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ASSOCIATION OF PLASMA TRANSFORMING GROWTH FACTOR-B1 LEVELS IN STAGE II HYPERTENSION PATIENTS WITH INDICATORS OF INSTRUMENTAL RESEARCH METHODS

Abstract. The aim of the study was to determine the associations between the plasma level of transforming growth factor-β1 (TGF-β1) in patients with stage II hypertension and parameters obtained by instrumental diagnostic methods. A total of 120 patients with stage II hypertension, with and/or without concomitant chronic coronary artery disease and frequent ventricular premature beats, were examined. All participants underwent echocardiography, and cardiac rhythm disturbances were assessed using Holter electrocardiographic monitoring. Chronic coronary artery disease was diagnosed using stress testing and/or coronary ventriculography. Four patient groups were distinguished: Group 1 (n = 30) – stage II hypertension without concomitant chronic coronary artery disease or frequent ventricular premature beats; Group 2 (n = 30) – stage II hypertension with concomitant frequent ventricular premature beats; Group 3 (n = 30) – stage II hypertension with concomitant chronic coronary artery disease; Group 4 (n = 30) – stage II hypertension with concomitant chronic coronary artery disease and frequent ventricular premature beats. The serum TGF-β1 level was measured by enzyme-linked immunosorbent assay using the commercial Human TGF-β1 (Transforming Growth Factor Beta 1) ELISA Kit (Elabscience Biotechnology Inc., USA). The median value (222 pg/mL) was used to define groups with relatively low (≤222 pg/mL) and relatively high (>222 pg/mL) marker levels. The results were analyzed using methods of variation statistics with Microsoft Excel (2019) and Statistica 12.0 (StatSoft, USA). It was found that a high plasma TGF-β1 level was associated with an increased mean nocturnal heart rate and a decreased circadian index, a significant increase in the number of cases and the daily count of recorded supraventricular premature beats, an increase in the number of cases and the daily and hourly counts of frequent ventricular premature beats, an increased number of cases of polytopic ventricular premature beats, and episodes of non-sustained ventricular tachycardia according to Holter monitoring. A marker level >222 pg/mL was associated with a higher prevalence of concomitant chronic coronary artery disease and obstructive chronic coronary artery disease, as well as a trend toward more severe coronary artery lesions based on coronary ventriculography. It was also demonstrated that a TGF-β1 level >222 pg/mL was associated with a reduced relative

wall thickness of the left ventricle, a significant decrease in the frequency of concentric left ventricular hypertrophy and an increase in eccentric left ventricular hypertrophy, as well as an increased frequency of instrumentally detected aortic valve calcification on echocardiography.

Keywords: transforming growth factor-β1, hypertension, echocardiography, chronic coronary disease, ventricular premature beats, cardiac remodelling

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АСОЦІАЦІЯ ВМІСТУ ТРАНСФОРМУЮЧОГО ФАКТОРУ РОСТУ-В1 В ПЛАЗМІ У ПАЦІЄНТІВ ІЗ ГІПЕРТОНІЧНОЮ ХВОРОБОЮ ІІ СТАДІЇ З ПОКАЗНИКАМИ ІНСТРУМЕНТАЛЬНИХ МЕТОДІВ ДОСЛІДЖЕННЯ

