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Research Article

# Diagnosis and treatment of arterial stiffness, pulmonary hypertension, diastolic cardiac dysfunction against the background of ischaemic heart disease in comorbid patients

Nadezhda N. Pribylova[1], Kristina O. Leonidova[1], Vladislav S. Pribylov[1], Evgeny A. Shabanov[1], Sergey A. Pribylov[1], Nikita V. Novikov[2]

*1 Kursk State Medical University, 3 K. Marksa St., Kursk 305041 Russia*
*2 Kursk Regional Multidisciplinary Clinical Hospital 45a Sumskaya St., Kursk 305007 Russia*

*Corresponding author: : Kristina O. Leonidova (k_leonidova@list.ru)*

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## Abstract

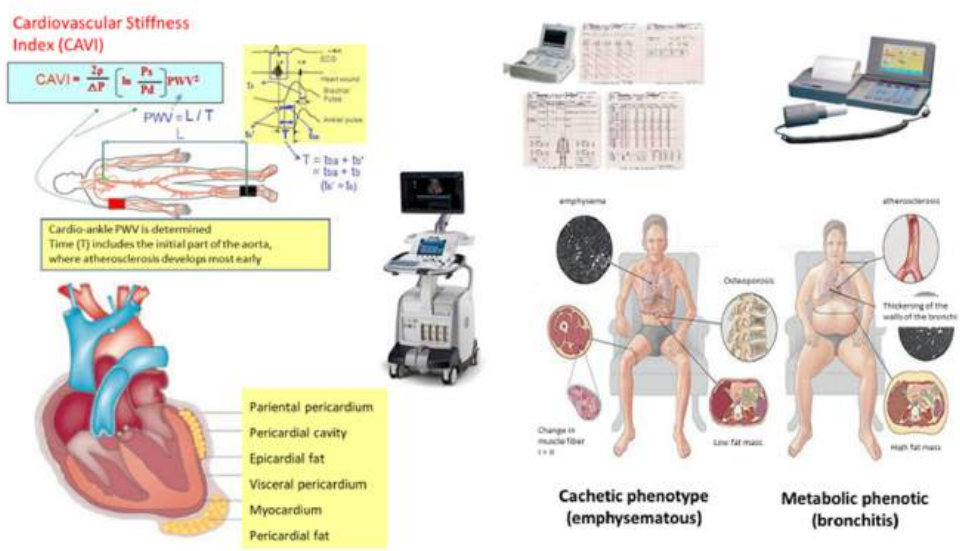
**Introduction:** In the context of cardiology and neurology, special attention is paid to the problems of cardiovascular and cerebrovascular pathologies, often caused by vascular dysfunction. Haemodynamic parameters, in particular arterial stiffness (AS), and epicardial fat thickness (EFT), play a significant role in the assessment of cardiovascular health. **The aim of the study was** to evaluate the correlation between arterial stiffness, pulmonary hypertension (PH), epicardial fat thickness and diastolic myocardial dysfunction in comorbid patients.

**Materials and Methods:** The comparative study was conducted in three groups of patients with the most frequent comorbid pathology. The first group (n=75) included patients with ischaemic heart disease (IHD), arterial hypertension stage II-III and chronic obstructive pulmonary disease (COPD) stage II-III. The second group (n=50) consisted of patients with IHD and arterial hypertension without COPD. The third group (n=33) included patients with IHD without comorbidities.

**Results:** The study revealed a significant correlation between indices of AS, blood pressure (BP), EFT and PH in patients with comorbid conditions. The study found that the addition of the combined antihypertensive drug amlodipine-perindopril to standard therapy contributed to normalization of AS, PH and BP during three months of treatment. There was also a significant improvement in the patients' quality of life, reduction of dyspnoea and heart failure symptoms.

**Conclusion:** The obtained data confirm the presence of correlation between AS, BP, PH and EFT in patients with IHD, AH and COPD, which may serve as indicators of comorbid diseases. The use of combined antihypertensive drug amlodipine-perindopril seems reasonable and scientifically justified, especially after coronary stenting.

