Safonova Yu. I., Kozhevnikova M. V., Danilogorskaya Yu. A.,
Zheleznykh E. A., Zektser V. Yu., Shchendrygina A. A., Ilgisonis I. S.,
Privalova E. V., Khabarova N. V., Belenkov Yu. N.
Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

Positive effects of perindopril on microvascular vessels in patients with chronic heart failure

Aim	To evaluate the effect of 12-month perindopril treatment on structure and function of microvasculature (MV) in patients with chronic heart failure with preserved (HFpEF) and intermediate (HFiEF) left ventricular ejection fraction.
Material and methods	30 patients with HFpEF and HFiEF were evaluated. Perindopril at a maximum tolerated dose was administered to all patients for 12 months. Changes in MV structure and function were assessed with photoplethysmography and capillaroscopy prior to the treatment onset and at 12 months, i.e., after completion of the perindopril treatment.
Results	The 12-month perindopril treatment was associated with improvement of the endothelial function evident as increases in the occlusion index (OI) and the phase shift (PS). OI increased from 1.45 [1.3; 1.6] to 1.8 [1.6; 2.2] (p=0.00004). PS increased from 7.1 ms [4.8; 10.2] to 9.2 ms [6.7; 13.2] (p=0.0003). Stiffness of muscular large blood vessels was decreased. Arterial stiffness index (aSI) decreased from 8.8 [6.6; 11.0] to 7.45 [6.5; 9.4] m/s (p=0.01). The perindopril treatment was associated with increased density of the capillary network at rest (p=0.008) and in tests with venous occlusion (p=0.003) and reactive hyperemia (p=0.0003).
Conclusion	The study showed an improvement of endothelial function associated with the 12-month perindopril therapy in patients with HFpEF and HFiEF.

Keywords	Chronic heart failure; preserved left ventricular ejection fraction; intermediate left ventricular ejection fraction; endothelial dysfunction; perindopril
For citation	Safonova Yu. I., Kozhevnikova M. V., Danilogorskaya Yu. A., Zheleznykh E. A., Zektser V. Yu., Shchendrygina A. A. et al. Positive effects of perindopril on microvascular vessels in patients with chronic heart failure. Kardiologiia. 2020;60(8):65–70. [Russian: Сафонова Ю. И., Кожевникова М. В., Данилогорская Ю. А., Железных Е. А., Зекцер В. Ю., Щендрыгина А. А. и др. Положительное влияние периндоприла на сосуды микроциркуляторного русла у больных с хронической сердечной недостаточностью. Кардиология. 2020;60(8):65–70]

Corresponding author	Safonova Yu. I. E-mail: thunderbird. 3194@gmail.com

More than 26 million people worldwide suffer chronic heart failure (CHF) [1]. This number is growing continuously each year. By approximately 2030, the prevalence of CHF is expected to increase by 46% [2]. In Russia, the prevalence of CHF is 7–10% [3]. More than 50% of all patients have CHF with preserved (HFpEF) and mid-range ejection fraction (HFmrEF), as shown by echocardiogram [4, 5].

Endothelial dysfunction is one of the mechanisms for the development of HFpEF. The endothelium is known to be involved in regulating vessel tone, leukocyte adhesion, and the processes of hemostasis and angiogenesis. The present understanding is that endothelial dysfunction is an imbalance between the synthesis of vasodilators and vasoconstrictors, angioprotective and prothrombotic factors, and antiproliferative and proliferative factors [6]. Concomitant diseases, such as anemia, chronic obstructive pulmonary disease, obesity, diabetes mellitus, contribute to the development of a pro-inflammatory state, the increased synthesis of reactive oxygen species, and oxidative stress, which alters vasomotor function, causing a decreased expression of eNOS and, thus, the reduced levels of nitric oxide (NO). The low bioavailability of NO contributes to reduced guanylate cyclase activity, a decrease in cyclic guanosine monophosphate (cGMP) levels, and abnormal titin phosphorylation.

These result in elevated collagen synthesis and diastolic resting membrane potential of cardiomyocyte. This increases myocardial stiffness and aggravates diastolic dysfunction [7, 8]. Vascular wall stiffness increases together with the vasomotor dysfunction. Increased stiffness is likely to be a presentation of artery remodeling accompanied by hypertrophy of the vascular walls [9].

