DOI 10.26724/2079-8334-2024-1-87-70-74
UDC 616-072.7:616.12-008.331.1:616.12-008.318.4

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APELIN-13 LEVEL, DIASTOLIC DYSFUNCTION, AND CARDIAC REMODELING IN PATIENTS WITH ARTERIAL HYPERTENSION AND EXTRASYSTOLE

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A total of 156 patients with stage II hypertension were examined, of whom 124 had frequent extrasystoles and 32 did not have any heart rhythm disorders. All patients included in the study underwent a complete clinical, laboratory, and instrumental examination, including measurement of serum apelin- 13, determination of diastolic dysfunction, and type of structural and geometric cardiac remodeling. The presence of frequent extrasystoles (both supraventricular and ventricular origin) in patients with stage II hypertension was associated with the presence of diastolic dysfunction, namely, with a deterioration in myocardial relaxation capacity. A significant inverse relationship between the level of serum apelin-13 and the presence of frequent extrasystoles, in particular of ventricular origin, male gender, smoking, and hereditary burden in patients with hypertension was established.

Key words: arterial hypertension, extrasystole, apelin-13, diastolic dysfunction, cardiac remodeling.

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РІВЕНЬ АПЕЛІНУ-13, ДІАСТОЛІЧНА ДИСФУНКЦІЯ ТА РЕМОДЕЛЮВАННЯ СЕРЦЯ У ХВОРИХ НА ГІПЕРТОНІЧНУ ХВОРОБУ І ЕКСТРАСИСТОЛІЮ

Було обстежено 156 хворих з гіпертонічною хворобою II стадії, серед них 124 мали часту екстрасистолію і 32 не мали будь-яких порушень серцевого ритму. Усім включеним у дослідження було проведено повне клініко-лабораторне та інструментальне обстеження, в тому числі вимірювання рівня апеліну-13 сироватки крові, визначення діастолічної дисфункції та типу структурно-геометричного ремоделювання серця. Наявність частої екстрасистолії (як суправентрикулярного, так і шлуночкового топічного варіанту) у хворих на гіпертонічну хворобу II стадії асоціювалось наявністю діастолічної дисфункції, а саме з погіршенням релаксаційних можливостей міокарда. Встановлений достовірний зворотній зв'язок між рівнем апеліну-13 сироватки і наявністю частої екстрасистолії, зокрема шлуночкової, чоловічою статтю, курінням і обтяженою спадковістю у пацієнтів на артеріальну гіпертензію.

Ключові слова: гіпертонічна хвороба, екстрасистолія, апелін-13, діастолічна дисфункція, ремоделювання серця.

The study is a fragment of the research project "Metabolic risk factors, cardiovascular remodeling andfunctional status ofthe kidneys inpatients with cardiovascular disease. Possibilities of pharmacological correction", state registration No. 0119U101849.

To date, there are indisputable reports of the association of left ventricular (LV) diastolic dysfunction with the occurrence of supraventricular extrasystole (SVE) in arterial hypertension (AH). According to some researchers, it is believed that SVE is less characteristic of hypertension and reflects severe diastolic LV dysfunction with the occurrence of mitral regurgitation. In other studies, a positive correlation was found between the frequency of SVE recordings and the time of isovolumetric relaxation and early diastolic blood flow deceleration. An inverse correlation was also observed with the ratios of early and late diastolic LV filling velocities [2, 5].

One of the first reports of ventricular extrasystole (VE) in the setting of high blood pressure and LV hypertrophy was published by Messerli et al. in 1984. It was found that patients with hypertension and ECG signs of LV hypertrophy have a greater number of VEs than those without hypertrophy and hypertension. These data were confirmed in several subsequent studies [6, 7]. To date, the question remains controversial: should we consider VE as a specific marker of malignant arrhythmias or as a marker of disease severity? If we look at it from the point of view that LV hypertrophy in hypertension is the leading factor linking high blood pressure and ventricular arrhythmias, it is logical to consider it as a predictor of VE [1, 6, 10].

To date, a certain relationship between various arrhythmias and hypertension has been proven. In the presence of high blood pressure and LV hypertrophy, the risk of SVE, VE, and sudden arrhythmic death increases significantly. Humoral and structural-functional factors also play an important role in the occurrence and further progression of arrhythmias. To study arrhythmia predictors, there are a large number of noninvasive techniques that have different diagnostic significance and availability. However, this issue is still open today and continues to be studied.