## Graphical abstract




## Keywords

coronary heart disease, arterial hypertension, chronic obstructive pulmonary disease, arterial stiffness, pulmonary hypertension, epicardial fat thickness, amlodipine-perindopril, coronary stenting

## Introduction

Integration of innovative achievements in the field of medicine into the practice of public health in the Russian Federation in recent decades has contributed to an increase in life expectancy and improvement of its quality (Roth et al. 2020; Bontsevich et al. 2021; Kobalava et al. 2021). Many age-related cardiovascular and cerebrovascular diseases arise due to vascular dysfunction or are aggravated by functional and structural changes in vessels (Drapkina et al. 2018; Boytsov et al. 2021).

In the context of ongoing scientific research, the haemodynamic effects due to increased arterial stiffness and the analysis of organ-specific obesity with epicardial fat thickness (EFT) assessment are of particular interest. This has a meaningful impact on research and clinical practice in the field of cardiology (Druzhilov and Kuznetsova 2019). According to Drapkina et al. (2018), EFT between 2.7 and 4.5 mm is associated with left ventricular diastolic dysfunction, while EFT thickness above 7.0 mm correlates with the development of arterial hypertension. Increased EFT is closely associated with the progression of cardiofibrosis one year after myocardial infarction and with increased levels of interleukin-33 (Belik et al. 2020; Murkamilov et al. 2021). Nevertheless, in the scientific literature of recent years, there is a lack of data on the relationship and correction of arterial stiffness, left ventricular hypertrophy, diastolic dysfunction of the heart and EFT in common comorbid conditions such as ischaemic heart disease, arterial hypertension and chronic obstructive pulmonary disease (Pribylova et al. 2016; Mustafina et al. 2022; Pribylov et al. 2024).

**The aim of the present study**: to establish the relationship between AS, PH, EFT and diastolic dysfunction of the heart in patients with IHD, AH in combination with COPD and to analyze the effect of amlodipine-perindopril combination drug against the background of baseline therapy in long-term use, especially in patients after coronary stenting.

## Materials and Methods

### Objects under study

To achieve the goal we analyzed the parameters in three comparative groups of patients: group 1 patients with stable angina pectoris II-III functional class, AH II-III stage, COPD II-III stage who were hospitalized for planned coronary angiography and decision on the possibility of surgical correction due to ineffectiveness of antianginal therapy, hypotensive therapy with perindopril or lisinopril alone (n=75). The second comparison group: patients with IHD, AH without COPD (n=50); and the third group: IHD without AH and COPD (n=33). Each comparison group consisted of 20 practically healthy individuals of similar age. On admission to hospital in patients of the main group, the target BP levels had not been reached, on the 2nd–3rd day of admission to hospital coronary catheterization was performed (n=75). Coronary artery stenting was also performed in 33 patients if indicated. All patients received the same basic disaggregation therapy (Cardiomagnil 75 mg once a day, Clopidogrel 75 mg once a day), lipid-lowering drug (Atorvastatin 40 mg once a day), beta-adrenoblockers (Bisoprolol 2.5 mg), antianginal drug (Trimetazidine 80 mg

once a day) and antihypertensive combined drug (Amplodipine/perindopril 10/5 mg). Baseline therapy of COPD was carried out according to the formulary system with inhalation through nebulizer 0.5 mL of Berodual 2 times a day and Ambroxol 15 mg 2 times a day, Carbocysteine (Fluifort) in sachet form as symptomatic therapy. The patients were observed for three months, including the average hospital stay (14 days); the investigations were performed in the first three days upon admission to the cardiology department and 3 months after outpatient treatment. Part of the patients of the main group (7 patients) with comorbid pathology did not receive the combined drug amlodipine/perindopril; though the dose of the drug was increased to the maximum 10/10 mg, the target BP level was not reached, due to intolerance (increased cough), which forced the transfer of the patients to amlodipine/indapamide. Approved by the Kursk Regional Ethics Committee of KSMU, Minutes №8 of 18.10.2022. Due to insufficient materials, it is not possible to include them in a separate group for comparative results, but it can be a kind of control for comparative effectiveness of amlodipine/perindopril pharmacotherapy evaluation after 3 months of treatment in the remaining 68 patients.

