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Comparative effects of antihypertensive therapy modes on the wall rigidity of various blood vessels

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Abstract

Objective. The purpose of the study was the comparative analysis of the vasoprotective effects of a fixed combination of perindopril and indapamide (Noliprel A-Bi-Forte, Servier) and the combination of enalapril and hydrochlorothiazide (Co-Renitec, MSD) on various sites of the arterial bed in hypertensive patients. **Design and methods.** Depending on the mode of antihypertensive therapy (AHT) the patients were randomized into 2 groups: patients of the 1st group (41 persons) received a fixed combination of perindopril A (10.0 mg) and indapamide (2.5 mg), and those from the 2nd group (34 persons) received a fixed combination of enalapril maleate (20.0) mg and hydrochlorothiazide (12.5 mg). The aorta and major arteries were assessed with the use of the device VaSera-1000 («Fukuda Denshi», Japan), and the following parameters were evaluated: velocity of propagation of pulse wave in the aorta, cardio-ankle vascular index and biological age of the arteries. The peripheral arteries were estimated using the device Pulse Trace PCA, and stiffness index, reflection index and vascular age were measured. All assessments were performed at baseline and at 1-, 3-and 6-months and at 1-year follow-up. **Results.** Both combinations resulted in a significant decrease of vascular wall stiffness of the aorta and major arteries, but in the 1st group of patients the changes were observed earlier (after 3 to 6 months), and were more expressed. At the same time vasoprotective effects in peripheral arteries were observed only in 1st group of patients who received perindopril and indapamide. **Conclusions.** Leading to a significant reduction of the vascular wall rigidity both in aorta, major and peripheral arteries, a combination of perindopril and indapamide provides the most effective vasoprotection.

Key words: arterial hypertension, arterial stiffness, vasoprotective effects of drugs

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Сравнительные эффекты режимов антигипертензивной терапии на показатели жесткости стенки различных артериальных сосудов

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Резюме

Цель исследования состояла в сравнительном анализе вазопротективных эффектов фиксированной комбинации периндоприла А и индапамида («Нолипрел А Би-форте», «Сервье») и сочетания эналаприла и гидрохлортиазида («Ко-Ренитек», MSD) на показатели жесткости сосудистой стенки различных участков артериального русла у больных артериальной гипертензией (АГ). **Материалы и методы.** В зависимости от режима антигипертензивной терапии (АГТ) больные АГ, включенные в исследование, были рандомизированы на 2 группы: больные 1-й группы (41 человек) получали фиксированную комбинацию периндоприла А (10,0 мг) и индапамида (2,5 мг), а 2-й группы (34 человека) — фиксированную комбинацию эналаприла малеата (20,0) мг и гидрохлортиазида (12,5 мг). Жесткость стенки аорты и магистральных артерий изучали на приборе «VaSera-1000» («Fukuda Denshi», Япония) по показателям скорости распространения пульсовой волны в аорте, сердечно-лодыжечного сосудистого индекса и биологического возраста артерий. Жесткость стенки периферических артерий оценивали, используя прибор «Pulse Trace PCA». Он позволял рассчитывать индекс жесткости, индекс отражения и сосудистый возраст. Определение показателей производили исходно и в динамике АГТ (через 1, 3, 6 месяцев и 1 год наблюдения). **Результаты.** Обе комбинации приводили к значимому снижению показателей жесткости сосудистой стенки аорты и магистральных артерий, однако в 1-й группе больных эта динамика была более ранней (через 3–6 месяцев терапии) и выраженной. Что же касается вазопротективных эффектов на периферические артерии, то они имели место только в 1-й группе больных при применении комбинации периндоприла А и индапамида. **Выводы.** Статистически значимое снижение показателей жесткости сосудистой стенки различных отделов сосудистого русла — аорты, крупных и периферических артерий — на фоне терапии периндоприлом А и индапамидом позволяют рекомендовать использование данной комбинации для обеспечения максимального вазопротективного эффекта.

Ключевые слова: артериальная гипертензия, жесткость сосудистой стенки, вазопротективные эффекты препаратов

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Introduction

Arterial hypertension (HTN) is still one of the leading causes of morbidity and mortality in developed countries [1]. Currently, its world prevalence is estimated as 40.8 % [2].

