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Possible pathway for heart failure with preserved ejection fraction prevention and treatment: the angiotensin-converting enzyme inhibitor effect on endothelial function in comorbid patients

Aim	To evaluate the effect of perindopril on the endothelial function and levels of endothelial dysfunction markers in groups of patients with heart failure with preserved (HFpEF) and mid-range (intermediate) left ventricular ejection fraction (HFmrEF).
Material and methods	40 patients with HFpEF (n=20) and HFmrEF (n=20) were evaluated. At baseline, parameters of the morpho-functional state of large blood vessels and of microvessels were evaluated with photoplethysmography, and levels of E-selectin and endothelin-1 (ET-1) were measured. The patients were prescribed perindopril, and after 12 months of treatment, photoplethysmographic parameters and endothelial dysfunction markers were determined again.
Results	After 12 months of the perindopril treatment, improvements in the endothelial function of both large blood vessels and microvessels were noted. The phase shift increased from 10.1 to 10.9 ms in the HFpEF group (p=0.001) and from 8.35 to 9.65 ms in the HFmrEF group (p=0.002). Furthermore, the occlusion index increased from 1.45 to 1.75 in patients with HFpEF (p=0.004) and from 1.5 to 1.75 in patients with HFmrEF (p=0.010). The E-selectin concentration decreased in both groups, from 57.25 to 42.4 ng/ml (p=0.00008) and from 40.5 to 35.7 ng/ml (p=0.010) in patients with HFpEF and HFmrEF, respectively. The ET-1 concentration decreased from pg/ml (p=0.010) in patients with HFpEF whereas in patients with HFmrEF, there was no significant change in the ET-1 concentration after 12 months of the perindopril treatment.
Conclusion	At 12 months, the endothelial function improved and E-selectin and ET-1 levels decreased in patients with HFpEF and HFmrEF.

Keywords	Chronic heart failure; preserved ejection fraction; mid-range ejection fraction; endothelial dysfunction; angiotensin-converting enzyme inhibitors; perindopril; biomarkers
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In recent years, phenotyping of HF has been much discussed in terms of determining a strategy for the challenging management of patients with heart failure (HF). According to the 2021 ESC Guidelines, three phenotypes were identified based on measurement of the left ventricular ejection fraction (LVEF). Although the management of HF withe reduced ejection fraction (HFrEF) and mid-range ejection fraction (HFmrEF) has been substantiated, there is not much evidence on the treatment of patients with HF with preserved ejection fraction (HFpEF) [1]. It should be noted that the HFpEF phenotype is largely determined by the contribution of comorbidities. Several studies have demonstrated the association of various diseases with a higher risk of death and hospitalization in patients with HFpEF and HFrEF [2–4]. This suggests that management aimed at treating concomitant diseases may slow down the progression of HFpEF and HFrEF to improve prognosis for these patients.

The paradigm of HFpEF pathogenesis, which is centered around endothelial dysfunction (ED) resulting from the pro-inflammatory state, has been much discussed in the literature. Most of the diseases underlying HFpEF are associated with ED. For example, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), diabetes mellitus (DM) and obesity lead to the development of oxidative stress. In addition, the

activation of NADPH oxidase and increased synthesis of reactive oxygen species (ROS), which break down endothelial nitric oxide synthase (eNOS) and reduce the synthesis of nitrogen oxide (NO), is associated with vasomotor dysfunction. Renin-angiotensin-aldosterone system (RAAS) is also involved in the development of ED. Angiotensin II is an activator of NADPH oxidase and activates the production of ROS, which leads to endothelial dysfunction. These processes cause the remodeling of the coronary microcirculatory system, resulting in the development of diastolic dysfunction [5–7]. Although the pathogenesis of HFmrEF has not been well studied, it is assumed that patients with HFmrEF demonstrate characteristics of HFpEF as well as HFrEF [8].

It is of interest to study the role of comorbidities (obesity, COPD, DM, CKD) in the development of low-level inflammation – and, thus, ED in patients with HFpEF.