Thus, endothelial dysfunction contributes to the accelerated development of myocardial fibrosis and remodeling. The pathogenesis of HFmrEF is less understood. However, it was reported that these patients have the features of both HFmrEF and HFpEF [10].

Given the essential role of the endothelium in the development of CHF, scientists satisfy their attention by studying and developing methods to assess endothelial function in this group of patients. Out of all available methods non-invasive examination techniques are preferred because they are easy to use and complication-free. Flow-mediated vasodilation (FMVD) is the gold standard of the evaluation of endothelial function. However, there is a more accessible option, computed photoplethysmography with evidence-based efficacy of assessing endothelial function in patients with cardiovascular diseases [11]. This method allows structural changes to be evaluated, as well as the endothelial function of microcirculatory and large vessels. The results do not depend on the experience and qualification of a person performing an examination and have a prognostic value comparable to FMVD [12–15].

Clinical and experimental data on the association of endothelial dysfunction with the progression of heart failure [16, 17] has been accumulated. Thus, a hypothesis has been proposed that restored endothelial function may improve the prognosis in patients with HFpEF and HFmrEF [18].

Drug therapy in CHF is based on neurohumoral blockade using angiotensin-converting enzyme (ACE) inhibitors. Perindopril offers the most significant evidential basis for improving endothelial function among the ACE inhibitors. Its beneficial effects on the endothelium were shown in patients with hypertension and coronary artery disease (CAD). However, the effect on endothelial function in patients with HFpEF and HFmrEF has not yet been studied [19–21].

This study aims to evaluate the effect of 12-month therapy with perindopril on the endothelial function using photoplethysmography and capillaroscopy in patients with HFpEF and HFmrEF.

Material and methods

A total of 30 patients with CHF (17 male and 13 female) with preserved (n=12) and mid-range (n=18) EF of NYHA functional class (FC) II–III were examined. The mean age of patients was 66 years (47–88 years). The general characteristics of patients are provided in Table 1 and the distribution of diseases in Figure 1.

All patients had hypertension, and CAD was confirmed in 90%. A history of myocardial infarction was reported in 4 patients with HFpEF and 12 patients with HFmrEF. Type 2 diabetes mellitus was identified in 6 patients with HFpEF and 12 patients with HFmrEF. HFmrEF was predominantly NYHA FC III CHF (n=14). An equal number of patients with HFmrEF had NYHA FC II and III with good tolerance of physical exercise (n=6 in each subgroup).

All patients had been using beta-blockers and mineralocorticoid receptor antagonists for a long time. 80% of patients received ACE inhibitors, excluding perindopril (Figure 2).

All patients signed informed consent. The study was approved by the Local Ethics Committee and was conducted following the principles of the Helsinki Declaration. The patients underwent a standard cardiological examination consisting of physical examination, a 6-minute walking test, electrocardiogram Holter monitoring, 24-hour blood pressure (BP) monitoring, echocardiogram, standard laboratory tests. HFmrEF and HFmrEF were diagnosed based on the clinical picture, levels of N-terminal pro-brain natriuretic peptide (more than 125 pg/mL) and echocardiogram (EF 40–49% in patients with HFmrEF and 50% or more in patients with HFpEF,

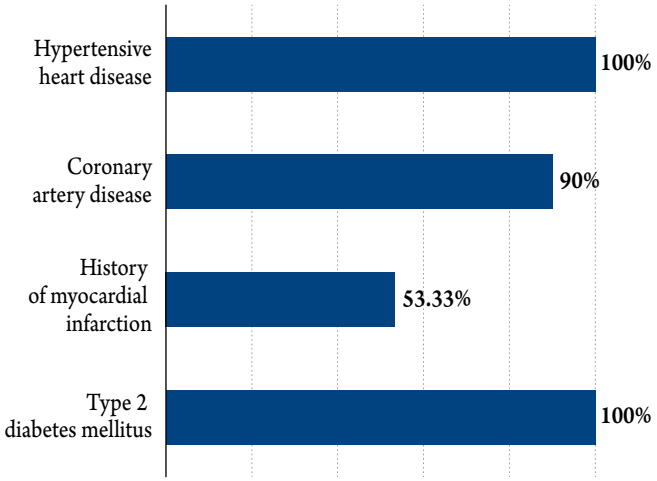
Table 1. General characteristics of the subjects