Disability and mortality of the working population remain high due to a high risk of HTN-related cardiovascular events (CVE), first of all stroke and myocardial infarction [3]. The protection of target organs (heart, kidneys, blood vessels, and brain) is believed to be one of the major tasks of antihypertensive therapy (HTNT), as their lesion significantly worsens prognosis.

That is why the European (2007) and Russian (2008) guidelines [4, 5] for HTN diagnosis and treatment vascular wall was announced for the first time as one of the target organs. The guidelines state that vascular function should be assessed in clinical practice, and the increased carotid-femoral pulse wave velocity (PWV) should be included in the list of the most important criteria of subclinical target organ damage in HTN patients. This parameter was also included in the new revision of the European guidelines adopted in 2013 but its threshold was reduced from 12 to 10 m/s [6].

The link between the increased PWV reflecting the rigidity of the vascular wall, and mortality was demonstrated as early as in the REASON classic study [7]. In recent years, new data have emerged, indicating the importance of vasoprotection, as regression of the vascular remodeling related to the effective HTNT contributes to the increase of life expectancy and reduction of CVE risk which are the main objectives of HTN treatment [8–11].

Obviously, the increased stiffness of the aorta and main arteries increases left ventricle (LV) afterload, contributing to the development of LV hypertrophy and diastolic dysfunction. Our previous studies established a quantitative relationship between the degree of vascular stiffness increase and the severity of LV diastolic dysfunction by the correlative regression analysis [12].

Based on the results, a mathematical model was developed and tested in the clinic of the Rostov Medical University, which allowed to predict the improvement of LV relaxation by the dynamics of PWV related to the HTNT with a distinct vasoprotective effect.

Although the interest to the vascular wall in HTN patients has recently increased, the structural and functional heterogeneity of the bloodstream is usually not comprehensively assessed [13]. Resistance vessels are known to significantly contribute to the high blood pressure (BP) and further progression of HTN. These vessels are represented by small arteries, arterioles, and venules of muscular type. They determine total peripheral vascular resistance, and its increase contributes to the development and worsening of HTN and LV hypertrophy.

Obviously, the maximal vasoprotective effect of HTNT can be achieved when various parts of the vascular system are controlled.

Objective of our study was a comparative analysis of vasoprotective effects of the fixed combination of perindopril A and indapamide (Noliprel A Bi-forte, Servier) and the combination of enalapril and hydrochlorothiazide (Co-renitec, MSD) on various parts of the arterial bed in HTN patients.

Design and methods

The study included 75 patients with a stage II HTN, HTN 2 degree, high cardiovascular risk.

The inclusion criteria were the following: age 40–65 years old; initially increased vascular stiffness (PWV); low efficiency of the previous HTNT; absence of symptomatic HTN; absence of associated clinical conditions.

Depending on the HTNT mode, the patients were randomized into 2 groups by the envelope method. Group 1 (41 people) included HTN patients treated with the fixed combination of perindopril A (10.0 mg) and indapamide (2.5 mg), and group 2 (34 people) included patients treated with the fixed combination of enalapril maleate (20.0 mg) and hydrochlorothiazide (12.5 mg). The drugs were taken once in the morning.

BP measurement was performed twice on the dominant arm at 2-minute intervals after 5-minute rest in a sitting position (OMRON M3 Expert automatic electronic tonometer, Japan).

The mean BP before the treatment in group 1 were the following: systolic BP (SBP) — 163.5 ± 5.8 mmHg, diastolic BP (DBP) — 95.1 ± 4.4 mmHg; in group 2 — 165.3 ± 3.7 and 92.9 ± 5.5 mmHg, respectively. Taking into account persistently high BP values, prior HTNT was considered ineffective.

The cardiovascular system was evaluated by a set of functional standard methods.

The main arteries were assessed using VaSera-1000 sphygmomanometer and sphygmog-raph (Fukuda Denshi, Japan). The study was conducted as follows: after entering the patient information, 4 occlusive cuffs were put on the shoulders and right and left legs, amorphous sensors were put on the projection points of the carotid and femoral arteries, and ECG electrodes and a microphone of phonocardiogram (PCG) were applied to receive the PCG signal (II intercostal space to the left of the sternum edge). After checking the pulse wave sensitivity, the arteries were compressed to register the indicators in the automatic mode.