Obesity is one of the most common causes of HF. Normally, perivascular fatty tissue secretes factors that increase the bioavailability of NO. However, this protective effect is lost in obese patients, due to perivascular fatty tissue switching to increased synthesis of pro-inflammatory cytokines (TNFα, interleukin 6, 1β), and ROS [9]. An increased RAAS activity is also described in patients with visceral obesity, which also contributes to the production of ROS [10]. All the above processes create a background of low-level inflammation, upset the balance of endothelin-1 (ET-1)/NO and cause the development of ED.

Along with obesity, DM is another pathogenetic factor of HFpEF. Hyperglycemia is associated with the formation of complex glycolysis end products, glucose oxidation and activation of protein kinase C, which triggers the activation of enzymes promoting the synthesis of ROS (NADPH oxidase) and a decrease in bioavailability of NO [11]. Moreover, DM is accompanied by increased RAAS activity [12, 13]. This is confirmed by Fiordaliso et al. [14], who showed a direct correlation between glucose levels and the expression of p53 responsible for angiotensin transcription and angiotensin II production.

COPD is the etiological factor of HFpEF in 13% of cases, [15]. In patients with COPD, endothelial cells begin to actively produce angiotensin-converting enzyme (ACE) in cell hypoxia, which also stimulates angiotensin II production [16]. The even more important activation of T-lymphocytes, neutrophils and macrophages, which is typical for this disease, results in the activation of NADPH oxidase, leading to increased synthesis of ROS and the aggravation of ED [17].

Therefore, it seems reasonable to use drug therapy for inhibiting RAAS in order to reduce the severity of oxidative stress and prevent the progression of ED in patients with HFpEF.

There are several laboratory and clinical approaches for evaluating endothelial function. In terms of clinical evaluation, these can be subdivided into invasive and non-invasive methods. Among the latter, finger photoplethysmography is the most convenient and inexpensive. The efficacy of this method in endothelial dysfunction has been consistently demonstrated in patients with various cardiovascular diseases.

There are a number of difficulties in applying laboratory methods. Changes in the concentrations of various substances produced by endothelium, such as NO, ET-1, von Willebrand factor, adhesion molecules (ICAM, E-selectin), which occur with the development of ED, allows these substances to be used as markers. While NO, ET-1 and von Willebrand factor are often evaluated in ED studies, the use of E-selectin as a marker of endothelial dysfunction remains hypothetical. However, since E-selectin is actively involved in inflammation processes, which can lead to the development of ED, it is interesting to study the levels of E-selectin in patients with HFpEF and HFmrEF and their trends during the use of perindopril.

Objective

To assess the effect of perindopril on endothelial function using computer-based photoplethysmography in order to determine the levels of suspected ED markers and identify possible association between the parameters of laboratory and clinical methods of diagnosis of ED in patients with HFpEF and HFmrEF.

Material and Methods

The study was approved by the local ethics committee and observed the principles enshrined in the Declaration of Helsinki. A total of 40 patients with HFpEF and HFmrEF and concomitant diseases were examined. All patients had such comorbidities as arterial hypertension, obesity, while some patients had records of DM, COPD and coronary artery disease (CAD). At baseline, each patient underwent echocardiography to determine the levels of E-selectin, ET-1 and N-terminal pro-brain natriuretic peptide (NT-proBNP). Computer photoplethysmography was performed to evaluate occlusion index (OI) and phase shift (PS) that characterize endothelial function of microcirculatory vessels and large vessels, respectively. In normal endothelial function, PS is less than 10 ms, while OI is more than 1.8. Indicators describing structural changes in large microcirculatory vessels were also determined: stiffness index (aSI) and reflection index (RI). Normally, aSI is less than 8 m/s, while RI is less than 30%.

Following examination, perindopril was prescribed to ACE inhibitor naive patients for 12 months ACE inhibitors were canceled for 48 hours in those patients

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who were taking ACE inhibitors other than perindopril, after which perindopril was ordered. The mean dose was 5 mg/day. The dose was titrated to the maximum tolerated dose of 10 mg/day. No dose modification was required when blood pressure (BP) <135/85 mm Hg was achieved. Twelve months later, the parameters of cardiac remodeling, structural and functional state of the endothelium were re-evaluated.