Apelin-13 (AP13) is considered to be one of the metabolic risk markers for cardiovascular complications that continue to be actively studied today. AP13 is known to be the most active form of the apelin protein. Apelin and its receptors (in particular, the G-protein-coupled apelin receptor, the old name – APG receptor) have been found in high concentrations in cardiomyocytes, vascular endothelium, smooth muscle cells, brain, kidneys, and adrenal glands [3, 4]. Apelin receptors regulate numerous biological functions and are involved in cardiovascular and metabolic homeostasis [13, 15].

The biological effects of apelin have been intensively studied over the past decade. Today, it is believed that apelin has a positive effect on the cardiovascular system, as it has effects opposite to the renin-angiotensin system, has hypotensive and positive inotropic effects, and has cardioprotective properties (reduces myocardial ischemia, improves cardiac contractility, and prevents the formation of cardiac hypertrophy) [3, 4, 9, 11]. There is evidence that low levels of apelin contribute to the occurrence of atrial fibrillation and other arrhythmias, including life-threatening ones [12, 13].

The purpose of the study was to evaluate diastolic dysfunction and cardiac remodelling in patients with hypertension and extrasystole and to establish reliable relationships between apelin- 13 and various clinical and instrumental parameters.

Materials and methods. The study included 124 patients with stage II arterial hypertension (AH) and frequent supraventricular (SVE) or ventricular (VE) extrasystoles aged 27 to 75 (mean 58.2±0.9) years, who formed the main clinical population of the study. In addition, we examined 32 patients with stage II AH without any cardiac arrhythmias (excluded by Holter electrocardiogram monitoring (HM ECG)) aged 32 to 72 (mean 55.9±1.7) years, who formed the comparison group in relation to the main clinical population.

All patients underwent a comprehensive clinical, instrumental, and laboratory examination, which included: 1) general clinical and anthropometric examination, blood pressure measurement; 2) ECG in 12 standard leads; 3) HM ECG; 4) echocardiographic examination (EchoCG); 5) determination of apelin-13 (AP13) in serum in pg/ml by enzyme-linked immunosorbent assay using the Human AP13 kit.

The statistical processing of the study results was carried out using the methods of variation statistics using the StatSoft "Statistica" v. 12.0 program according to the recommendations. The results were presented in the form of median and interquartile range with the indication of the 25th and 75th percentiles and in the form of percentages (%), which reflected the frequency of the trait in the sample. A comparison of relative values (%) was performed using criterion χ^2, and Spearman's rank correlation analysis was used to determine the relationship between individual parameters.

Results of the study and their discussion. Signs of diastolic dysfunction were determined according to current recommendations adjusted for patient age. At the same time, we registered echocardiographic signs of diastolic myocardial dysfunction in 75.0 % of patients with stage II AH without arrhythmias, in 91.9 % of patients with frequent SVE and 98 % of patients with AH, that is, only 2 % of patients with AH and 8.1 % of patients with SVR had a normal type of diastolic transmitral blood flow, which was significantly different from patients without arrhythmias, in which there were 25 % of such patients ($p<0.02$). The vast majority of patients in all groups had a rigid type of diastolic transmitral blood flow, with the highest percentage recorded in the group of patients with frequent VE and tended to be more reliable compared with patients without extrasystoles (86 % vs. 68.8 %, $p=0.06$). In turn, a pseudo-normal type of blood flow was recorded in 6.2 % of patients with hypertension without cardiac arrhythmias, in 10.8 % of patients with SVE, and 12.0 % of patients with VE (Fig. 1).

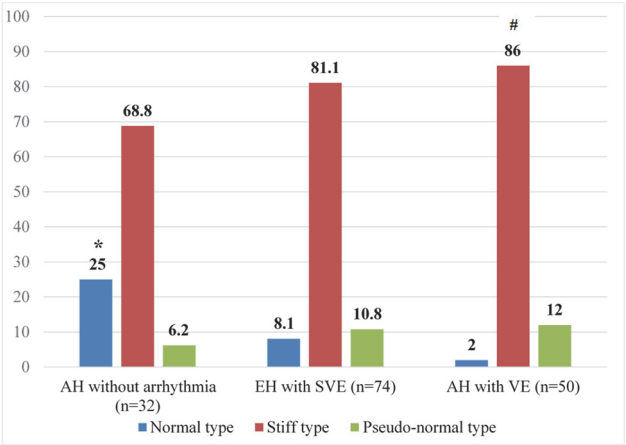

Fig.1. Diastolic transmitral blood flow (distribution in %) in patients with hypertension and various variants of extrasystole. Note: * – a significant difference in percentage compared with patients with AH and SVE and patients with AH and VE ($p=0.02$ and 0.001, respectively) and # – the trend towards significance compared with patients without arrhythmia ($p=0.06$) calculated by the $\chi 2$