Exclusion criteria: bronchial asthma, diabetes mellitus, myocarditis, cardiomyopathies, cardiac rhythm, and conduction disorders. There were no age differences between the main groups, the average age ranging from 53 to 58 years, with men predominating: in the first group – 82% of men, of whom 78% were smokers; in the second group – 55% of men, of whom 38 % were smokers, and in the third group – 64% of men, of whom 62% were smokers.

### Research methods

Patients underwent Doppler echocardiographic study with intracardiac haemodynamics, with calculation of systolic pulmonary artery pressure, end-diastolic, systolic volumes of the right and left ventricles, LV and RV ejection fraction. Epicardial fat thickness was determined by B-mode Echo-CG in the standard left parasternal position along the long and short axis of the left ventricle on a GE Logiq E9 device.

External respiratory function was investigated using Micro Medical SuperSpiro apparatus according to the generally accepted methodology. The 6-minute walk test was performed according to the standard protocol.

To determine endothelium-dependent vasodilatation, we used cuff test with reactive hyperaemia according to Celermajer-Sorensen for vasomotor reaction of the brachial artery. To analyze the functional state of the vascular wall, we performed volumetric sphygmography using VS-1500 apparatus (Fukuda Denshi, Japan).

The following parameters were analyzed: ankle-shoulder index (ASI) for the right and left limbs (R-CAVI and L-CAVI), pulse wave velocity (PWV), diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse blood pressure, and body mass index (BMI).

### Statistical analysis

The obtained data was statistically processed using Statistica 10 (StatSoft Inc., USA). In case of normal distribution, the value was presented as mean value and standard deviations (M±SD), and the parametric Student's T-criterion was calculated for analysis. For categorical variables, data were presented as fractions (percentages). Pearson's paired linear correlation coefficient was calculated, with $p<0.05$ being considered statistically significant.

## Results and Discussion

In the course of the study, the highest arterial stiffness indices were diagnosed in patients with IHD, stable angina II-III FC with AH II-III st. and COPD II-III st.: PWV up to 12.12±0.18 m/s compared to the group of IHD, AH, without COPD (9.53±0.21 m/s), and group 3 of IHD without AH and COPD (8.67±0.30 m/s). High figures of central systolic blood pressure (SBPao), central pulse arterial pressure (cPAP), CAVI, and AI. Pulmonary artery systolic pressure (PASP) (Table 1) in patients of this group was maximal and was 42±3.35 mmHg (with a norm of 20.0±2.5 mmHg). When estimating diastolic dysfunction of LV in patients in combination with AH and COPD, it was found that indices of early and late filling of LV were significantly lower with a decrease in E/A ratio to 0.68±0.08. Disturbance of LV diastolic dysfunction (E/A=0.49±0.07) was combined with pronounced indices of right and left ventricular hypertrophy. The mean value of EFT in patients were increased in this group of patients up to 0.77±0.02 cm, in parallel with high levels of total cholesterol, triglycerides (TG), low-density lipoproteins (LDL) and Apo-B lipoproteins (up to 146±2.8 mg/dL).