Baseline characteristics of patients with HFpEF and HFmrEF

The mean age of patients with HFpEF and HFmrEF was 66 and 68 years, respectively. There were no differences between patient groups in age, sex, and drug therapy administered. All patients had hypertensive heart disease and obesity; 95% and 90% of patients with HFpEF and HFmrEF had a history of CAD, respectively. History of myocardial infarction was more common among patients with HFmrEF than patients with HFpEF (p=0.010). DM type 2 was confirmed in 11 patients with HFpEF and 14 patients with HFmrEF. All patients had used beta-blockers and mineralocorticoid receptor antagonists. NT-proBNP elevation was observed in both groups. Due to the prevalence of obese patients in these groups, mean NT-proBNP was lower than expected at 320.5 pg/mL and 307.5 pg/mL, respectively. E-selectin was elevated, and ET-1 remained within the normal range. No differences in the levels of NT-proBNP and ET-1 and myocardial remodeling parameters (left atrial volume index and left ventricular myocardial mass index) were found between patients with HFpEF and HFrEF. However, E-selectin was higher in the HFpEF group than in the HFrEF group (Table 1). High adherence to perindopril treatment was observed in both patient groups; all patients continued to participate in the study.

The data obtained were processed using Statistica 12.0. Quantitative data are expressed as the median and upper and lower quartiles. The differences between two dependent parameters were estimated using the Wilcoxon test. The differences between two independent groups were evaluated using the Mann-Whitney test. The correlation between parameters was evaluated using the Spearman rank correlation coefficient. The data are given in Tables 1–4.

Differences were significant with p less than 0.05.

Results

Effect of perindopril on the endothelial structure and function

According to computer photoplethysmography, the functional state of large and microcirculatory vessels improved in patients with HFpEF during the use of perindopril. PS increased from 10.1 [6.65; 12.1] to 10.9 [7.75; 13.75] ms (p=0.001). OI increased from 1.45 [1.15; 1.75] to 1.75 [1.55; 1.85] (p=0.004).

Similar changes were also observed in the HFmrEF group. PS increased from 8.35 [4.75; 10.6] to 9.65 [6.9; 13.1] ms (p=0.002). OI increased from 1.5 [1.4; 2.0] to 1.75 [1.55; 2.2] (p=0.015).

Table 1. Baseline characteristics of patients with HFpEF and HFmrEF

Parameter	HFpEF	HFmrEF	p
Age, years	66 [61.5; 75]	68 [62.5; 74.5]	0.570
Sex, male, n (%)	8 (40)	13 (65)	0.11
BMI, kg/m^2	32 [28.7; 37.9]	30.7 [27.6; 34.4]	0.189
Number of patients with HF (NYHA), n (%)			
FC II	9 (45)	4 (20)	0.09
FC III	11 (55)	16 (80)	
Laboratory findings			
Creatinine, mg/dL	0.99 [0.75; 1.19]	1.05 [0.9; 1.22]	0.417
GFR, mL/min/1.73m^2	82 [56.5; 110.1]	82.2 [51.4; 90.9]	0.343
NT-proBNP, pg/mL	320.5 [270; 394.5]	307.5 [249; 369]	0.533
Endothelin-1, pg/mL	0.86 [0.36; 1.05]	0.94 [0.49; 1.50]	0.261
E-selectin, ng/mL	57.25 [43.35; 72.7]	40.5 [28.9; 59.5]	0.025
Echocardiographic parameters			
LVEF, %	57 [54; 59]	46 [44; 47]	0.0000001
LAVI, mL/m^2	35.9 [34; 40.2]	37.2 [34.4; 42.3]	0.239
LVEDV, mL	105.5 [95.5; 118.5]	137.5 [109; 168]	0.011
LVEDD, mm	49.5 [47; 52.5]	56.5 [51; 60]	0.001
LVMI, g/m^2	112 [102; 122]	112 [103; 130]	0.533
Comorbidities, n (%)			
CAD	19 (95)	18 (90)	0.54
Myocardial infarction	6 (30)	14 (70)	0.01
Diabetes mellitus	11 (55)	14 (70)	0.32
Atrial fibrillation	6 (30)	13 (65)	0.026
COPD	3 (15)	2 (10)	0.632
Treatment, n (%)			
ACE inhibitors other than perindopril	17 (85)	15 (75)	0.42
ARBs	3 (15)	5 (25)	0.42
Diuretics	2 (10)	5 (25)	0.21