Parameter	Patients with CHF (n=30)
Male	17 (56.66%)
Female	13 (48.33%)
Age, years	66 [61; 69]
BMI, kg/m^2	32.25 [29.07; 37.18]
Glucose, mmol/L	5.95 [5; 7.4]
Total cholesterol, mmol/L	4.33 [3.75; 5.61]
LDL-C, mmol/L	2.7 [2.15; 3.73]
SBP, mm Hg	160 [155; 172]
DBP, mm Hg	96 [90; 100]
Creatinine, mg/dL	0.97 [0.81; 1.18]
NT-proBNP, pg/mL	305 [250; 361]
GFR, mL/min/1.73m^2	89.15 [70.8; 107.2]
LVEF, %	47 [45; 53]
LVMI, g/m^2	113 [101; 130]
LA volume index, mL/m^2	36.61 [34.4; 41.14]
NYHA FC II CHF	10 (33.33%)
NYHA FC III CHF	20 (66.66%)

CHF, chronic heart failure; BMI, body mass index; LDL-C, low-density lipoproteins; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal natriuretic peptide; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LA, left atrium; FC, functional class.

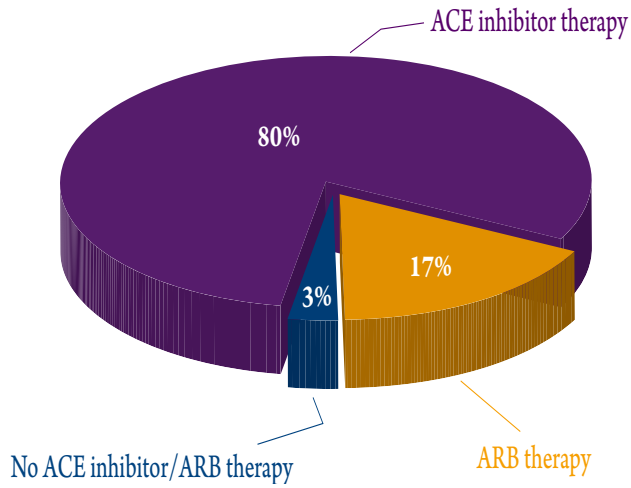
ISSN 0022-9040. Kardiologiia. 2020;60(8). DOI: 10.18087/cardio.2020.8.n1216

Figure 1. Distribution of diseases in the included patients with CHF (%)



left atrial volume index more than 34 mL/m^2). The exclusion criteria were unstable angina, FC IV CHF, valvular heart disease, cancer, chronic viral and bacterial infections, chronic kidney disease stage V, mental illnesses, pregnancy, and lactation. All patients included underwent photoplethysmography and capillaroscopy, in order to assess the structural and functional state of the microcirculatory vessels and large arteries. Photoplethysmography included such measurements as phase shift (PS) and occlusion index (OI) characterizing the endothelial function of large muscle-type and microcirculatory vessels. PS less than 10 ms and OI more than 1.8 are indicative of the preserved endothelial function. Moreover, the stiffness index (aSI) was determined, characterizing structural changes in the vascular wall of large vessels. Normal stiffness is less than 8 m/s. The reflection index (RI) was calculated, in order to assess the structure of microcirculatory vessels. RI is used to evaluate the remodeling of arterioles. Its normal value is less than 30%. The dysfunction and structure of the capillaries were assessed by computed videocapillaroscopy using a Capillaroscan-1 device. Capillary density at rest (CDr), capillary density after venous occlusion test (CDvo), and capillary density during reactive hyperemia (CDrh) were determined. Patients who had been treated with other ACE inhibitors or sartans were transferred to perindopril after a 48-hour washout period. In the case of those patients who had not taken ACE inhibitors or sartans, perindopril was administered for the first time with titration to the maximum tolerated dose. After 12 months of perindopril therapy, the structural and functional state of the microcirculatory and large vessels was assessed again.