Table 2 presents the results of the study of the main group of patients with comorbid pathology depending on body weight. It is noteworthy that when comparing arterial stiffness parameters in the 2nd group of IHD, AH and COPD patients with those in patients with normal weight and overweight, high arterial stiffness parameters were registered in obese patients. We have established the fact that the mean EFT in patients with stable AH was significantly higher than in patients with labile AH (0.54±0.05 and 0.46±0.03, $p<0.01$) and EFT should be considered as a marker of forming visceral fat and metabolically active adipose tissue contributes to the development of AH in comorbid patients. In the main group, EFT was significantly correlated with EchoCG parameters – left ventricular end-systolic size (LVESS) ($r=0.8$, $p=0.01$), left ventricular end-diastolic size (LVEDS) ($r=0.59$, $p<0.01$), left ventricular end-systolic volume (LVESV) ($r=0.64$, $p<0.01$), left ventricular end-diastolic volume (LVEDV) ($r=0.51$, $p<0.01$), pulmonary artery systolic pressure (PASP) ($r=0.64$, $p<0.01$), pulmonary artery diastolic pressure (PADP) ($r=0.58$, $p<0.01$).

Table 3 shows the results of treatment after 3 months in 2 groups: group 1 – baseline therapy + amlodipine/perindopril, group 2 – baseline therapy + amlodipine/perindopril + coronary stenting. We observed for the first time that direct correlation of EFT coincided with arterial stiffness indices – PWV ($r=0.57$, $p<0.01$), AI ($r=0.53$, $p<0.01$), SBPao ($r=0.74$, $p<0.01$) and inverse correlation was found between cPAP ($r=-0.51$, $p<0.01$) and FEV1 ($r=-0.62$, $p<0.01$) and EFT.

There was a significant decrease in pulmonary hypertension from 39.8±1.8 mmHg to 25.3±2.2 mmHg. A statistically significant increase in tolerance to physical load was registered: the test with 6-minute walking increased from 295.5±7.3 to 383.8±5.3 ($p=0.003$).

**Table 1.** Indices of arterial stiffness, pulmonary hypertension, EFT in patients with comorbid pathology (IHD, AH, COPD) in comparison with the group of patients with IHD+AH without COPD and IHD without AH, COPD

| Indices | IHD, AH, COPD (n=75) | IHD, AH without COPD (n=50) | IHD without AH, COPD(n=33) | Practically healthy (n=20) |
|---|---|---|---|---|
| PWV, m/s | 12.12±0.18* | 9.53±0.21* | 8.67±0.30 | 8.14±0.21 |
| AI | 1.59±0.18* | 1.23±0.12* | 1.13±0.16 | 1.10±0.11 |
| SBPao, mmHg. | 165±23.2* | 153±16.8* | 144±14.6 | 132±10.3 |
| cPAP, mmHg. | 48±13,2* | 49±12.7* | 39±16.4 | 35±10.2 |
| R–CAVI | 9.93±0.83* | 9.89±0.76* | 8.64±0.32 | 8.12±0.16 |
| L–CAVI | 9.76±0.71* | 9.79±0.56* | 8.73±0.28 | 8.22±0.12 |
| R–ABI | 1.14±0.16* | 1.12±0.18* | 1.16±0.17 | 1.11±0.10 |
| L–ABI | 1.14±0.13 | 1.1±0.21 | 1.15±0.12 | 1.10 ± 0.12 |
| EFT, cm | 0.77±0.02* | 0.68±0.04* | 0.59±0.23 | 0.45±0.02 |
| PASP, mmHg. | 42±3.35* | 38.5±4.17* | 21.3±2.12 | 20.0±1.5 |
| SBP, mmHg. | 173±14* | 169±21* | 131±11 | 128±9.6 |
| DBP, mmHg. | 103±10* | 100±12* | 75±8.2 | 70±4.2 |
| Cho, mmol/L | 6.9±1.3* | 6.4±1.7* | 5.9±1.2* | 4.3±1.3 |
| LDL, mmol/L | 4.85±0.78* | 4.25±0.23* | 4.3±0.05 | 3.4±0.12 |
| TG, mmol/L | 2.1±0.7* | 1.8±0.3* | 1.5±0.3 | 1.5±0.3 |
| Apo-B lipoproteins, mg/dL | 146±2.8* | 140±3.2* | 120±7.1 | 110±8.2 |

***Note:*** * – statistically significant differences compared to the group of patients with IHD without AH and COPD ($p<0.05$); PWV – pulse wave velocity, AI – augmentation index, SBPao – central systolic blood pressure, cPAP – central pulse arterial pressure, EFT – epicardial fat thickness, PASP – pulmonary artery systolic pressure, SBP – systolic blood pressure, DBP – diastolic blood pressure, Cho – serum total cholesterol level, LDL – low-density lipoproteins, TG – triglycerides.