We assessed the following indicators: aortal pulse wave velocity (PWVa), cardio-ankle vascular index (CAVI), and biological age of main arteries (VA main). CAVI, a new widely used indicator is an analogue of PWV. It allows to assess the main arteries stiffness independent of BP level and the reflected wave in the vessel between the valve and the leg [14].

Peripheral arteries of resistive type were evaluated using Pulse Trace PCA which is based on the method of pulse wave contour analysis. A photoplethysmographic sensor placed on the distal phalanx of the thumb allows to calculate such indicators as stiffness index (SI), reflection index (RI), and vascular age (VA per.).

The mentioned indicators of vascular stiffness in various parts of the vascular system were assessed at baseline and at follow-up (after 1, 3, 6 months and 1 year).

All patients provided written informed consent to participate in the study.

The study was approved by an independent local ethics committee.

The results were processed with the use of Statistica 8.0. The differences between the indicators were considered significant at p-level ≤ 0.05. Mean values are presented as M ± SD.

Results and discussion

General characteristics of HTN patients in groups 1 and 2 are shown in Table 1.

The target BP level in the vast majority of HTN patients in both groups was achieved by the 3rd month of HTNT. The number of patients who achieved the target BP level was 84 % and 72 % in group 1 and 2, respectively.

Vascular stiffness index in various parts of the arterial bed in group 1 and 2 at baseline and follow-up are presented in Tables 2 and 3, respectively.

Table 1

CHARACTERISTICS OF HYPERTENSIVE PATIENTS IN GROUPS 1 AND 2

Parameter	Croup 1 (n = 41)	Group 2 (n = 34)
Gender, Male/Female	21/20	18/16
Age, years	57.0 ± 6.3	55.8 ± 4.6
Duration of HTN, years	4.8 ± 1.08	5.5 ± 2.1
Family history of HTN, %	52.2	46.5
SBP DBP	163.5 ± 5.8 95.1 ± 4.4	165.3 ± 3.7 92.9 ± 5.5
Risk factors: – 1–2 RF – ≥ 3 RF	 7 34	 5 29
Diabetes mellitus	–	–
Symptomatic CVD, CKD stage ≥ 4 or diabetes mellitus with TOD/RFs	–	–

Note: HTN — arterial hypertension; SBP — systolic blood pressure; DBP — diastolic blood pressure; CKD — chronic kidney disease; CVD — cardiovascular disease; TOD — target organ damage; RF — risk factor.

Table 2

VASCULAR STIFFNESS INDEX IN VARIOUS REGIONS OF THE ARTERIAL BED (M ± m) IN GROUP 1 (n = 41) AT BASELINE AND AT FOLLOW-UP

Parameter	Baseline	After 1 month	After 3 months	After 6 months	After 12 months
PWV a, m/s	11.0 ± 1.37	10.6 ± 1.5	9.7 ± 1.21	8.8 ± 1.39*	8.4 ± 1.57*
CAVI	9.7 ± 0.62	9.1 ± 1.11	8.5 ± 0.52*	8.3 ± 0.91*	8.0 ± 0.67*
VA main, years	70.2 ± 2.18	68.9 ± 3.59	64.4 ± 3.19*	60.2 ± 4.51*	58.9 ± 5.21*
SI, m/s	10.9 ± 1.09	9.2 ± 1.68	8.4 ± 1.53*	8.9 ± 0.81*	7.9 ± 1.46*
RI, %	65.9 ± 14.48	66.3 ± 12.91	64.6 ± 12.85	66.3 ± 13.91	64.9 ± 11.07
VA per., years	69.7 ± 1.45	66.6 ± 3.08	65.7 ± 2.77	65.4 ± 2.41*	59.8 ± 5.11*

Note: PWV a — pulse wave velocity in aorta; CAVI — cardio-ankle vascular index; VA main — biological age of main arteries; SI — stiffness index; RI — reflection index; VA per. — peripheral vascular age; * — significant differences compared to baseline values $p \leq 0.05$

Table 3

VASCULAR STIFFNESS INDEX IN THE VASCULAR WALLS OF VARIOUS REGIONS OF THE ARTERIAL BED (M ± m) IN GROUP 2 (n = 34) AT BASELINE AND AT FOLLOW-UP