Figure 2. Renin-angiotensin-aldosterone system inhibitor therapy in the included patients with chronic heart failure



The data was processed using the Statistica software. Quantitative data is expressed as the median and the interquartile range. Categorical data is presented in terms of absolute values (quantity) and percentage. The significance of differences in the quantitative values was evaluated using the Wilcoxon test for two related samples. Differences were significant at $p<0.05$.

Results

The 12-month therapy with perindopril led to positive changes, such as the improved endothelial function of microcirculatory and large muscle-type vessels (Table 2). Photoplethysmography showed statistically significant increases in OI and PS in patients with HFpEF and HFmrEF. OI increased from 1.45 [1.3; 1.6] to 1.8 [1.6; 2.2], and PS increased from 7.1 [4.8; 10.2] to 9.2 [6.7; 13.2] ms. The structural state of the large vessels also improved. The stiffness index (aSI) was elevated to 8.8 [6.6; 11.0] m/s before therapy. After 12 months of perindopril use, vessel stiffness decreased, and aSI was 7.45 [6.5; 9.4] m/s. The tone of arterioles increased during perindopril therapy, as evidenced by a statistically significant increase in RI (normal values are less than 30%).

Capillaroscopy showed an increased number of capillaries during perindopril therapy at rest, during reactive hyperemia, and after venous occlusion tests (Table 3). CDr before the start of perindopril therapy was 53.66 [39; 67.33] capillaries/mm^2, increasing to 54.5 [44; 70] capillaries/mm^{2}12 months later. Moreover, there was a statistically significant increase in CDrh from 60.83 [44.66; 73.33] to 64 [56; 78] capillaries/mm^2 and CDvo from 63.5 [49.33; 83.33] to 68.5 [51; 87] capillaries/m^2. Thus, the improvement in both structural and functional states of capillaries was shown.

Table 2. Changes in the structural and functional state of the vascular wall during perindopril therapy in patients with HFpEF and HFmrEF

Parameter	Before therapy (n=30)	After 12 months of therapy (n=30)	p
OI (normal < 1.8)	1.45 [1.3; 1.6]	1.8 [1.6; 2.2]	0.00004
PS, ms (normal > 10 ms)	7.1 [4.8; 10.2]	9.2 [6.7; 13.2]	0.0003
aSI, m/s (normal <8 m/s)	8.8 [6.6; 11.0]	7.45 [6.5; 9.4]	0.01
RI, % (normal <30%)	47.05 [28.2; 58.6]	55.05 [29.2; 61.8]	0.00002

HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; OI, occlusion index; PS, phase shift; SI, stiffness index; RI, reflection index.

Table 3. Changes in the structural and functional state of the finger skin capillaries in patients with HFpEF and HFmrEF

Parameter	Before therapy (n=30)	After 12 months of therapy (n=30)	p
CDr, capillaries/mm^2	53.66 [39; 67.33]	54.5 [44; 70]	0.008
CDvo, capillaries/mm^2	63.5 [49.33; 83.33]	68.5 [51; 87]	0.003
CDrh, capillaries/mm^2	60.83 [44.66; 73.33]	64 [56; 78]	0.0003

HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; Cdr, capillary density at rest; CDrh, capillary density during reactive hyperemia; CDvo, capillary density after venous occlusion test.

Discussion

Perindopril has a proven effect on endothelial function. It is an ACE inhibitor and implements its effect by suppressing the renin-angiotensin-aldosterone system (RAAS). RAAS is actively involved in the development of systemic inflammation. There is information in the literature that RAAS induces increased synthesis of reactive oxygen species and adhesion molecules through the vessel wall inflammation processes, disturbing the endothelial function [22]. On the contrary, RAAS inhibition is expected to improve endothelial function, including in patients with HFpEF and HFmrEF, since their pathogenesis is based on endothelial dysfunction caused by systemic inflammation. In patients with diabetes mellitus and normal blood pressure Marketou et al. [23] demonstrated decreased cytokine levels and oxidative stress during perindopril therapy. The authors assumed that the effect of perindopril was associated with a decreased activity of systemic inflammation. Other trials also confirmed this assumption. Tousoulis et al. [24] demonstrated a reduction in C-reactive protein and fibrinogen levels and an improved vasodilation response of the forearm arteries during reactive hyperemia after 4-week perindopril therapy. Given the role of inflammation in the pathogenesis of HFpEF and HFmrEF and our findings, we expect perindopril also to reduce inflammation processes in the vascular wall and contribute to the improvement of endothelial function in patients with HFpEF and HFmrEF.

