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Vasoprotective Effects of Prolonged Therapy with Perindopril A in Patients with Hypertension Including Concomitant Type 2 Diabetes Mellitus

Objective	Investigate the dynamics of morphological and functional markers of vascular remodeling in patients with arterial hypertension (AH), including those with concomitant type 2 diabetes mellitus (DM2), during 12-month administration of perindopril A.
Materials and Methods	The study included patients with grade I-II AH, with and without DM2 (30 and 32 patients, respectively), who underwent outpatient correction of initially ineffective antihypertensive therapy and administration of perindopril A, 10 mg/day. Morphological and functional parameters of vascular remodeling were evaluated in all patients at baseline and at 12 months using photoplethysmography. Stiffness index (SI) and phase shift (PS) were measured in large vessels. Reflection index (RI) and occlusion index (OI) were measured in microvessels. Computed nailfold videocapillaroscopy was used to determine capillary density (CD) at rest (CDr), CD during venous occlusion test (CDvo), and CD during reactive hyperemia test (CDrh). Data are medians [interquartile range].
Results	After 12-month administration of perindopril A, the morphological and functional parameters of vascular remodeling in AH patients without DM2 significantly improved at all vascular levels. SI decreased to 9.25 [7.8; 10.93] m/s and PS increased to 7.4 [5.6; 9.05] ms. In microvasculature, a statistically significant reduction was observed in RI, 31 [27; 36.5], and an increase was observed in OI, which characterizes endothelium function, 1.75 [1.68; 1.9]. Capillary CDr significantly increased to 40.5 [34.93; 46] cap/mm2, as did CDvo and CDrh. At the same time, in the group of patients with AH and DM2, a significant improvement was observed for the large vessels. SI decreased to 9.8 [9.08; 10.58] m/s, and PS increased to 6.95 [5.13; 10.08]. The RI index, reflecting the structural condition of arterioles, significantly decreased to 34 [25.9; 45.53]%, and the OI index, characterizing endothelial function, did not change significantly, 1.4 [1.3; 1.6]. Capillary CDr significantly increased to 31.55 [27.68; 34.7] cap/mm2; however, CDvo and CDrh did not change significantly. Renal function improved in both groups.
Conclusion	Both groups demonstrated improvement of morphological parameters at all levels of the arterial bed. However, patients with AH and concomitant DM2 showed no improvement of the endothelial function of arterioles and capillaries compared to improvement in AH patients without DM2. This reflected the more severe endothelial dysfunction present in AH patients with DM2.

Keywords	Vascular remodeling; arterial stiffness; type 2 diabetes mellitus; arterial hypertension; endothelial dysfunction; perindopril
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In the 21st century, arterial hypertension (AH) and diabetes mellitus (DM) became pandemic, and the incidence is likely only to increase [1, 2]. AH and DM have proved to be mutually confounding. The significance of the combination of AH and type 2 DM (DM2) is due to the similar adverse effect of these pathologies on the target organs, which contributes to the increased risk of cardiovascular complications (CVCs) [3].

After investigating mechanisms of target organ damage in AH patients, researchers have concluded that the critical factor is the remodeling of vascular walls, which is characterized by an increase in arterial stiffness, decrease in elasticity, endothelial dysfunction, and increased vascular tone. The 2013 guidelines of the European Society of AH/European Society of Cardiology (ESH/

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ESC) for the treatment of AH suggested that arterial stiffness is an independent risk factor for development of CVCs [4].

Changes in vessel wall morphology, i.e., structure, and in vessel wall function involve a complex, multifactorial process of altering the properties of smooth muscle cells and extracellular matrix components [5]. Activation of the following systems is the most studied factor responsible for transformation of the vascular wall components.