Анотація. Метою роботи було визначити асоціації вмісту трансформуючого фактору росту-β1в плазмі у пацієнтів із гіпертонічною хворобою ІІ стадії із показниками інструментальних методів дослідження. Обстежено 120 пацієнтів із гіпертонічною хворобою ІІ стадії з та/без супутніх хронічної коронарної хвороби та частою шлуночковою екстрасистолією. Обстеженим проведена ехокардіографія та визначено порушення ритму серця з використанням холтерівського моніторування електрокардіограми. Хронічну коронарну хворобу визначено за допомогою стрес-тестів і/або коронаровентрикулографії. Виділено 4 групи пацієнтів: 1 група, n=30 – із гіпертонічною хворобою ІІ стадії без супутніх хронічної коронарної хвороби та частої шлуночковоїекрасистолії; 2 група, n=30 – пацієнти із гіпертонічною хоробоюІІ стадії та супутньою частою шлуночковою екстрасистолією; 3 група, n=30 – пацієнти із гіпертонічною хворобою ІІ стадії та супутньою хронічною коронарною хворобою; 4 група, n=30 – пацієнти із гіпертонічною хворобою ІІ стадії та супутніми хронічною коронарною хворобою та частою шлуночковою екстрасистолією. Вміст трансформуючого фактору росту-β1 в сироватці кровівизначали імуноферментним методом з використанням комерційного набору «HumanTGF-β1 (Transforming Growth Factor Beta 1) ELISAKit» («Elabscience Biotechnology Inc.», США). Медіану показника (222 пг/мл) використано для виділення груп з відносно малим (≤222 пг/мл) і відносно великим вмістом маркеру (>222 пг/мл). Оцінку отриманих результатів зроблено за допомогою методів варіаційної статистики з використанням програми Microsoft Excel (2019) і Statistica 12.0 (Statsoft, USA). Визначено, що високий вміст трансформуючого фактору росту-β1 у плазмі асоційованийіз зростанням величини середньо-нічної частоти серцевих скорочень і зменшенням величини циркадного індексу, із значним зростанням випадків і добовою кількістю

зареєстрованої надшлуночкової екстрасистолії, зростанням випадків, добової і годинної кількості частої шлуночкової екрасистолії, збільшенням випадків політропної шлуночкової екстрасисолії та епізодів нестійкої шлуночкової тахікардії за даними холтерівського моніторування кардіограми. Встановлено, що рівень маркеру >222 пг/мл асоційований зі зростанням частоти визначеної супутньої хронічної коронарної хвороби, та обструктивної хронічної коронарної хвороби, а також тенденцією до більш тяжких уражень коронарних артерій за даними коронаровентрикулографії. Доведено, що рівень ТФР-β1 >222 пг/мл асоційований зі зменшенням величини відносної товщини стінки лівого шлуночка, значним зменшенням випадків концентричної гіпертрофії лівого шлуночка і збільшенням ексцентричної гіпертрофії лівого шлуночка, а також збільшенням випадків з інструментально визначеним кальцинозом аортального клапану за даними ехокардіографії.

Ключові слова: трансформуючий фактор росту-β1, гіпертонічна хвороба, ехокардіографія, хронічна коронарна хвороба, шлуночкова екстрасистолія, ремоделювання серця

Statement of the problem. Myocardial fibrosis develops in many cardiovascular diseases and is associated with an increased risk of ventricular tachycardia (VT) and ventricular fibrillation. Transforming growth factor-β1 (TGF-β1) has been shown to promote myocardial fibrosis [1].

TGF-β1 mediates angiotensin II–induced cardiac hypertrophy [2]; therefore, TGF-β1 is closely linked to the pathogenesis of hypertensive target-organ damage [3].

There are many conflicting views regarding the role of TGF-β1 in the development of proarrhythmogenic effects in cardiovascular diseases. This study aims to determine whether the plasma level of TGF-β1 is associated with changes in instrumental parameters in individuals with stage II hypertension and concomitant chronic coronary artery disease (CCAD) and frequent ventricular premature beats (VPBs).

The aim of the study is to determine the associations of plasmatransforming growth factor-β1levels in patients with stage II hypertension with indicators of instrumental research methods.

Researchobjectsandmethods.A total of 120 patients with stage II hypertension (HTN) [4, 5], with and/or without concomitant chronic coronary artery disease (CCAD) and frequent ventricular premature beats (VPBs), were examined. The mean age of the participants was 57.3±0.9 years. All patients underwent echocardiography (EchoCG), and cardiac rhythm disturbances were assessed using Holter electrocardiographic monitoring [6]. CCAD was diagnosed using stress testing and/or coronary ventriculography (CVG) [7, 8]. Four patient groups were identified: Group 1 (n=30) – stage II HTN without concomitant CCAD or frequent VPBs; Group 2 (n=30) – stage II HTN with concomitant frequent VPBs; Group 3 (n=30) – stage II HTN with concomitant CCAD; Group 4 (n=30) – stage II HTN with concomitant CCAD and frequent VPBs.