Ghiadoni et al. [19] conducted one of the first trials to study the effects of drug therapy on endothelium function and showed statistically significant improvement in endothelium function according to FMVD during perindopril therapy in patients with hypertension. In 2007, the PERTINENT trial also demonstrated the beneficial effect of perindopril on endothelial function in patients with CAD. The trial included 87 patients. Endothelial function was assessed by means of laboratory testing (blood levels of von Willebrand factor, endothelial NO-synthase [eNOS], angiotensin II, tumor necrosis factor-α [TNF-α]) and apoptosis assay by flow cytometry. Of these 87 patients, 43 received perindopril, and 44 received a placebo. During the 12 month course of perindopril therapy, a statistically significant decrease was observed in the levels of the von Willebrand factor, angiotensin II, TNF-α and the number of apoptosis cells, and the activity and expression of eNOS increased [20]. In 2007, double-blind, randomized, placebo-controlled trial PERFECT was also conducted to assess the effect of perindopril on endothelial function. The trial included 333 patients with CHF. All patients underwent ultrasound evaluation of endothelial function by perindopril-dependant brachial dilatation, repeated in 6 months of follow-up. 167 and 166 patients were randomized to the perindopril and placebo groups, respectively. The trial showed a significant improvement of endothelial function in 6 months [21]. The Department of Hospital Therapy No. 1 of Sechenov University of the Ministry of Healthcare of Russia also actively studied endothelial function changes during mono- and combination therapy. One of the trials demonstrated improved endothelial function according to a computed photoplethysmography and

ISSN 0022-9040. Kardiologiia. 2020;60(8). DOI: 10.18087/cardio.2020.8.n1216

video capillaroscopy during the 12-month therapy with perindopril and amlodipine in patients with hypertension [25].

Given the contribution of endothelial dysfunction to the development and progression of HFpEF and HFmrEF, the evaluation of the perindopril effect on endothelial function in those groups of patients seems interesting.

This study has demonstrated improvement in microcirculatory endothelial function after 12 months of perindopril therapy. Patients had a better functional state of the endothelium (OI and PS) according to photoplethysmography and of the capillaries, as evidenced by improved CDhr in videocapillaroscopy.

Despite the small number of patients, the findings of this pilot study appear promising and pathogenetically substantiated in patients with HFpEF and HFmrEF.

Conclusion

The evidence of our findings show the beneficial effect of 12-month therapy with perindopril on the endothelial function of microcirculatory vessels and the structural and functional state of large muscle-type vessels in patients with HFpEF and HFmrEF. The results in the subgroups of patients with heart failure with preserved and mid-range left ventricular ejection fraction were unidirectional, which allowed their combination. However, larger placebo-controlled clinical trials are required to assess the effects of perindopril on the endothelial function and correlate the improved endothelial function with the prognosis for the patients with HFpEF and HFmrEF.

No conflict of interest is reported.