Parameter	Baseline	After 1 month	After 3 months	After 6 months	After 12 months
PWV a. m/s	10.5 ± 1.62	10.3 ± 3.52	9.7 ± 2.69	9.7 ± 2.19	8.6 ± 1.08*
CAVI	9.2 ± 1.03	9.1 ± 1	8.7 ± 0.84	8.2 ± 0.98	7.9 ± 0.69*
VA main, years	69.7 ± 2.52	69.0 ± 4.51	67.6 ± 3.33	66.2 ± 3.96	63.9 ± 2.22*
SI, m/s	10.2 ± 2.02	9.8 ± 2.42	9.5 ± 1.93	9.5 ± 1.76	9.4 ± 2.44
RI, %	66.6 ± 10.94	66.0 ± 9.51	65.4 ± 8.91	67.2 ± 10.02	66.4 ± 12.49
VA per., years	67.6 ± 2.24	67.3 ± 3.54	66.3 ± 3.55	65.9 ± 2.92	65.7 ± 2.11

Note: PWV a — pulse wave velocity in aorta; CAVI — cardio-ankle vascular index; VA main —biological age of main arteries; SI — stiffness index; RI — reflection index; VA per. — peripheral vascular age; * — significant differences compared to baseline values $p \leq 0.05$.

The changes in the stiffness indicators of the main vessels in groups during follow-up are shown in Figures 1–3.

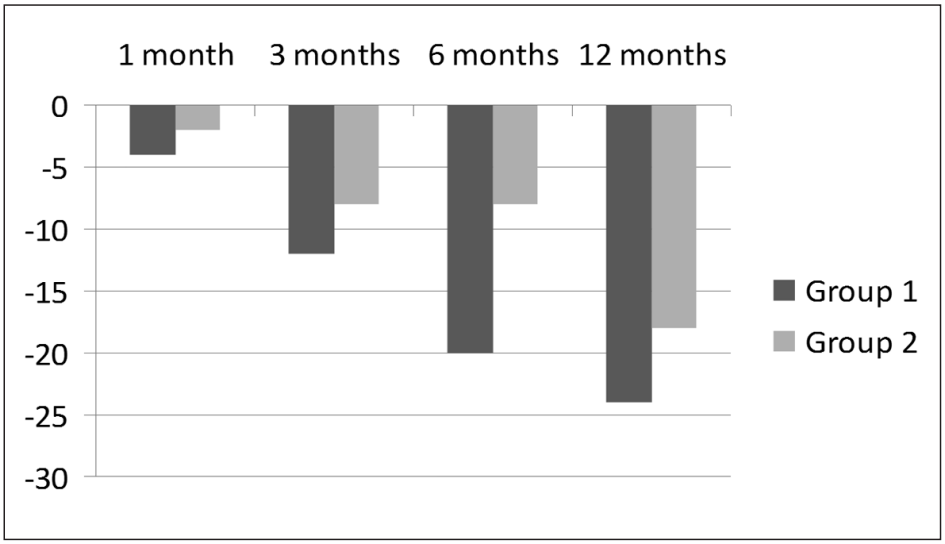
The following features of vasoprotective effects of different HTNT modes were found.

Both groups demonstrated positive changes in the main stiffness indicators of aorta (PWVa) and main arteries (CAVI, VA main). However, significant reduction in the vascular stiffness and the vascular age was registered relatively earlier in the group treated with perindopril A and indapamide. Regression of the remodeling of the aorta and main arteries manifested in the reduction of PWVa by 20% from baseline after 6 months. CAVI decreased by 12% after 3 months of HTNT ($p \leq 0.05$).

The biological age of main vessels also reduced significantly by 8% ($p \leq 0.05$) after 3 months of therapy, and reached the patient passport age by the 6th month. The positive effect of the fixed combination of perindopril A and indapamide grew during follow-up, and the growth was confirmed in 1 year.

