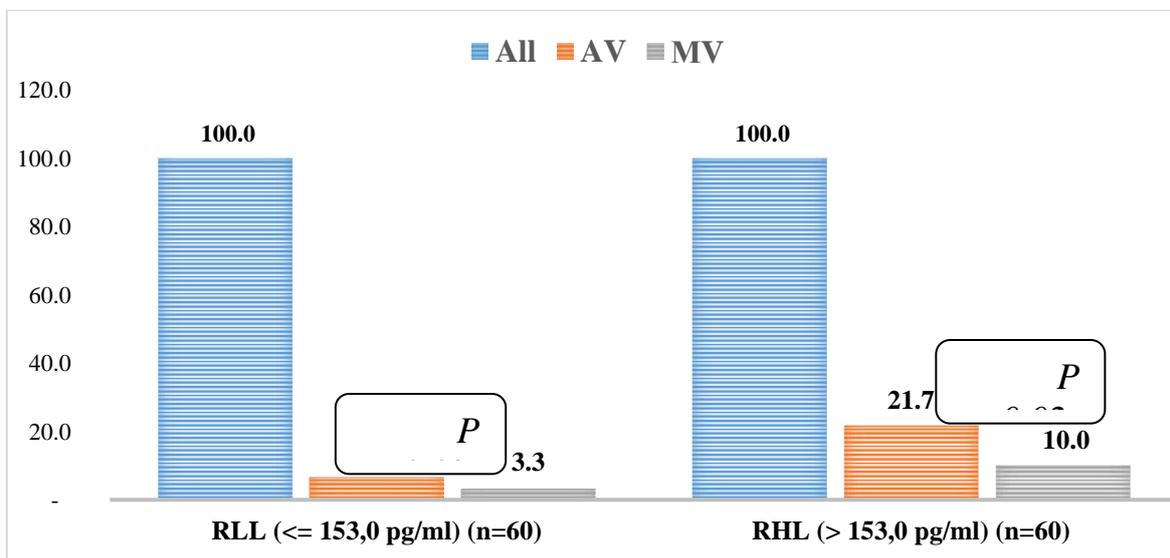


Fig. 5. Frequency of registration of aortic and mitral valve calcification depending on the plasma aldosterone content (in %).

Notes: 1. AV – aortic valve; MV – mitral valve, RLL and RHL – relatively low and relatively high aldosterone levels in plasma.

2. Significant intergroup difference % calculated by the χ^2 criterion for independent samples is indicated.

In Fig. 5, the results of the analysis of the frequency of aortic valve (AV) and mitral valve (MV) calcification in the general cohort of patients with HTN depending on plasma aldosterone content are presented. The obtained data demonstrate that the RHL of the marker is associated with an increased frequency of AV calcification (21,7 % (n=13) versus 6,7 % (n=4), $p=0,02$) and does not show such a dependence with signs of MV calcification (10,0 % (n=6) versus 3,3 % (n=2), $p=0,14$). Therefore, it is reasonable to consider that elevated aldosterone content in patients with HTN can be regarded as a marker of AV calcification and of the subsequent development of its stenosis.

In studies by other researchers, in young and middle-aged patients with Stage II HTN, high aldosterone content was associated with an increase in LA volume indices [7]; in patients with Stage II HTN and frequently recurrent atrial fibrillation, a relatively high aldosterone content was associated with an increased frequency of detection of moderate mitral and tricuspid regurgitation on EchoCG [8].

Conclusions. It was found that RHL of plasma aldosterone is associated with a significant increase in cases of CCD and cases of verified obstructive CCD (occlusion or subocclusion of at least one coronary artery according to coronaroveniculography data).

It was shown that RHL of plasma aldosterone is associated with signs of worsening diastolic filling of the LV (an increase in the absolute and relative size of the LA and a decrease in the EDS and EDV of the LV) and with an increased frequency of cases of AV calcification.

Prospects for further research. In the future, the study of associative relationships between plasma aldosterone levels in patients with stage II HTN and indicators of instrumental research methods will allow for improved diagnostics and, accordingly, treatment aimed at aldosterone, which will improve the prognosis of cardiovascular diseases.

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