The article was received on 15/06/2020

REFERENCES

1. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M et al. The Global Health and Economic Burden of Hospitalizations for Heart Failure. Journal of the American College of Cardiology. 2014;63(12):1123–33. DOI: 10.1016/j.jacc.2013.11.053
2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP et al. Heart Disease and Stroke Statistics – 2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56–528. DOI: 10.1161/CIR.0000000000000659
3. Polyakov D.S., Fomin I.V., Vaysberg A.R. EPOCHA-D-CHF: gender differences in the prognosis of patients with CHF af-ter acute decompensation (part 2). Kardiologiia. 2019;59(4S):33–43. [Russian: Поляков Д.С., Фомин И.В., Вайсберг А.Р. ЭПОХА–Д–цХСН: гендерные различия в прогнозе жизни больных с ХСН при острой декомпенсации сердечной недостаточности (часть 2). Кардиология. 2019;59(4S):33-43]. DOI: 10.18087/cardio.2654
4. Hsu JJ, Ziaeian B, Fonarow GC. Heart Failure With Mid-Range (Borderline) Ejection Fraction. Clinical Implications and Future Directions. JACC: Heart Failure. 2017;5(11):763–71. DOI: 10.1016/j.jchf.2017.06.013
5. Kanorskii S.G., Borisenko Yu. V. Chronic Heart Failure with Preserved Ejection Fraction: Effective Treatment Possible? Kardiologiia. 2018;58(6):85–9. [Russian: Канорский С.Г., Борисенко Ю.В. Хроническая сердечная недостаточность с сохраненной фракцией выброса: возможно ли эффективное лечение? Кардиология. 2018;58(6):85-9]. DOI: 10.18087/cardio.2018.6.10154
6. Kireeva V.V., Koch N.V., Lifschitz G.I., Apartsin K.A. Endothelial dysfunction as cornerstone of cardiovascular events: molecular and pharmaceutic aspects. Russian journal of Cardiology. 2015;19(10):64–8. [Russian: Киреева В.В., Кох Н.В., Лифшиц Г.И., Апарцин К.А. Дисфункция эндотелия как краеугольный камень сердечно-сосудистых событий: молекулярно- и фармакогенетические аспекты. Российский кардиологический журнал. 2014;19(10):64-8]. DOI: 10.15829/1560-4071-2014-10-64-68
7. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. Journal of the American College of Cardiology. 2013;62(4):263–71. DOI: 10.1016/j.jacc.2013.02.092
8. Franssen C, Chen S, Unger A, Korkmaz HI, De Keulenaer GW, Tschöpe C et al. Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction. JACC. Heart failure. 2016;4(4):312–24. DOI: 10.1016/j.jchf.2015.10.007
9. Nakamura M, Sugawara S, Arakawa N, Nagano M, Shizuka T, Shimoda Y et al. Reduced vascular compliance is associated with impaired endothelium-dependent dilatation in the brachial artery of patients with congestive heart failure. Journal of Cardiac Failure. 2004;10(1):36–42. DOI: 10.1016/S1071-9164(03)00585-2
10. Nauta JF, Hummel YM, van Melle JP, van der Meer P, Lam CSP, Ponikowski P et al. What have we learned about heart failure with mid-range ejection fraction one year after its introduction? European Journal of Heart Failure. 2017;19(12):1569–73. DOI: 10.1002/ejhf.1058
11. Belenkov Yu.N., Shchendrygina A.A., Privalova E.V., Kuznetsov A.P., Kuznetsov M.I. Method for assessing the state of the vascular bed in healthy individuals with cardiovascular risk factors and in cardiovascular patients. RU 2508900 C1. Zayavka 2012156011/14 from 24.12.2012. 2012. [Russian: Беленков Ю.Н., Щендрыгина А.А., Привалова Е.В., Кузнецов А.П., Кузнецов М.И. Способ оценки состояния сосудистого русла у здоровых лиц с факторами риска развития сердечно-сосудистых заболеваний и больных сердечно-сосудистыми заболеваниями. Патент RU 2508900 C1. Заявка 2012156011/14 от 24.12.2012. Доступно на: https://yandex.ru/patents/doc/RU2508900C1_20140310]
12. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. European Heart Journal. 2010;31(9):1142–8. DOI: 10.1093/eurheartj/ehq010
13. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. American Heart Journal. 2003;146(1):168–74. DOI: 10.1016/S0002-8703(03)00094-2
14. Weisrock F, Fritschka M, Beckmann S, Litmeier S, Wagner J, Tahirovic E et al. Reliability of peripheral arterial tonometry in patients with heart failure, diabetic nephropathy and arterial hypertension. Vascular Medicine. 2017;22(4):292–300. DOI: 10.1177/1358863X17706752
15. Fujisue K, Sugiyama S, Matsuzawa Y, Akiyama E, Sugamura K, Matsubara J et al. Prognostic Significance of Peripheral Microvascular Endothelial Dysfunction in Heart Failure With Reduced Left Ventricular Ejection Fraction. Circulation Journal. 2015;79(12):2623–31. DOI: 10.1253/circj.CJ-15-0671