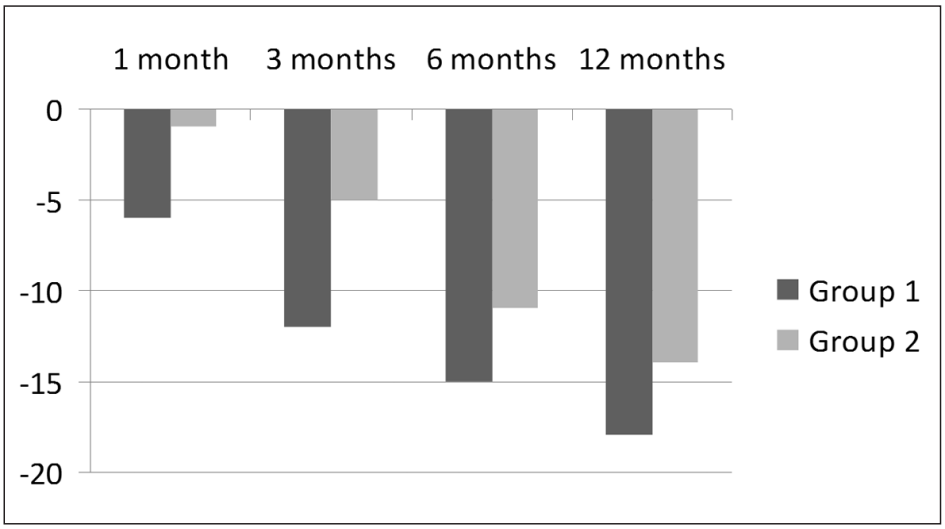
A comparative analysis of the changes in the main stiffness indicators of the peripheral arteries in HTN patients receiving HTNT (Fig. 4–6)

Figure 1. The changes of pulse wave velocity in aorta during follow-up



Note: the change of each parameter is expressed as percentages (Δ %) in relation to the baseline value of the parameter in each group, taken as 100 %; * — significant differences between the groups $p \leq 0.05$.

Figure 2. The changes of cardio-ankle vascular index during follow-up



Note: the change of each parameter is expressed as percentage (Δ %) in relation to the baseline value of the parameter in each group, taken as 100 %; * — significant differences between the groups $p \leq 0.05$.

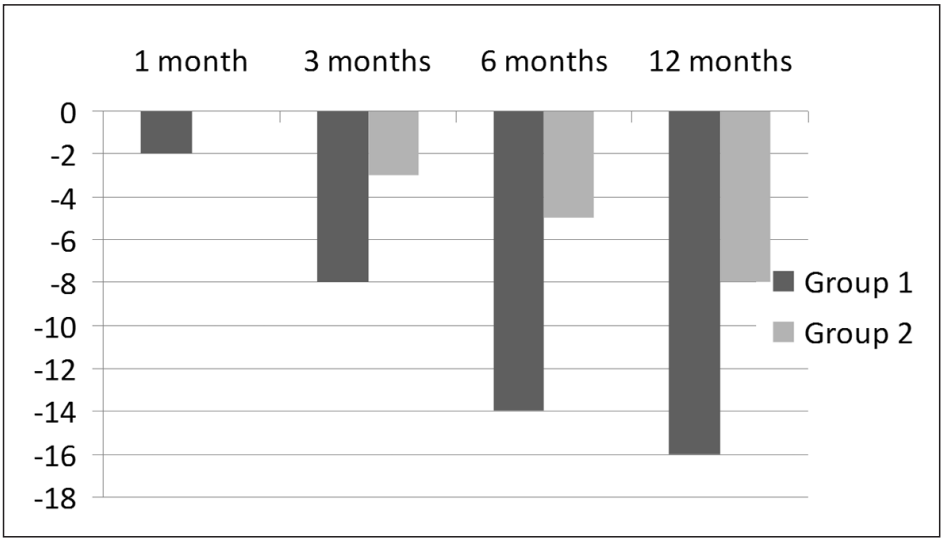
confirmed different beneficial effects of perindopril A and indapamide.

Thus, there was a reduction of SI (reflecting the stiffness of the peripheral arteries) by 23 % after 3 months of HTNT ($p \leq 0.05$), and by the end of the year, the vasoprotective effect of this combination reached the maximum level (SI decreased by 28 % from baseline).

Obviously, the visco-elastic state of the vascular wall and the structural and functional characteristics of the endothelium are closely linked to the biological vascular age [15]. So reduction of the biological age of the peripheral arteries found in group 1 seems consequent upon the improvement of the vascular wall, e. g. VA per. decreased by 6 % after 6 months and by 14 % after 1 year ($p \leq 0.05$) when it became comparable with the patients' passport age.