**Table 2.** Parameters of arterial stiffness, haemodynamics and epicardial fat thickness in a group of patients with cardiorespiratory pathology with normal and excessive body weight

| Indices | IHD control group. BMI<25 kg/m² (n=45) | IHD, AH II-III st + COPD II-III st. BMI<25 kg/m² (n=45) | IHD, AH II-III st + COPD II-III st. BMI>30 kg/m² (n=23) |
|---|---|---|---|
| PWV, m/s | 8.6±0.20 | 10.32±0.11* | 11.48±0.13*/** |
| AI | 1.13±0.14 | 1.24±0.12* | 1.58±0.16*/** |
| R–CAVI | 8.58±0.22 | 9.81±0.68* | 9.99±0.77* |
| L–CAVI | 8.68±0.24 | 9.77±0.62* | 10.88±0.37*/** |
| SBPao, mmHg | 134.0±10.3 | 158±12.4* | 169±18.2*/** |
| cPAP, mmHg | 37±12.2 | 47±11.1* | 51±12.8*/** |
| PAD, cm | 2.27±0.10 | 2.42±0.12* | 2.84±0.20*/** |
| RA, cm | 3.26±0.21 | 3.38±0.17* | 3.98±0.14 */** |
| RVESS, cm | 2.25±0.13 | 2.41±0.14* | 2.91±0.42*/** |
| RVEDS, cm | 2.45±0.23 | 2.57±0.16* | 3.84±0.22*/* |
| E/A | 0.85±0.12 | 0.68±0.08* | 0.55±0.05*/** |
| PASP, mmHg | 23.2±2.3 | 29.2±2.8* | 44.4±3.5*/** |
| PADP, mmHg | 12.3±1.4 | 16.2±1.2 | 23.7±1.8*/** |
| mPAP, mmHg | 19.5±1.4 | 23.4±2.2 | 35.5±2.3*/** |
| EFT, cm | 0.41±0.01 | 0.49±0.03* | 0.77±0.02*/** |

***Note:*** * – $p<0.05$ compared to the control group according to Student's criterion; ** – $p<0.05$ compared to the group with IHD, AH II-III st + COPD II-III st, BMI < 25 kg/m² and IHD, AH II-III st. + COPD II-III st., BMI>30 kg/m²; PWV – pulse wave velocity, AI – augmentation index, SBPao – central systolic blood pressure, cPAP – central pulse arterial pressure, PAD – pulmonary artery diameter, RA – right atrium, RVESS – right ventricular end-systolic size, RVEDS – right ventricular end-diastolic size, PASP – pulmonary artery systolic pressure, PADP – pulmonary artery diastolic pressure, mPAP – medium pulmonary artery pressure, EFT – epicardial fat thickness.

In the third group of patients. we analyzed the effect of amlodipine/perindopril on these parameters in patients who had undergone planned coronary artery stenting. There was a significant decrease in arterial stiffness indices: pulse wave velocity decreased from 12.7±1.2 to 9.0±1.5 ($p<0.01$), aortic augmentation index – from 1.55±0.11 to 1.14±0.14, SBPao – from 155.3±5.4 to 128±2.2 mm Hg ($p<0.01$), and cPAP – from 45.4±7.2 mmHg to 35.3±8.1 ($p<0.01$). We achieved an improvement in left ventricular diastolic function, with an elevation of E/A from 0.54±0.05 to 0.98±0.10, in the two compared groups, indicating an increase in diastolic blood flow with an increase in favour of early filling velocity. We found a significant decrease in PASP in this group of patients from 39.8±1.8 to 22.3±1.2 mmHg. LVEF increased from 42.5±1.3% to 68.4±1.2%. EFT decreased from 0.68±0.01 cm to 0.42±0.01 cm, which is presented in Table 3.