- Metalloproteinases/tissue inhibitors of metalloproteinases that regulate collagen content in the walls of arteries and arterioles and thus participate in the pathogenesis of cardiovascular diseases [6-8].
- Neurohumoral systems, particularly, the renin-angiotensin-aldosterone system. Angiotensin II stimulates production of type 1 collagen by smooth muscle cells and transforming growth factor β_1 (TGF-β_1) that activates fibrotic changes in the cardiovascular system [9, 10].
- Endothelial systems, which activate endothelin-1 synthesis and reduce NO synthesis. Endothelin-1 binds to endothelin receptors on smooth muscle cells, causing vasoconstriction with subsequent proliferation and hypertrophy of smooth muscle cells [10–12]. DM2 in hypertensive patients significantly exacerbates the processes of vascular remodeling and accelerates the development of atherosclerosis [13]. In addition, hyperglycemia and insulin resistance are key promoting factors of fibrosis, including increased synthesis of TGF-β_1 and disrupted myogenic autoregulation [14, 15].

Thus, the effectiveness of treatment and prognosis for AH patients, particularly those with concomitant DM2, depends not only adjusting blood pressure (BP) but also on reducing the degree of vascular remodeling. Numerous multicenter trials (HOPE, PROGRESS, EUROPE, ADVANCE) proved that, of all groups of antihypertensive drugs, angiotensin-converting enzyme (ACE) inhibitors could both effectively control blood pressure and reduce the risk of adverse outcomes, such as stroke, myocardial infarction, and heart failure [16-20].This seems to be due to the ability of ACE inhibitors to positively influence structural and functional parameters of vascular walls in addition to controlling blood pressure.

The objective of this study was to investigate the dynamics of structural and humoral markers of vascular remodeling in patients with AH, including patients with concomitant DM2, during administration of the ACE inhibitor, perindopril A.

Material and Methods

The study was performed in University Clinical Hospital no.1 of I.M. Sechenov First Moscow State Medical University, Moscow, Russia. The open-label, nonrandomized survey included patients with grades I-II AH, including patients with decompensated DM2, who visited a cardiologist in the outpatient clinic for the correction of antihypertensive therapy due to its ineffectiveness, and who had not previously taken perindopril products. Only previously prescribed ACE inhibitors and angiotensin II receptor antagonists were changed to perindopril A, 10 mg/day. Other concomitant treatments were not modified.

Patients were examined twice in the cardiology department, at baseline and after 12 months of antihypertensive therapy with perindorpil A, 10 mg/day. Variables measured included systolic BP (SBP), diastolic blood pressure (DBP), heart rate, electrocardiography, echocardiography, blood biochemistry. Photoplethysmography (Angioscan-01) was also performed at these times to assess the structural and functional state of large vessel walls, e.g., aorta, brachial artery, radial artery, and to assess the functional state of the microvasculature, i.e., arterioles. Evaluated parameters of vessel wall remodeling included stiffness index (SI) of the large vessels and reflection index (RI) of the microvasculature. A reactive hyperemia test was performed to assess endothelial function. For this test, CD was measured following release of a cuff, which had been inflated to 220 mm Hg for 5 min. The endothelial function of the large vessels and microvasculature was assessed from the phase shift (PS) and from the occlusion index (OI), respectively.

Computed nailfold videocapillaroscopy with a Capillaroskan-1 device (TU 9442-001-82402834-2008) was performed to examine the skin capillary network of a finger. The structural state of the capillary network was evaluated from the capillary density (CD) at rest (CDr) and by the venous occlusion test (CDvo). The functional state was evaluated by the reactive hyperemia test (CDrh).

Data were analyzed using a Statistica 7.0 software package. Quantitative data are presented as median and interquartile range, and qualitative characteristics as absolute (n) and relative values (%). Statistical significance of differences between quantitative parameters was determined with the Wilcoxon test for comparison of two related groups. Differences were considered to be statistically significant with $p<0.05$. The statistical significance of intergroup differences in the qualitative parameters was evaluated using Fisher's exact test with 2x2 contingency tables. Hypotheses were tested at the level of significance $p=0.05$.