Serum TGF-β1 levels were measured by enzyme-linked immunosorbent assay using the commercial Human TGF-β1 (Transforming Growth Factor Beta 1) ELISA Kit (Elabscience Biotechnology Inc., USA) in accordance with the manufacturer's instructions. The obtained results were evaluated using methods of variation statistics with Microsoft Excel (2019) and Statistica 12.0 (StatSoft, USA).

Presentation of the main material.

Research results and their discussion.

Using methods of variation statistics, it was determined that the plasma TGF-β1 level in the patient cohort (n=120) ranged from 70.6 to 489.0 pg/mL (mean value, 238.3±97.2 pg/mL). The results are presented as the median (222.0 pg/mL) and the interquartile rangethe 25th and 75th percentiles (165.5 and 303.0 pg/mL). Comparisons were performed using nonparametric statistical methods. The median value was used to define groups with a relatively low (≤222 pg/mL) and a relatively high (>222 pg/mL) TGF-β1 level in the overall patient cohort (hereafter, the low-level and high-level groups, respectively).

Figure 1 shows that a high plasma TGF-β1 level, compared with a low marker level, was associated with a higher prevalence of verified concomitant CCAD (69.5% vs 31.1%, p<0.0001), and vice versa.

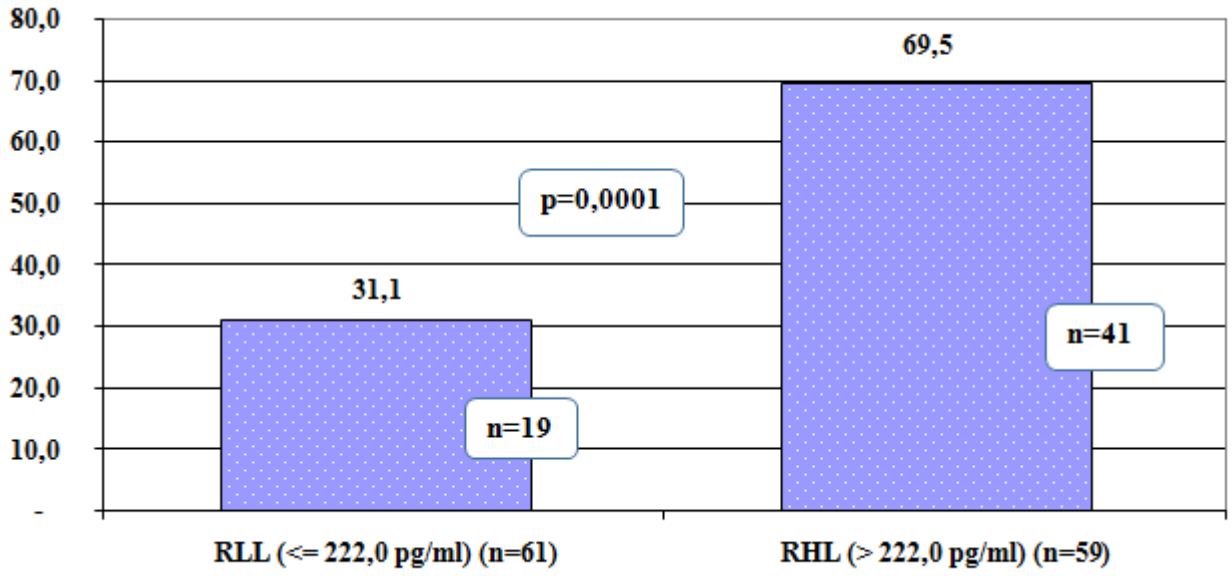

Fig. 1. Frequency of chronic coronary artery disease in patients with hypertension depending on plasma transforming growth factor-β1 levels (in %).