16. Shantsila E, Wrigley BJ, Blann AD, Gill PS, Lip GYH. A contemporary view on endothelial function in heart failure. European Journal of Heart Failure. 2012;14(8):873–81. DOI: 10.1093/eurjhf/hfs066
17. Giannitsi S, Maria B, Bechlioulis A, Naka K. Endothelial dysfunction and heart failure: A review of the existing bibliography with emphasis on flow mediated dilation. JRSM Cardiovascular Disease. 2019;8:204800401984304. DOI: 10.1177/2048004019843047
18. Premer C, Kanelidis AJ, Hare JM, Schulman IH. Rethinking Endothelial Dysfunction as a Crucial Target in Fighting Heart Failure. Mayo Clinic Proceedings: Innovations, Quality & Outcomes. 2019;3(1):1–13. DOI: 10.1016/j.mayocpiqo.2018.12.006
19. Ghiadoni L, Magagna A, Versari D, Kardasz I, Huang Y, Taddei S et al. Different Effect of Antihypertensive Drugs on Conduit Artery Endothelial Function. Hypertension. 2003;41(6):1281–6. DOI: 10.1161/01.HYP.0000070956.57418.22
20. Ceconi C, Fox K, Remme W, Simoons M, Bertrand M, Parrinello G et al. ACE inhibition with perindopril and endothelial function. Results of a substudy of the EUROPA study: PERTINENT. Cardiovascular Research. 2007;73(1):237–46. DOI: 10.1016/j.cardiores.2006.10.021
21. Bots ML, Remme WJ, Lüscher TF, Fox KM, Bertrand M, Ferrari R et al. ACE Inhibition and Endothelial Function: Main Findings of PERFECT, a Sub-Study of the EUROPA Trial. Cardiovascular Drugs and Therapy. 2007;21(4):269–79. DOI: 10.1007/s10557-007-6041-3
22. Brasier AR, Recinos A, Eledrisi MS. Vascular Inflammation and the Renin-Angiotensin System. Arteriosclerosis, Thrombosis, and Vascular Biology. 2002;22(8):1257–66. DOI: 10.1161/01.ATV.0000021412.56621.A2
23. Marketou ME, Zacharis EA, Koukouraki S, Stathaki MI, Arfanakis DA, Kochiadakis GE et al. Effect of angiotensin-converting enzyme inhibitors on systemic inflammation and myocardial sympathetic innervation in normotensive patients with type 2 diabetes mellitus. Journal of Human Hypertension. 2008;22(3):191–6. DOI: 10.1038/sj.jhh.1002310
24. Tousoulis D, Kourtellaris P, Antoniades C, Vasiliadou C, Papageorgiou N, Tentolouris C et al. Effects of irbesartan and perindopril on forearm reactive hyperemia and inflammatory process, in normotensive patientswith coronary artery disease. International Journal of Cardiology. 2008;124(1):127–9. DOI: 10.1016/j.ijcard.2006.11.206
25. Danilogorskaya Yu.A., Zheleznykh E.A., Privalova E.V., Shchendrygina A.A., Belenkov Yu.N., Ilgisonis I.S. et al. Influence of the combination drug Prestans (perindopril A, amlodipine) on morpho-functional parameters of arterial bed in essential hypertension. Russian Journal of Cardiology. 2017;22(12):113–9. [Russian: Данилогорская Ю.А., Железных Е.А., Привалова Е.В., Щендрыгина А.А., Беленков Ю.Н., Ильгисонис И.С., Тишман М.И. Влияние фиксированной комбинации Престанс (периндоприл А и амлодипин) на морфофункциональные показатели состояния артериального русла у больных с гипертонической болезнью. Российский кардиологический журнал. 2017;22(12):113-9]. DOI: 10.15829/1560-4071-2017-12-113-119

ISSN 0022-9040. Kardiologiia. 2020;60(8). DOI: 10.18087/cardio.2020.8.n1216