In patients with frequent extrasystole, compared with patients without arrhythmias, a significant decrease in the ratio of early-to-late diastolic filling velocity was observed ($p<0.03$), at the same time, the lowest values of the ratio were recorded in patients with ventricular extrasystole, which was significantly different not only from patients without arrhythmias (1.18 vs. 1.45, $p=0.001$) but also from patients with

supraventricular arrhythmia (1.18 vs. 1.34, respectively, p=0.03). These data indicate the presence of more severe impairment of left ventricular myocardial relaxation in patients with stage II AH and frequent extrasystoles (especially ventricular variant).

The analysis of the nature of structural and geometric LV remodeling according to Ganau in different clinical groups showed that concentric LV hypertrophy prevailed in all examined groups of patients (59.4 % in patients with AH without extrasystoles, 54.1 % in patients with AH and SVE, and 60.0 % in patients with AH and frequent V E . At the same time, eccentric LV hypertrophy was recorded in 37.5 % of patients without arrhythmias, in 33.8 % of patients with SVE, and 28 % of patients with VE. Concentric LV remodeling was detected in 5.4 % of patients with supraventricular variant and 4 % of patients with ventricular variant of extrasystole and was not recorded in n o o n e of patients without arrhythmias. The normal type of LV geometry was recorded in 3.1 % of patients with AH without extrasystoles, in 6.8 % of patients with AH and SVE, and 8.0 % of patients with AH and frequent VE. The difference in data in groups of subjects was not statistically significant (p>0.05) (Fig. 2A, 2B, 2C).

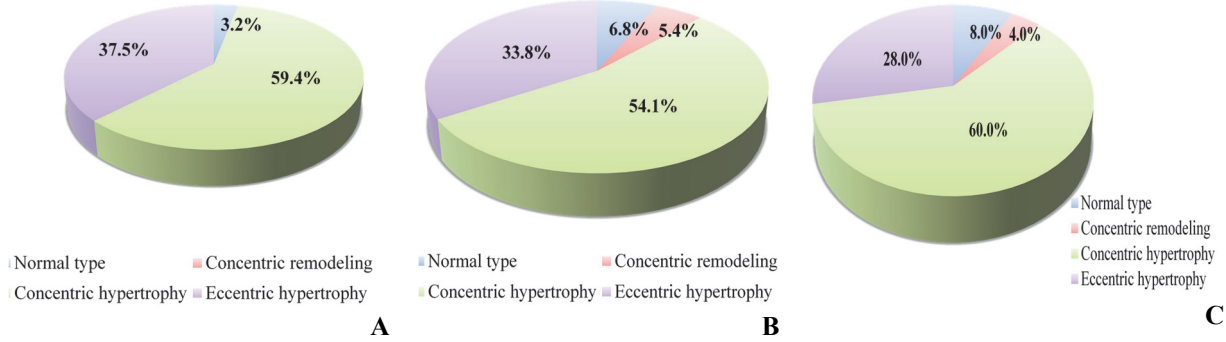

Fig. 2. The nature of structural and geometric remodelling according to Ganau LV (distribution in %) in patients with hypertension: A – without arrhythmias (n=32), B – with SVE (n=74), C – with VE (n=50). Notes: here and further the intergroup difference in percentages was not statistically significant (p>0.05) according to the χ^2