Patients included in the study

Patients with grades I-II AH were divided into two groups (Table 1), AH with DM2 (n=30, 19 females and

11 males) and AH without DM2 (n=32, 18 females and 14 males). The groups were comparable in age, sex, duration of AH, total cholesterol (TC), low-density lipoprotein cholesterol (LDL) and high-density cholesterol (HDL). However, AH patients with DM2 were obese, had significantly higher BP values, and a 1.5 times higher rate of coronary artery disease.

Assessment of the vascular state in the two groups detected signs of structural and functional changes of large vessels, specifically increased SI combined with reduced PS, and of microvessels, specifically increased RI combined with reduced OI, CDr, and CD (Table 2).

Results

The 12-month follow-up examination of AH patients without DM2 and treated with regular antihypertensive therapy, including perindopril A 10 mg/day, revealed significant decreases in SBP (17%), DBP (9%), myocardial hypertrophy of both the left ventricular (LV) posterior wall and interventricular septum (8%) (Table 3). LV ejection fraction did not change significantly.

Morphological and functional parameters for both large and microvessels showed significant improvement (Table 4). For morphological parameters, large vessel SI decreased to 7.4 [7.08; 7.93] m/s and PS increased to 7.4 [5.6; 9.05] ms. Microvasculature RI decreased to 31 [27; 36.5] %. OI, characterizing endothelial function, increased to 1.75 [1.68; 1.9]). Capillary CDr increased significantly to 40.5 [34.93; 46] cap/mm2. CDrh and CDvo (Table 4).

In AH patients with DM2, SBP decreased by 12.7% ($p<0.05$) and DBP decreased by 8.5% [80; 84], which was associated with improved morphological and functional cardiac parameters, i.e., significant increase in LVEF by 1.8%, and decrease in LV hypertrophy (Table 4). Statistically significant improvements in morphological and functional parameters was shown for both large and microvessels. SI decreased to 9.25 [7.8; 10.93] m/s, PS increased to 7.4 [5.6; 9.05] ms) and microvasculature

Table 1. Comparative characteristics of AH patients with and without DM2

Parameter	AH+ DM2 (n=30)	AH (n=32)	p
Age, years	60.5 [56; 64.75]	58.5 [54.75; 65.0]	<0.01
Male / female	11 / 19	14 / 18	-
Duration of AH, years	12 [9.25; 15]	12.0 [9.0; 14.25]	<0.01
CAD, %	70	47	-
BMI, kg/m^2	35.6 [33.7; 37.8]	28.66 [26.82; 29.83]	<0.01
TC, mmol/l	5.9 [5.3; 6.4]	5.5 [5.1; 6.4]	0.36
LDL, mmol/l	3.8 [3.2; 4.3]	3.7 [2.52; 4.2]	0.39
HDL, mmol/l	0.96 [0.8; 1.15]	1.12 [0.98; 1.4]	0.02
TG, mmol/l	2.0 [1.49; 2.96]	2.0 [1.1; 2.8]	0.53
Glucose, mmol/l	6.3 [6.0; 7.43]	5.1 [4.8; 5.2]	<0.01
Glycolated hemoglobin, %	6.65 [6.23; 6.98]	-	-
Creatinine, mg/dL	1.14 [0.9; 1.25]	0.86 [0.8; 0.99]	<0.01
GFR, mL/min/1,73 m^2	62.09 [52.73; 71.65]	76.99 [72.00; 94.01]	<0.01
LVPW thickness, mm	1.2 [1.1; 1.2]	1.2 [1.1; 1.2]	0.14
IVS thickness, mm	1.2 [1.1; 1.28]	1.2 [1.1; 1.2]	0.06
LVEF, %	55 [54; 57.8]	62 [59; 65]	<0.01
SBP, mm Hg	158 [156; 163.5]	156 [153; 160]	0.02
DBP, mm Hg	94 [90; 97.5]	88 [86; 90]	<0.01