Figure 1 shows the mean values of EFT in the studied groups of patients. The highest values of EFT were in patients with IHD, AH and COPD, especially in the presence of excessive body weight (BMI>30 kg/m$^2$). Maximum values were registered in patients with cardio-respiratory pathology (IHD, AH, COPD) before treatment. After three months of treatment, there was a significant decrease in EFT in all patients, but the lowest values of EFT were found in patients with coronary stenting receiving baseline therapy and antihypertensive therapy with Amplodipine/perindopril.

Our studies have confirmed the important role of such arterial stiffness parameters as PWV, CAVI, ABI in the development of AH and complications in IHD. Murkamilov et al. (2021) also found a close relationship between arterial stiffness and Echo-CG parameters in patients with COPD. Those researchers, as well as Pribylova et al. (2016) raised one of the main problems in clinical practice – the wide use of arterial stiffness parameters in the approach to etiopathogenetic therapy of many comorbid diseases. Having analyzed the close relationship of arterial stiffness with Echo-CG parameters of cardiac hemodynamics, indicators of endothelial dysfunction and diastolic dysfunction of the heart, it is possible to predict the main complications in IHD in combination with AH and COPD, as well as to use these parameters to assess the effectiveness of etiopathogenetic therapy of comorbid pathology.

The problem of cardiac obesity, determination of epicardial adipose tissue thickness in comorbid pathology seems to be especially relevant in recent years. After 2 weeks of in-patient treatment in the studied groups, there was an improvement: decreased blood pressure figures – SBPao to 121.2±1.8 and cPAP to 80.2±1.2, decreased number of angina attacks per week from 6.5±0.5 to 2.5±0.3 $p<0.01$, and decreased pulmonary hypertension from 39.8±1.8 to 25.3±1.2 mmHg.

In 7 patients treated with amlodipine/indapamide, we obtained achievement of the target BP levels, but the PWV values (11.2±1.8) were significantly higher, and E/A less than 0.52±0.2 than in the group of patients with amlodipine/perindopril therapy (E/A 0.68±0.2).

**Table 3.** Effect of amlodipine/perindopril and coronary stenting on arterial stiffness, pulmonary hypertension, haemodynamics, EFT in patients with comorbid pathology –IHD, AH with COPD after 12 weeks of treatment

| Indices | Initially (n=68) | After 3-month treatment: baseline therapy + amlodipine/ perindopril (n=35) | After 3-month treatment: Baseline therapy+amlodipine/perindopril + coronary stenting (n=33) |
|---|---|---|---|
| PWV, m/s | 12.7±1.2 | 10.2±1.6* | 9.0±1.5*/** |
| AI | 1.42±0.11 | 1.25±0.12* | 1.14±0.11*/** |
| SBPao, mmHg | 155.3±5.4 | 133.2±3.2* | 128±2.2*/** |
| cPAP, mmHg | 45.4±7.2 | 37.4±7.1* | 35.3±8.1*/** |
| LVEDV, mL | 152.2±3.8 | 129±2.1* | 118±3.2*/** |
| LVESV, mL | 77.2±2.7 | 63.5±2.8* | 60.1±2.2*/** |
| LVEF, % | 42.5±1.3 | 64.8±1.8* | 68.4±1.2*/** |
| E/A LV | 0.54±0.05 | 0.68±0.1* | 0.98±0.1*/** |
| RVEDV, mL | 49.9±1.8 | 42.1±1.7* | 36.2±1.9*/** |
| RVESV, mL | 27.2±1.2 | 24.1±1.4* | 21.2±15*/** |
| RVSV, mL | 14.8±1.5 | 18.2±1.1* | 22.4±1.2 */** |
| RVEF, % | 38.2±1.7 | 44.3±1.8* | 49.5±1.7*/** |
| E/A RV | 0.81±0.12 | 0.98±0.4* | 1.2±0.3*/** |
| PASP, mmHg | 39.8±1.8 | 25.3±1.2* | 22.3±1.2*/** |
| EFT, cm | 0.68±0.01 | 0.48±0.02* | 0.42±0.01*/** |