Given our interest in the problem of the association of apelin-13 with cardiac arrhythmias in patients with uncomplicated AH, we performed a Spearman Rank Order Correlations analysis between AP13 and other clinical and instrumental parameters. The results of the rank correlation analysis showed that serum apelin-13 levels showed significant inverse correlations with the presence of frequent VE (r=-0.347; p<0.0001), the total number of VEs per 1 hour of study (r=-0.514; p<0.0001), the presence of paired VEs (r=-0.384; p<0.0001) and the presence of frequent extrasystoles regardless of their topical variant (r=-0.298; p=0.009). Significant inverse correlations were also found between AP13 and male gender (r=-0.193; p=0.02), smoking (r=-0.224; p=0.01), and a burdened heredity for cardiovascular disease (r=-0.169; p=0.04), mean nocturnal SBP (r=-0.224; p=0.009), SBP time index (r=-0.287; p=0.008), LV index (r=-0.254; p=0.009), LA to EDD LV ratio (r=-0.213; p=0.02), normal type of heart geometry according to Ganau (r=-0.324, p=0.0004). At the same time, direct correlations were found between the level of AP13 and the presence of frequent SVE (r=0.276, p=0.01), the total number of SVEs per 1 hour (r=0.417, p<0.0001) (Table 1).

Having assessed the diastolic function and cardiac remodeling according to the EchoCG, it can be said that the presence of frequent extrasystoles (especially ventricular variant) in patients with stage II hypertension is associated with a decrease in the number of patients with a normal type of transmitral blood flow, as well as with a deterioration in myocardial relaxation capacity. It should be noted that the overload of the right and left hearts in patients with hypertension is the pathomorphologic basis for the occurrence of myocardial electrical instability and cardiac arrhythmias. Increased myocardial stress in the setting of hypertension along with excessive afterload stimulates myocardial hypertrophy, its structural remodeling with a disproportionate increase in fibrous tissue, a decrease in coronary blood flow, and the occurrence of myocardial diastolic dysfunction [2, 5, 14]. In addition to high blood pressure, other factors, such as angiotensin, demographic determinants, and genetic polymorphism, play an important role in the occurrence and progression of hypertrophy, as evidenced by the weak correlation between blood pressure and LV myocardial mass [6]. Myocardial hypertrophy leads to impaired myocardial kinetics of Ca2+, Mg2+, Na+, and K+ ions, which contributes to the prolongation of the action potential and is a trigger in the mechanism of re-entry, early postdepolarization, and trigger activity [5, 10]. Along with LV hypertrophy, endothelial vascular dysfunction plays a role in the occurrence of arrhythmias. The presence of both of these factors significantly increases the risk of future cardiac events, including arrhythmias.

Table 1

Association of apelin-13 level with various clinical and instrumental parameters (Spearman's rank correlation)

Clinical and instrumental indices	Spearmen R	p-value
The presence of frequent extrasystoles, points (1 – yes, 0 – no)	-0.298	0.009
Presence of frequent VE, points (1 – yes, 0 – no)	-0.347	<0.0001
Presence of frequent SVE, points (1 – yes, 0 – no)	0.276	0.01
Male gender, points (1 – yes, 0 – no)	-0.193	0.02
Smoking, points (1 – yes, 0 – no)	-0.224	0.01
Burdened heredity for AH, points (1 – yes, 0 – no)	-0.169	0.04
SBPnight, mmHg (by ABPM)	-0.224	0.02
SBP TI, % (by ABPM)	-0.287	0.008
LAI mm/m^2 (by echocardiography)	-0.254	0.009
LA/EDD (by echocardiography)	-0.213	0.02
The normal type of LV geometry according to Ganau, points (1 – yes, 0 – no) (by echocardiography)	-0.324	0.0004
Total number of SVEs per 1 hour (according to the HM ECG)	0.417	<0.0001
Total number of VE per 1 hour (according to HM ECG)	-0.514	<0.0001
Presence of paired VE, points (1 – yes, 0 – no) (according to the HM ECG)	-0.384	<0.0001

Notes. VE – ventricular extrasystole, SVE – supraventricular extrasystole, HT – hypertension, SBP night – mean nighttime systolic blood pressure, SBP TI – systolic blood pressure time index, ABPM – automatic blood pressure monitoring, EDD – end-diastolic dimension, LV – left ventricle, HM ECG – Holter monitoring of ECG

Hypertension and extrasystole (especially ventricular variant) are known to lead to cardiac remodeling and dysfunction. It is known that cardiac remodeling is accompanied by certain inflammatory changes (apoptosis, atrial fibrosis, impaired calcium transport, and regulation of connexin, etc.). Our data to some extent coincide with the results of other researchers on the inherent antihypertensive and antiarrhythmic properties of apelin-13, which are associated with the functioning of the apelin-APJ receptor system, which has effects opposite to the renin-angiotensin system, as well as with the vasodilatory effect of nitric oxide, which is one of the main mediators of the protective effect of apelin-13 [8, 12, 13].