Values are medians and [interquartile range]. AH, arterial AH; DM2, type 2 diabetes mellitus; CAD, coronary artery disease; BMI, body mass index; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; GFR, glomerular filtration rate; LVPW, left ventricular posterior wall; IVS, interventricular septum; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Structural and functional changes of the arterial bed in AH patients with and without DM2

Parameter	AH+ DM2 (n=30)	AH (n=32)	p
Structural changes in the vascular wall			
Large vessels			
Stiffness index (SI), m/s (normal <8 m/s)	11.15 [10.05; 12.35]	10.15 [8.83; 11.83]	0.04
Microvasculature			
Reflection index (RI),% (normal <30%)	37.6 [26.58; 48.03]	38.0 [32; 43]	0.42
Capillaries			
CD at rest, cap/mm^2 (CDr) (normal >45 cap/mm^2)	26.35 [24.23; 27.6]	35.1 [33.0; 45.00]	<0.01
CD after venous occlusion test (CDvo), cap/mm^2 (normal >56 cap/mm^2)	32.5 [28.25; 35.5]	40.0 [35.0; 43.25]	<0.01
Functional changes in the vascular wall			
Large vessels			
Phase shift (PS), ms (normal >10 ms)	5.8 [4.0; 7.8]	5.2 [3.15; 7.03]	0.38
Microvasculature			
Occlusion index (OI) (normal >1.8)	1.4 [1.3; 1.6]	1.3 [1.1; 1.53]	0.34
Capillaries			
CD after reactive hyperemia test, (CDrh) cap/mm^2 (normal >56 cap/mm^2)	30 [26.25; 33.75]	40.0 [33.0; 45.0]	<0.01

Values are medians and [interquartile range]. AH, arterial hypertension; DM2, type 2 diabetes mellitus; CD, capillary density.

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(RI decreased to 31 [27; 36.5] %. OI, characterizing the endothelial function, increased to 1.75 [1.68; 1,9]. Capillaries showed significant increases in CDr, CDrh, and CDvo.

In patients with AH and DM2, structural and functional parameters of macro- and microvessels demonstrated significant improvements (Table 5). In large vessels, SI decreased to 9.8 [9.1; 10,58] m/s but phase shift increased to 6.95 [5.13; 10.08]). Microvascular RI significantly decreased to 34 [25.9; 45.53] % but OI, characterizing the endothelial function, did not change significantly and remained 1.4 [1.3; 1.6]). Capillary CDr significantly increased to 31.55 [27.68; 34.7] cap/mm2 but CDrh and CDvo did not change significantly)

By the end of the study, both groups had a significant decrease in body mass index and improved lipid profile (Tables 3 and 6). Improved renal function was evidenced by reduced creatinine concentrations and by increased estimated glomerular filtration rate.

Discussion

Laboratory and instrumental parameters showed a beneficial effect of perindopril A on target organs, in particular, arteries at different levels, heart, and kidney, and on metabolic parameters in both study groups.

It is noteworthy that in AH patients without DM2, positive changes were observed in the structural changes of arterial vessels at all levels and also in capillaries. In contrast, AH patients with DM2 did not attain any significant improvement in endothelial function of arterioles and capillaries during treatment with perindopril A, even with significant positive changes in metabolic parameters. This may have been due to several factors that affect the state of blood vessels. Specifically, these factors include vascular stiffness, which depends on structural components, i.e., the ratio of collagen and elastin in the vessel walls and on adhesion molecules. In addition there is a dynamic component dependent on smooth muscle cell tone. This tone is determined by

Table 3. Dynamics of laboratory and instrumental parameters in AH patients without DM2 during the follow-up period