HFpEF – heart failure with preserved ejection fraction; HFmrEF – heart failure with mid-range ejection fraction; BMI – body mass index; FC – functional class; GFR – glomerular filtration rate; NT-proBNP – N-terminal pro-brain natriuretic peptide; LVEF – left ventricular ejection fraction; LAVI – left atrial volume index; LVEDD – left ventricular end-diastolic dimension; LVEDV – left ventricular end-diastolic volume; LVMI – left ventricular mass index; CAD – coronary artery disease; COPD – chronic obstructive pulmonary disease; ACE – angiotensin-converting enzyme; ARB – angiotensin II receptor blocker.

Table 2. Changes in morphological and functional parameters of large and microcirculatory vessel wall during the use of perindopril for 12 months

	Parameter	Before treatment	After 12 months of treatment	p
HFpEF	OI (normal >1.8)	1.45 [1.15; 1.75]	1.75 [1.55; 1.85]	0.004
	PS, ms (normal >10 ms)	10.1 [6.65; 12.1]	10.9 [7.75; 13.75]	0.001
	aSI, m/s (normal <8 m/s)	8.2 [6.9; 9.75]	8.0 [7.25; 9.05]	0.040
	RI, % (normal <30%)	38.3 [30.4; 57.75]	36.6 [29.1; 61.2]	0.204
HFmrEF	OI (normal >1.8)	1.5 [1.4; 2.0]	1.75 [1.55; 2.2]	0.015
	PS, ms (normal >10 ms)	8.35 [4.75; 10.6]	9.65 [6.9; 13.1]	0.002
	aSI, m/s (normal <8 m/s)	8.4 [6.45; 10.45]	7.45 [6.7; 9.15]	0.038
	RI, % (normal <30%)	43.9 [28; 56.2]	48.3 [29; 60.1]	0.006

HFpEF – heart failure with preserved ejection fraction; HFmrEF – heart failure with mid-range ejection fraction; OI – occlusion index; PS – phase shift; aSI – stiffness index; RI – reflection index; p – significance of intergroup differences; Wilcoxon test.

The stiffness of large vessels was reduced in both groups: stiffness index decreased from 8.2 m/s to 8.0 m/s (p=0.040) and from 8.4 m/s to 7.45 m/s (p=0.038) in the HFpEF and HFmrEF groups, respectively. Statistically significant structural changes in the microcirculatory vessels were only found in patients with HFmrEF, p=0.006 (Table 2).

Myocardial remodeling parameters during the use of perindopril

There were no changes in the left ventricular myocardial mass index and left ventricular end-diastolic dimension following 12 months of perindopril therapy. Left ventricular end-diastolic volume relatively decreased in the HFmrEF group; the decrease was not statistically significant in the HFpEF group. Although the left atrial OI decreased during treatment in patients with HFmrEF from 37.2 mL/m^2 to 36.1 mL/m^2, the changes were statistically insignificant (p=0.067). LVEF increased in 4 of 20 patients with HFmrEF; thus, they were considered as patients with HF with improved LVEF (Table 3).

Changes in the levels of potential endothelial dysfunction biomarkers

The levels of E-selectin and ET-1 decreased statistically significantly in patients with HFpEF. E-selectin decreased from 57.25 [43.3; 72.7] ng/mL to 42.4 [34.5; 65.6] ng/mL (p=0.00008), while ET-1 decreased from 0.86 [0.36; 1.05] pg/mL to 0.70 [0.36; 0.88] pg/mL (p=0.001). E-selectin decreased 40.5 [28.9; 59.5] ng/mL to 35.7 [23.7; 48.8] ng/mL (p=0.011) in the HFmrEF group.