Conclusions

1. Frequent extrasystoles (regardless of their topical variant) in patients with stage II AH are associated with impaired diastolic function of the heart, namely, with deterioration of myocardial relaxation capacity.

2. The presence of frequent VE in patients with stage II AH is associated not only with a deterioration in myocardial relaxation capacity but also with a decrease in the frequency of normal transmitral blood flow.

3. We found no direct association between Apelin 13 levels and diastolic cardiac function, but a significant inverse relationship between serum Apelin 13 levels and normal LV geometry according to Ganau, the presence of frequent extrasystoles, in particular ventricular, SBPnight and SBPIR, male gender, smoking, and a burdened heredity in patients with hypertension.

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Стаття надійшла 4.03.2023 р.

DOI 10.26724/2079-8334-2024-1-87-74-79
UDC 618.145-007.415-091.8-078.33

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MECHANISMS OF ENDOMETRIAL HYPERPLASIA DEVELOPMENT IN WOMEN OF REPRODUCTIVE AGE

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Data from studies of 88 women were examined during a diagnostic endometrial biopsy for abnormal uterine bleeding or increased endometrial thickness. The patients were between 40 and 55 and divided into the main and control groups. A high expression of estrogen-α receptors and a low expression of progesterone hormones were found, indicating proteins' pro-oncogenicity in patients with complex endometrial hyperplasia. Pathogenetic mechanisms of endometrial hyperplasia were factors of proliferation and apoptosis, which is confirmed by a significant increase in the proliferation marker Ki67 of epithelial cells in complex endometrial hyperplasia in endometrial biopsies and a decrease in the apoptosis marker p53. A differentiated approach to diagnosing endometrial hyperplasia is based on the determination of molecular markers (Ki67, p53), which allows one to predict the course of the hyperplastic process and assess the effectiveness of the treatment.

Key words: endometrial hyperplasia, morphological features, hormonal status, therapeutic tactics, expression of estrogen and progesterone receptors, molecular markers.

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МЕХАНІЗМИ РОЗВИТКУ ГІПЕРПЛАЗІЇ ЕНДОМЕТРІЮ У ЖІНОК РЕПРОДУКТИВНОГО ВІКУ

Проаналізовано дані досліджень 88 жінок у яких під час діагностичної біопсії ендометрію з приводу аномальних маткових кровотеч або збільшення товщини ендометрію було визначено його структуру. Пацієнтки знаходились у віці від 40 до 55 років та були розподілені на основну та контрольну групи. Було встановлено високу експресію рецепторів естрогену-α та низьку до прогестеронових гормонів, що свідчить про проонкогенність білків у пацієнток зі складної гіперплазією ендометрію. Патогенетичними механізмами гіперплазії ендометрію були фактори проліферації і апоптозу, що підтверджується достовірним підвищенням маркера проліферації Ki67 клітин епітелію при складній гіперплазії ендометрію в біоптатах ендометрію, а також зниженням маркера апоптозу p53. Диференційований підхід до діагностики гіперплазії ендометрію заснований на визначенні молекулярних маркерів (Ki67, p53) дає змогу не тільки прогнозувати перебіг гіперпластичного процесу, а й оцінити ефективність проведеного лікування.

Ключові слова: гіперплазія ендометрію, морфологічні особливості, гормональний статус, лікувальна тактика, експресія рецепторів естрогену і прогестерону, молекулярні маркери.

The study is a fragment of the research project "Optimization of clinical, diagnostic and therapeutic approaches to the management of gynecological patients taking into account age and the presence of extragenital pathology", state registration No. 0122U000257.

Endometrial hyperplastic processes (EHP) are one of the essential problems of gynecology, which consists of pathological changes in the uterine mucosa and becomes the background for the development of malignant processes [7]. The endometrium is a hormone-sensitive tissue that is capable of cyclic renewal of the cellular composition in response to the hormonal influence of sex hormones and is also sensitive to the action of estrogens, which cause proliferative changes in progesterone and lead to the development of hyperplasia [1].

Regulators of proliferation and apoptosis are essential in the pathogenesis of endometrial hyperplasia (EH) development. Determining markers of programmed cell death disruption in EHP