Notes (here and after): 1.RLL – relatively low and RHL – relatively high plasma transforming growth factor-β1 content, respectively.

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

Figure 2 shows that a high plasma TGF-β1 level, compared with a low marker level, is associated with the frequency of obstructive chronic coronary artery disease as determined by coronary ventriculography (CVG).

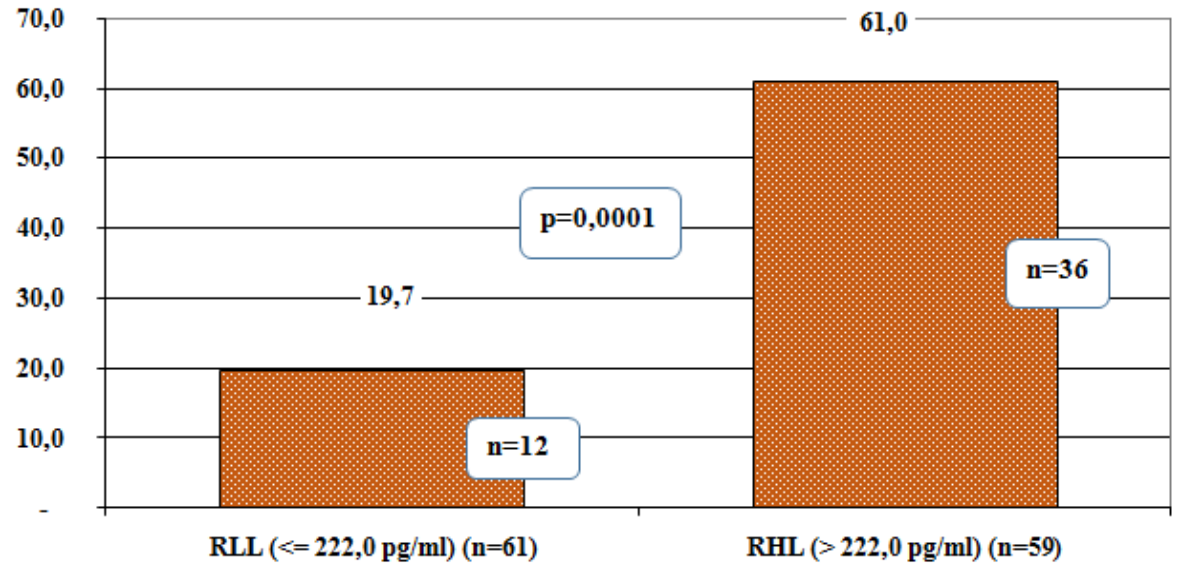

Fig. 2. Frequency of registration of cases of obstructive chronic coronary artery disease in patients with hypertension depending on the content of transforming growth factor-β1 in plasma (in %).

As shown in Figure 2, the group with a high plasma TGF-β1 level exhibited a significantly higher frequency of obstructive CCAD compared with the low-level group (61.0% vs 19.7%, p<0.0001).

When analyzing the frequency of single-, double-, and multivessel coronary artery (CA) lesions according to the plasma TGF-β1 level (Figure 3), no differences were found (p>0.50) in the pattern of anatomic CA involvement between patients with low and high biomarker levels.