There were no statistically significant changes in ET-1 in patients with HFmrEF during the use of perindopril. NT-proBNP decreased from 320.5 [270; 394.5] pg/mL to 258 [197.5; 325.5] pg/mL in patients with HFpEF (p=0.00008) and from 307.5 [249; 369] pg/mL to 243.5 [196.5; 291.5] pg/mL in patients with HFmrEF (p=0.00008) (Table 4).

There were no statistically significant direct correlations between laboratory markers and the structural and functional characteristics of the vessels (p > 0.05).

Table 3. Parameters of myocardial remodeling during the use of perindopril in patients with HFpEF and HFmrEF for 12 months

Parameter		Before treatment	After 12 months of treatment	p
HFpEF	LAVI, mL/m^2	35.9 [34; 40.2]	35.8 [31.8; 41.5]	0.910
	LVMI, g/m^2	112 [102; 122]	113.3 [99.3; 126.7]	0.478
	LVEDD, mm	49.5 [47; 52.5]	49 [47; 52.0]	0.444
	LVEDV, mL	105.5 [95.5; 118.5]	99.5 [94.5; 116.5]	0.112
	LVEF, %	57 [54; 59]	56.5 [54; 59]	0.609
HFmrEF	LAVI, mL/m^2	37.2 [34.4; 42.3]	36.1 [33.7; 42.7]	0.067
	LVMI, g/m^2	112 [103; 130]	113.3 [101; 130.4]	0.204
	LVEDD, mm	56.5 [51; 60]	55.5 [50; 59.5]	0.055
	LVEDV, mL	137.5 [109; 168]	134 [106.5; 164.5]	0.017
	LVEF, %	46 [44; 47]	48 [46; 49]	0.0002

HFpEF – heart failure with preserved ejection fraction; HFmrEF – heart failure with mid-range ejection fraction; LAVI – left atrial volume index; LVMI – left ventricular mass index; LVEDD – left ventricular end-diastolic dimension; LVEDV – left ventricular end-diastolic volume; LVEF – left ventricular ejection fraction

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Table 4. Changes in potential markers of endothelial dysfunction and NT-proBNP in patients with HFpEF and HFmrEF during the use of perindopril

Parameter		Before treatment	After 12 months of treatment	p
HFpEF	E-selectin, ng/mL	57.25 [43.35; 72.7]	42.4 [34.5; 65.6]	0.00008
	ET-1, pg/mL	0.86 [0.36; 1.05]	0.70 [0.36; 0.88]	0.001
	NT-proBNP, pg/mL	320.5 [270; 394.5]	258 [195; 324]	0.00008
HFmrEF	E-selectin, ng/mL	40.5 [28.9; 59.5]	35.7 [23.7; 48.8]	0.011
	ET-1, pg/mL	0.94 [0.49; 1.50]	0.98 [0.61; 1.32]	0.525
	NT-proBNP, pg/mL	307.5 [249; 369]	243.5 [196.5; 291.5]	0.00008

HFpEF – heart failure with preserved ejection fraction; HFmrEF – heart failure with mid-range ejection fraction; ET-1 – endothelin-1; NT-proBNP – N-terminal pro-brain natriuretic peptide.

Changes in exercise tolerance in patients with HFpEF and HFmrEF during perindopril therapy

A 6-minute walk distance test demonstrated a decrease in functional class of HF in patients with HFmrEF and an increase in the walk distance in patients with HFpEF. The walk distance decreased from 280 [260; 298] m to 354 [328; 379] m (p=0.003) in patients with HFmrEF and from 300 [[297; 419] m to 374 [360; 476] m (p=0.0003) in patients with HFpEF.

Discussion

Since the efficacy of drugs used to treat patients with HFmrEF has not been demonstrated for patients with HFpEF, there is an interest in identifying drug therapies that can improve quality of life and prognosis for this category of patients [1].