Parameter	Baseline	At 12 months	p
BMI, kg/m²	28.66 [26.82; 29.83]	28.31 [26.53; 29.61]	0.02
TC, mmol/L	5.5 [5.1; 6.4]	5.26 [4.94; 5.88]	<0.01
LDL, mmol/L	3.7 [2.52; 4.2]	3.25 [2.48; 3.74]	<0.01
LDL, mmol/L	1.12 [0.98; 1.4]	1.25 [1.1; 1.4]	<0.01
TG, mmol/L	2.0 [1.1; 2.8]	1.95 [1.09; 2.43]	0.01
Glucose, mmol/L	5.1 [4.8; 5.2]	4.95 [4.67; 5.3]	0.03
Creatinine, mmol/L	0.86 [0.8; 0.99]	0.8 [0.75; 0.9]	<0.01
GFR, mL/min/1,73 m²	76.99 [72.00; 94.01]	86.68 [77.77; 97.67]	<0.01
LVPW thickness, mm	1.2 [1.1; 1.2]	1.1 [1.0; 1.13]	<0.01
IVS thickness, mm	1.2 [1.1; 1.2]	1.1 [1.0; 1.1]	<0.01
LVEF, %	62 [59; 65]	68 [63.5; 70]	0.37
SBP, mm Hg	156 [153; 160]	129 [121.5; 134]	<0.01
DBP, mm Hg	88 [86; 90]	80 [78; 86]	<0.01

Values are medians and [interquartile range]. AH, arterial AH; DM, diabetes mellitus; CAD, coronary artery disease; BMI – body mass index; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; GFR, glomerular filtration rate; LVPW, left ventricular posterior wall; IVS, interventricular septum; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 4. Dynamics of structural and functional changes of the arterial bed in AH patients without DM2 during the follow-up period

Parameter	Baseline	At 12 months	p
Structural changes in the vascular wall			
Large vessels			
Stiffness index (SI), m/s (normal <8 m/s)	10.15 [8.83; 11.83]	9.25 [7.8; 10.93]	<0.01
Microvasculature			
Reflection index (RI),% (normal <30%)	38 [32; 43]	31 [27; 36.5]	<0.01
Capillaries			
CD at rest, cap/mm² (CDr) (normal >45 cap/mm²)	35.0 [30.75; 43.03]	40.5 [34.93; 46]	<0.01
CD after venous occlusion test (CDvo), cap/mm² (normal >56 cap/mm²)	39.5 [135.75; 45.0]	40.5 [36.75; 44.25]	0.01
Functional changes in the vascular wall			
Large vessels			
Phase shift (PS), ms (normal >10 ms)	5,2 [3.15; 7.03]	7,4 [5.6; 9.05]	<0.01
Microvasculature			
Occlusion index (OI) (normal >1.8)	1.3 [1.1; 1.53]	1.75 [1.68; 1.9]	<0.01
Capillaries			
CD after reactive hyperemia test (CDrh), cap/mm² (normal >56 cap/mm²)	37 [32.75; 43]	38.5 [33.75; 42.25]	0.02

Values are medians and [interquartile range].
AH, arterial hypertension; DM, diabetes mellitus; CD, capillary density.

Table 5. Dynamics of structural and functional changes of the arterial bed in AH patients with DM2 during the follow-up period

Parameter	Baseline	At 12 months	p
Structural changes in the vascular wall			
Large vessels			
Stiffness index (SI), m/s (normal <8 m/s)	11.15 [10.05; 12.35]	9.8 [9.1; 10.58]	<0.01
Microvasculature			
Reflection index (RI),% (normal <30%)	37.6 [26.58; 48.03]	34 [25.9; 45.53]	<0.01
Capillaries			
CD at rest, cap/mm² (CDr) (normal >45 cap/mm²)	26.35 [24.23; 27.6]	31.55 [27.68; 34.7]	<0.01
CD after venous occlusion test (CDvo), cap/mm² (normal >56 cap/mm²)	32.5 [28.25; 35.5]	36.5 [33.0; 39.75]	0.24
Functional changes in the vascular wall			
Large vessels			
Phase shift (PS), ms (normal >10 ms)	5.8 [4.0; 7.8]	6.95 [5.13; 10.08]	<0.01
Microvasculature			
Occlusion index, (normal >1.8)	1.4 [1.3; 1.6]	1.4 [1.3; 1.6]	0.16
Capillaries			
CD after reactive hyperemia test (CDrh), cap/mm² (normal >56 cap/mm²)	30 [26.25; 33.75]	34 [31.25; 36.75]	0.51

Values are medians and [interquartile range]. AH, arterial hypertension; DM2, type 2 diabetes mellitus; CD, capillary density.