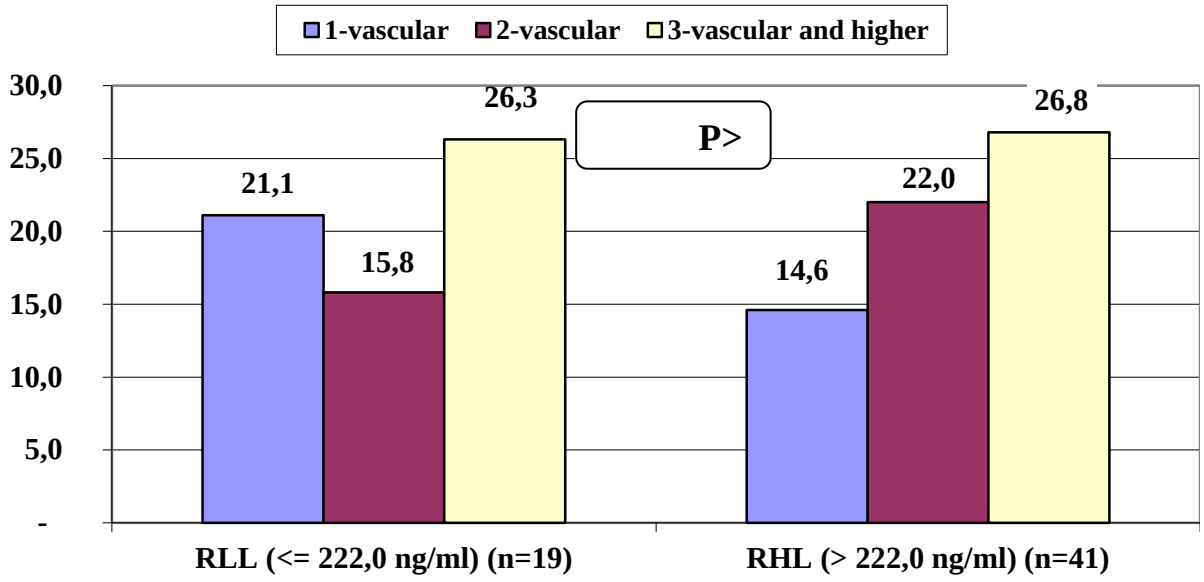

Fig. 3. Frequency of registration of single-, double- and multi-vessel coronary lesions depending on the content of transforming growth factor-β1 in plasma (in %).

The data in Table 1 show that a high plasma TGF-β1 level (>222 pg/mL) was accompanied by a significant increase in mean nocturnal heart rate (70 vs 67 beats/min, p=0.009) and a decrease in the circadian index (CI) (1.11 vs 1.26 arbitrary units, p=0.0004). The decrease in CI may be explained by an insufficient reduction in heart rate during the nighttime period against the background of increased sympathoadrenal activity in patients.

Table1

Holter test findings of the general patient population againstplasma TGF-β1 concentration (pg/ml)

Holterindicators	RLL(≤222 pg/ml) (n=61)	RHL(>222pg/ml) (n=59)	P
CR $_{diurnal}$, beats/minute	73 (67; 81)	74 (67; 83)	0,57
CR $_{daytime}$, beats/minute	81 (72; 93)	81 (72; 92)	0,66
CR $_{nighttime}$, beats/minute	67 (61; 72)	70 (65; 77)	**0,009**
CI	1,26 (1,11; 1,43)	1,11 (1,07; 1,25)	**0,0004**
SVPBs, incidence (%)	36 (59,0 %)	54 (91,5 %)	**<0,0001**
SVPBs, number/day	501 (92; 1147)	880 (302; 1879)	**0,04**
Frequent VE, incidence (%)	23 (37,7 %)	37 (62,7 %)	**0,006**
VPBs, number/day	1568 (1097; 3456)	2692 (1663; 3592)	**0,03**
VPBs, number/hour	65 (45; 144)	112 (69; 149)	**0,03**
Polytopic VPBs, incidence (%)	8 (13,1 %)	21 (35,6 %)	**0,004**
Paired VPBs, incidence (%)	6 (9,8 %)	7 (11,9 %)	0,72
Paired VPBs, number/day	2 (1; 2)	3 (2; 4)	0,28
VT, incidence (%)	0 (0)	4 (6,8 %)	**0,04**
VT, number/day	0	1 (1; 1)	1,00
Maximum duration of VT, s	-	4,5 (4,0; 5,5)	-

Notes: 1. RLL – relatively low and RHL – relatively high plasma galectin-3 content, respectively, CR $_{diurnal}$, CR $_{daytime}$ and CR $_{nighttime}$ – average daily, daytime and nighttime heart rate; CI – circadian index; SVPBs – supraventricular premature beats; VPBs - ventricular premature beats; VT – ventricular tachycardia.