Taking into consideration the new paradigm and contribution of comorbidities to the development of HFpEF, the importance of managing risk factors (normalization of weight, BP, blood glucose, control of COPD and CKD) in order to prevent the progression of HFpEF can be assumed.

The study by Nedogoda et al. [18] to assess the effect of perindopril in patients with obesity and arterial hypertension included 120 patients. They were divided into four groups of 30 patients who used perindopril 10 mg, enalapril 20 mg, losartan 100 mg or telmisartan 80 mg. The effect of treatment was evaluated in 24 weeks by the following parameters: BP, leptin levels, body mass index, intima-media thickness and carotid-femoral pulse wave velocity. Patients receiving perindopril had the best values of BP and leptin levels. In this group, a decrease in carotid-femoral pulse wave velocity by 29% and carotid intima-media thickness was also observed.

In the PERSUADE 1502 study, perindopril or placebo was administered in patients with CAD and DM. Cardiovascular mortality, as well as the incidence of non-fatal myocardial infarction and HF, decreased in the group of patients taking perindopril in 4.3 years [19].

The efficacy of perindopril was assessed in patients with COPD only in terms of BP normalization and the presence of side effects [20]. However, due to the increased oxidative stress and elevated ROS in COPD, the use of perindopril was shown to reduce the severity of low-level inflammation and ED, which may reduce the risk of HF in patients with COPD [21, 22].

Beneficial effects of perindopril were also observed in patients with CKD. Nosrati et al. [23] found that levels of protein in the urine decreased and albumin in the blood increased in patients with nephrotic syndrome in one year of perindopril therapy. This effect was maintained with continuous drug use.

The PROGRESS study confirmed the positive effects of perindopril in patients with CKD. Perindopril reduced the risk of severe vascular complications and stroke by 30% and 35%, respectively [24].

Our study demonstrated the significant contribution of CAD to the development of HFpEF, as well as the listed comorbidities and arterial hypertension. Based on earlier studies, perindopril was shown to be effective in patients with CAD in reducing the incidence of cardiovascular events [19, 25].

HF develops in the presence of such risk factors as arterial hypertension, CAD, obesity, DM, COPD and CKD. Given the beneficial effects of perindopril in patients at risk of developing HF, a study was conducted to evaluate the efficacy of this drug in patients with HF. In the PEP-CHF study, 107 and 100 patients were allocated to the placebo and perindopril groups, respectively. Along with an improved clinical picture, exercise tolerance increased and the number of hospitalizations for HF decreased over a period 12 months [26]. However, there is no data on the efficacy of perindopril in HFpEF.

This positive effects of perindopril for patients with HFpEF and HFmrEF demonstrated by this study, such as increased PS and OI in both patient groups, indicates the reversibility of ED. Comparable results were obtained in our previous studies, in which patients with HFmrEF and

HFpEF were analyzed in the same group [27]. Along with the improved endothelial function, photoplethysmography showed a decrease in the E-selectin and ET-1 levels in patients with HFpEF. During perindopril therapy, the 6-minute walk distance also improved in both groups.

Since patients with HFmrEF and HFpEF mainly had similar comorbidities, the efficacy of perindopril may be assumed in both groups. When prescribing treatment, a focus should probably be placed on the presence of concomitant diseases accompanied by the activation of RAAS and the development of endothelial dysfunction, rather than HF that aims to achieve ED reversibility as the main aspect of HFpEF progression, improvement of HF functional class and prognosis.

Conclusion

The results of our study show the positive effect of perindopril on endothelial structure and function, along with the ability to reduce the levels of endothelial dysfunction markers (E-selectin and endothelin-1) in patients with concomitant diseases and heart failure with preserved and mid-range left ventricular ejection fraction. Given the role of endothelial dysfunction in the progression of heart failure with a preserved and moderately reduced (intermediate) left ventricular ejection fraction, the reversibility of endothelial dysfunction during the treatment with perindopril can be used as a major entry point in the treatment of this category of patients.

Limitations

The limitation of this study is a small sample of patients. Large, randomized trials in this area are required to confirm the positive effects of perindopril on endothelial function and the prognosis for patients with HFpEF and HFmrEF.

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