***Note:*** * – $p<0.01$ – degree of reliability of changes before and after treatment; ** – $p<0.01$ – degree of reliability of changes between parameters before and after baseline therapy+amlodipine/perindopril and baseline therapy+amlodipine/perindopril+coronary stenting; PWV – pulse wave velocity, AI – augmentation index, SBPao – central systolic blood pressure, cPAP – central pulse arterial pressure, LVEDV – left ventricular end-diastolic volume, LVESV – left ventricular end-systolic volume, LVEF – left ventricular ejection fraction, RVEDV – right ventricular end-diastolic volume, RVESV – right ventricular end-systolic volume, RVSV – right ventricular stroke volume, RVEF – right ventricular ejection fraction, PASP – pulmonary artery systolic pressure, EFT – epicardial fat thickness.

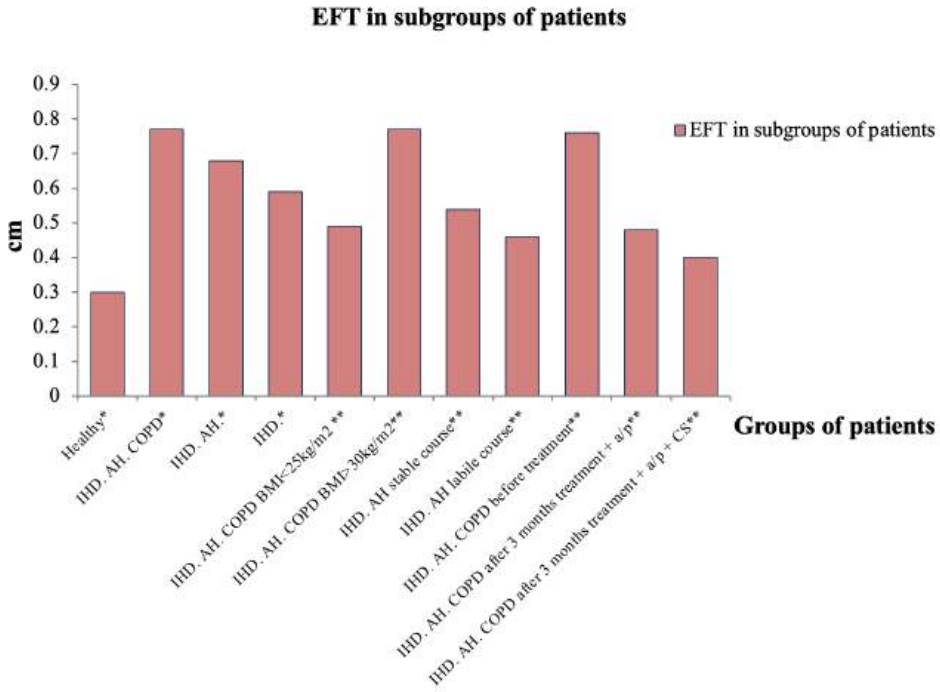



**Figure 1.** Epicardial fat thickness in the studied groups of patients. ***Note:*** * – p<0.05 compared to control group by Student's criterion; ** – p<0.05 when comparing CHD, AH I-II st. and COPD II-III st., 25<IMT<30 kg/m² with CHD, AH I-II st. and COPD II-III st, BMI>30 kg/m2.