2. The intergroup reliability of the results by quantitative values was calculated using the t-test, by relative values (%) - using the χ^2 criterionfor independent samples.

A high plasma TGF-β1 level was associated with a significant increase in ventricular arrhythmogenic myocardial activity compared with a low marker level (≤222 pg/mL). This was reflected by a higher prevalence of supraventricular premature beats (SVPBs) (91.5% vs 59.0%, p<0.0001) and a higher daily SVPBs count (880 vs 501 episodes/day, p=0.04), a higher prevalence of frequent ventricular premature beats (VPBs) (62.7% vs 37.7%, p=0.006) and higher daily and hourly VPBs counts (2692 vs 1568 episodes/day and 112 vs 65 episodes/hour, respectively, p=0.03), an increased prevalence of polytopic VPBs (35.6% vs 13.1%, p=0.004), and episodes of non-

sustained VT (6.8% vs 0, p=0.04). These data indicate a substantial impact of a high plasma TGF-β1 level on the development of electrical instability in both atrial and ventricular myocardium.

Table 2 presents an analysis of echocardiographic changes according to the plasma TGF-β1 level. No differences were demonstrated for almost all analyzed parameters, except for relative wall thickness (RWT) of the left ventricle (LV), which was lower in patients with a high marker level compared with those with a low level (0.44 vs 0.46 arbitrary units, p=0.04). This finding suggests a certain influence of plasma TGF-β1 on the pattern of LV structural geometry.

Table2

Echocardiographic parameters in patients with hypertension depending on plasma transforming growth factor-β1 content (in pg/ml)

Echocardiography indicators	RLL (<=222,0pg/ml) (n=60)	RHL (>222,0pg/ml) (n=60)	P
LVEDD, mm	50 (48; 51)	52 (48; 54)	0,11
LVESD, mm	34 (33; 37)	33 (32; 37)	0,12
LVEDV, ml	120 (108; 131)	129 (107; 140)	0,19
LVESV, ml	47 (44; 58)	50 (44; 58)	0,64
SV, ml	77 (63; 83)	77 (70; 85)	*0,09*
LA AP, mm	40 (37; 42)	40 (38; 42)	0,33
LA AP /LVEDD	0,77 (0,75; 0,81)	0,76 (0,72; 0,80)	0,65
PWTd, mm	12,0 (11,0; 12,0)	12,0 (11,0; 12,0)	0,98
IVSTd, mm	12,0 (12,0; 12,5)	12,0 (12,0; 13,0)	0,51
LVMI, g/m^2	118 (116; 137)	118 (115; 129)	0,42
RWT, conditionalunits	0,46 (0,44; 0,50)	0,44 (0,42; 0,46)	**0,04**
Ao, mm	34 (32; 36)	33 (31; 36)	0,42
Ao /LA AP	0,85 (0,77; 0,97)	0,82 (0,76; 0,88)	0,17
RV AP, mm	26 (26; 27)	26 (25; 27)	0,56
RV AP /LVEDD	0,50 (0,48; 0,55)	0,49 (0,47; 0,54)	0,14
LVEF, %	60 (57; 64)	59 (57; 64)	0,28
E/A	0,90 (0,74; 1,20)	0,83 (0,75; 0,95)	0,11

Notes: 1. RLL and RHL – relatively low and relatively high transforming growth factor-β1levels 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 – anteroposteriordiameter 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.

Figure 4 shows the characteristics of left ventricular (LV) structural-geometric remodeling according to the Ganau classification in patients with different plasma TGF-β1 levels. In the high-level group, compared with the low-level group, a significant decrease in concentric LV hypertrophy (LVH) and a corresponding increase in eccentric LVH were observed (74.6% and 25.4% vs 90.2% and 9.8%, p=0.02).

In children with primary hypertension, the plasma TGF-β1 level was positively correlated with the presence of LVH [9].