Table 6. Dynamics of laboratory and instrumental parameters in AH patients with DM2 during the follow-up period

Parameter	Baseline	At 12 months	p
BMI, kg/m²	35.64 [33.71; 37.81]	34.79 [32.51; 36.86]	<0.01
TC, mmol/L	5.9 [5.3; 6.4]	5.4 [5.1; 5.8]	<0.01
LDL, mmol/L	3.78 [3.17; 4.34]	3.39 [2.64; 3.80]	<0.01
LDL, mmol/L	0.96 [0.8; 1.15]	0.95 [0.8; 1.11]	0.43
TG, mmol/L	2.0 [1.49; 2.96]	1.93 [1.5; 2.9]	0.04
Glucose, mmol/L	6.3 [6.0; 7.43]	6.1 [5.8; 6.3]	<0.01
Glycolated hemoglobin, %	6.65 [6.23; 6.98]	6.4 [6.2; 6.58]	<0.01
Creatinine, mmol/L	1.14 [0.9; 1.25]	1.1 [0.9; 1.2]	<0.01
GFR, mL/min/ 1,73 m²	62.09 [52.73; 71.65]	65.75 [56.08; 75.08]	0.01
LVPW thickness, mm	1.2 [1.1; 1.2]	1.2 [1.1; 1.2]	<0.01
IVS thickness, mm	1.2 [1.1; 1.28]	1.2 [1.1; 1.2]	0.07
LVEF, %	55 [54; 57.8]	56 [55; 58]	<0.01
SBP, mm Hg	158 [156; 163.5]	138 [132; 140]	<0.01
DBP, mm Hg	94 [90; 97.5]	86 [84; 89.5]	<0.01

AH, arterial AH; DM, diabetes mellitus; CAD, coronary artery disease; BMI, body mass index; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; GFR, glomerular filtration rate; LVPW, left ventricular posterior wall; IVS, interventricular septum; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure.

vasoactive substances produced by the endothelium due to various factors, particularly high blood pressure.

Thus, inhibition of the renin-angiotensin-aldosterone system indirectly reduces the tone of smooth muscle cells and improves structural parameters of remodeling of large vessels and arterioles, e.g., SI and RI. These parameters, in combination with the hypotensive effect, reduce the hemodynamic load on the endothelium and improve its function, as indexed by PS and OI. However, high blood pressure is not the only factor contributing to development of endothelial dysfunction. Experimental and clinical data have demonstrated that hyperinsulinemia and hyperglycemia in AH patients with DM2 injure endothelial cells, decrease NO production, which, in combination with elevated BP, exacerbates the vascular wall remodeling process. These detrimental effects are due to both a dynamic component and to structural changes [21-23]. It seems that these factors prevented achieving a significant improvement of endothelial function in arterioles and capillaries in the current study.

The combination of potent mechanisms of endothelial damage in DM2 patients requires using more stringent criteria for gauging treatment effectiveness, including lower target levels of BP and LDL in combination with effective hypoglycemic therapy.

Conclusion

A 12-month antihypertensive therapy with perindopril A, 10 mg/day, in nondiabetic, hypertensive patients produced not only a significant reduction in blood pressure, but also a beneficial effect on cardiovascular remodeling, endothelial function, and renal function. There were also beneficial effects of perindopril on metabolic parameters measured in blood plasma. Photoplethysmography and videocapillaroscopy are effective methods for assessing vascular remodeling in patients with AH and also for evaluating the effectiveness of AH treatment.

No conflict of interest is reported.

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