# Conclusion

1. The pharmacological efficacy of the combined hypotensive drug amlodipine/perindopril in the complex therapy of patients with comorbid pathology in the combination of IHD with COPD, especially in the group after coronary stenting was proved.
2. The direct correlation between the levels of SBP, SBPao, arterial stiffness indicators (PWV, AI, CAVI), pulmonary hypertension, diastolic dysfunction of the left and right ventricles and epicardial fat thickness in comorbid patients with IHD, PICS, stable angina II-II FC, AH II-III st., COPD II-III st. was stated.
3. An inverse medium strength relationship between cPAP and EFT in obese patients has been proved. Epicardial fat thickness contributes to the formation of AH in comorbid pathology.
4. The indicators of the 6-minute walk test in patients with IHD, AH and COPD had a negative correlation with FEV1, with the parameters of pulmonary hypertension, arterial stiffness, and diastolic function of the heart.
5. The positive effect of combined hypotensive drug amlodipine/perindopril against the background of complex therapy with antilipidic, anti-ischaemic and bronchodilating drugs, especially 3 months after coronary stenting, on the parameters of arterial stiffness, diastolic dysfunction of the heart, and pulmonary hypertension in patients with the most frequent comorbid pathology of IHD, AH and COPD was established for the first time.

### Conflict of interest

The authors have declared that no competing interests exist.

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The authors have no funding to report.

### Data availability

All of the data that support the findings of this study are available in the main text.

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## Author contributions

- **Nadezhda N. Pribylova**, Doctor Habil. of Medical Sciences, Professor, Honoured Physician of the Russian Federation, Professor of the Department of Internal Medicine, Institute of Continuing Education, Kursk State Medical University, Kursk, Russian Federation; e-mail: pribylova_nadezda@mail.ru; **ORCID ID:** https://orcid.org/0000-0001-6788-518X. Concept and design development, data analysis and interpretation, review of publications on the topic of the article, writing the text of the article, and approval of the final version of the article before submission for publication.

- **Kristina O. Leonidova**, co-researcher of the Department of Internal Medicine, Institute of Continuing Education, Kursk State Medical University, Kursk, Russian Federation; e-mail: k_leonidova@list.ru; **ORCID ID:** https://orcid.org/0000-0001-6120-6748. Review of publications on the topic of the article, writing the text of the article, graphic design, approval of the final version of the article before submission for publication.

- **Vladislav S. Pribylov**, co-researcher of the Department of Pharmacology, FGBOU VO KSMU, Russian Federation, 305041, Kursk region, Kursk, K. Marksa street, 3. e-mail: pribylov.vlad@mail.ru; **ORCID ID:** https://orcid.org/0000-0002-4545-9339. Review of publications on the topic of the article, writing the text of the article, translation into English, and approval of the final version of the article before submission for publication.

- **Evgeny A. Shabanov**, Candidate of Medical Sciences, Associate Professor, Department of Internal Medicine, Institute of Continuing Education, Kursk State Medical University, Kursk, Russian Federation; e-mail: dr.evgeniy85@mail.ru; **ORCID ID:** https://orcid.org/0000-0002-5790-4196. Data analysis and interpretation, review of publications on the topic of the article, writing the text of the article, scientific advice, and approval of the final version of the article before submission for publication.

- **Sergey A. Pribylov**, Doctor Habil. of Medical Sciences, Professor, Department of Internal Medicine, Institute of Continuing Education, Kursk State Medical University, Kursk, Russian Federation; e-mail: pribylov_serg@mail.ru; **ORCID ID:** https://orcid.org/0000-0002-2913-493X. Data analysis and interpretation, review of publications on the topic of the article, writing the text of the article, scientific advice, and approval of the final version of the article before submission for publication.

- **Nikita V. Novikov**, Head of the ultrasound diagnostics department, Kursk Regional Multidisciplinary Clinical Hospital. e-mail: dr.novikovnikita@yandex.ru; **ORCID ID:** https://orcid.org/0009-0001-3666-9465 . Data analysis and interpretation, review of publications on the topic of the article, writing the text of the article, ultrasound examination of patients, and approval of the final version of the article before submission for publication.

All authors contributed substantially to the search and analysis work and preparation of the article, read and approved of the final version before publication.