In addition, patients with a high plasma TGF-β1 level, compared with those with a low level, had a significantly higher proportion of cases with echocardiography-detected aortic valve (AV) calcification (23.7% vs 4.9%, p=0.003), with no significant difference in the frequency of mitral valve calcification (Figure 5).

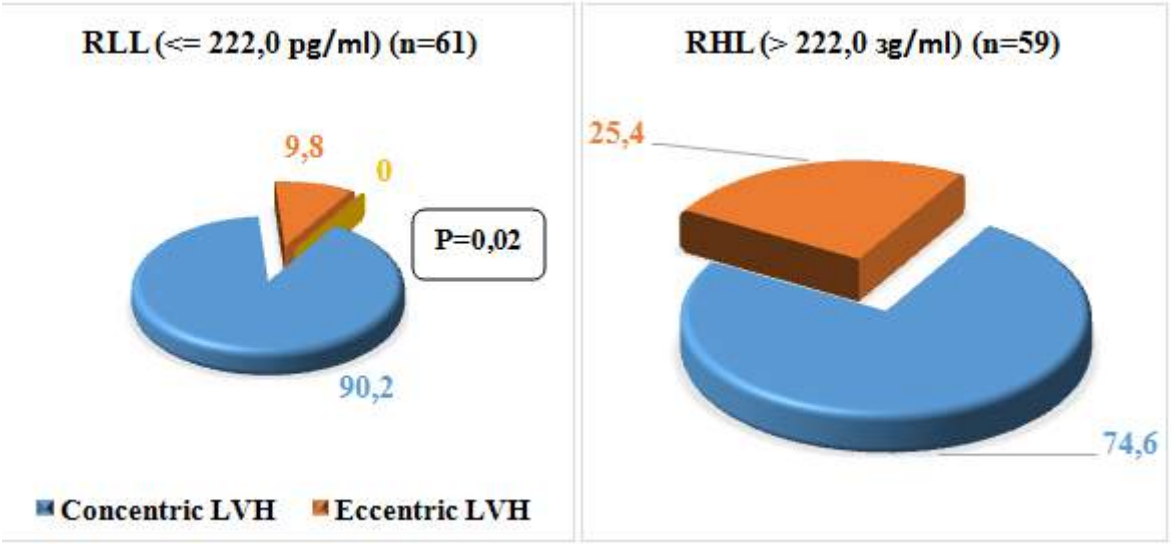

Fig. 4. Frequency of registration of different types of structural and geometric remodeling of the left ventricle depending on the content of transforming growth factor-β1 in plasma (in %).

Notes: 1. LVH – left ventricular hypertrophy, RLL and RHL – relatively low and relatively high transforming growth factor-β1 levels in plasma.

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

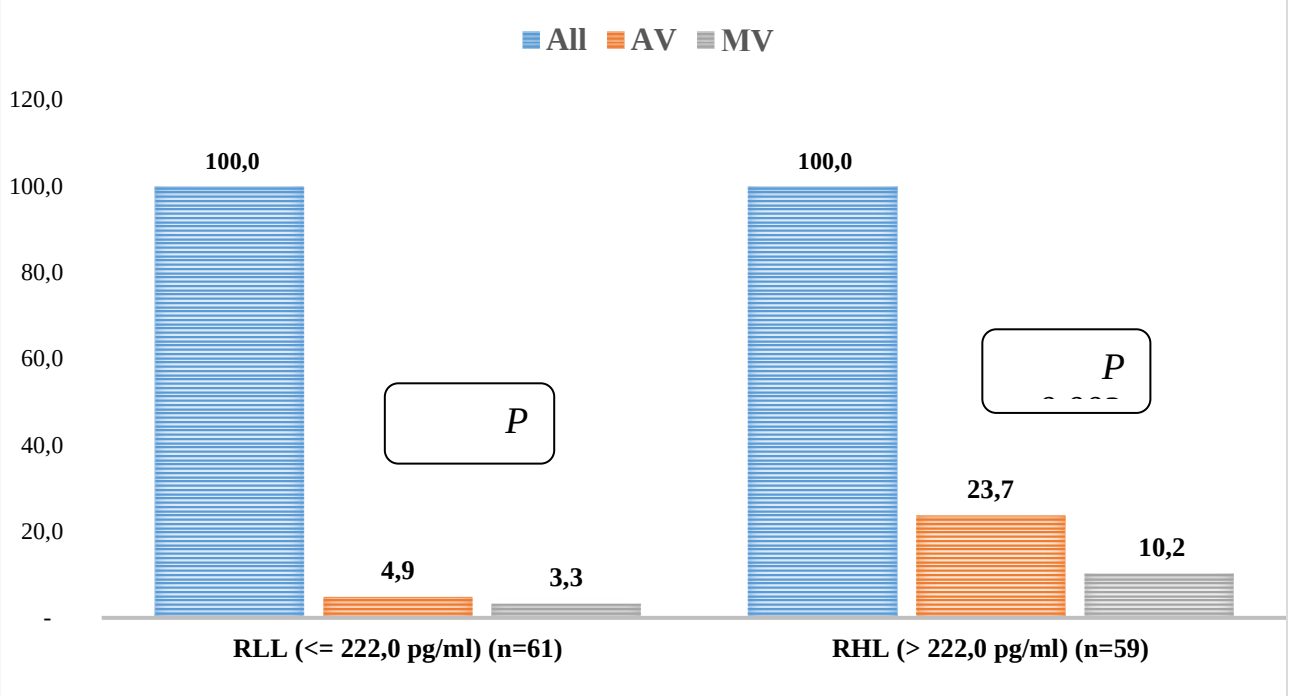

Fig. 5. Frequency of registration of aortic and mitral valve calcification depending on the plasma transforming growth factor-β1 content (in %).

Notes: 1. AV – aortic valve; MV – mitral valve, RLL and RHL – relatively low and relatively high transforming growth factor-β1 levels in plasma.

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

In the study by Rakoczy B. et al. [10], a significant association was found between TGF-β1 levels and left ventricular (LV) diastolic dysfunction, as well as with arrhythmia risk in post–myocardial infarction patients.

It was determined that a high plasma TGF-β1 level (>222 pg/mL) was associated with an increased mean nocturnal heart rate and a decreased circadian index, as well as with a significant increase in the proportion of cases with recorded supraventricular premature beats (SVPBs) and in the daily SVPB count, an increased proportion of cases with frequent ventricular premature beats (VPBs), higher daily and hourly VPB counts, a higher proportion of polytopic VPBs, and episodes of non-sustained ventricular tachycardia according to Holter electrocardiographic monitoring.

It was established that a TGF-β1 level >222 pg/mL was associated with a higher prevalence of concomitant chronic coronary artery disease (CCAD) and obstructive CCAD, as well as a trend toward more severe coronary artery lesions based on coronary ventriculography (CVG).

It was demonstrated that a TGF-β1 level >222 pg/mL was associated with a reduced relative wall thickness, a significant decrease in the frequency of concentric LV hypertrophy and a corresponding increase in eccentric LV hypertrophy, as well as an increased frequency of instrumentally detected aortic valve calcification on echocardiography.

Conclusions. A high plasma TGF-β1 level (>222 pg/mL) in patients with stage II hypertension was associated with less favorable 24-hour heart rate profile parameters and increased arrhythmogenic activity, including more frequent detection of supraventricular and ventricular premature beats, polytopic VPBs, and episodes of non-sustained ventricular tachycardia on Holter monitoring.

Elevated TGF-β1 was also related to a higher prevalence of concomitant and obstructive chronic coronary artery disease and a trend toward more severe coronary artery lesions based on coronary ventriculography.

At the level of cardiac structural changes, a TGF-β1 level >222 pg/mL was associated with reduced left ventricular relative wall thickness, a shift in remodeling toward eccentric left ventricular hypertrophy, and more frequent echocardiographic verification of aortic valve calcification, which may be relevant for risk stratification in this patient population.

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