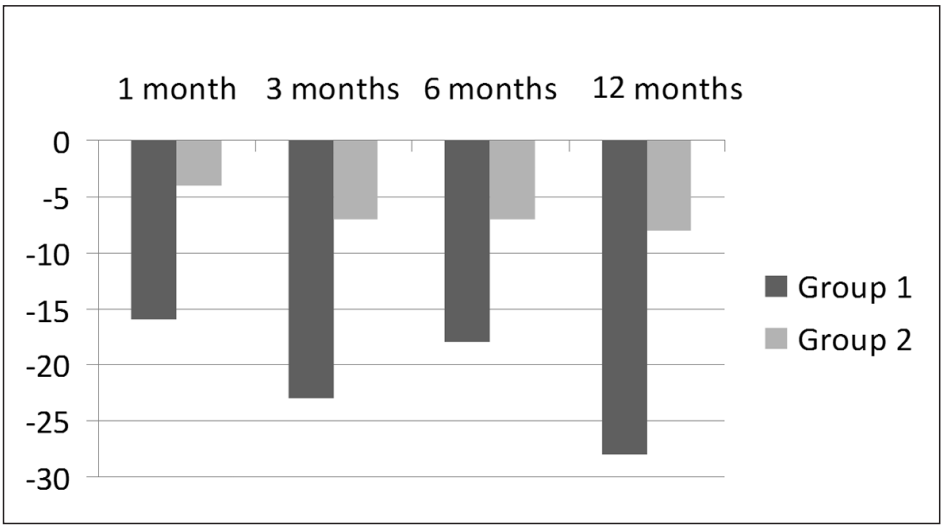
At the same time no significant dynamics of the vascular indicators of the peripheral arteries was found regarding SI or VA per. in patients of the group 2 who received combination of enalapril and hydrochlorothiazide.

Figure 3. The changes in vascular age of the main arteries during follow-up



Note: the change of each parameter is expressed as percentage (Δ %) in relation to the baseline value of the parameter in each group, taken as 100 %; * — significant differences between the groups $p \leq 0.05$.

Figure 4. The change of stiffness index during follow-up



Note: the change of each parameter is expressed as percentage (Δ %) in relation to the baseline value of the parameter in each group, taken as 100 %; * — significant differences between the groups $p \leq 0.05$.

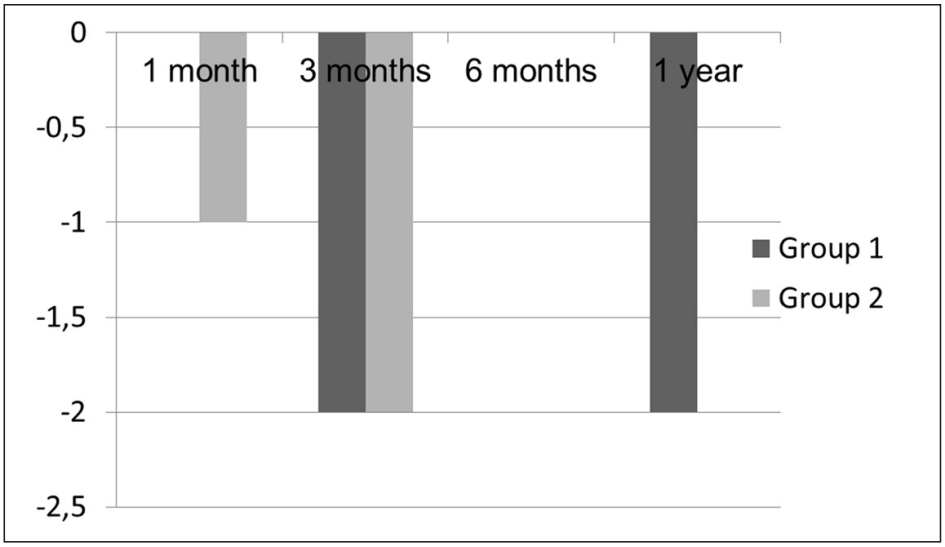
As for RI (reflection index), at baseline it was within reference range in both groups, and its value remained unchanged at follow-up.

Our results demonstrate vasoprotective effects of both fixed HTNT combinations, namely their impact on the vascular walls of the aorta and main arteries. Importantly, vasoprotective effect of the fixed perindopril A and indapamide combination became evident earlier and was more pronounced, indicating benefits of this combination in reducing the HTN-related cardiovascular risk.

At the same time, experimental and clinical studies showed that underestimation of the role of peripheral arterial remodeling and its adverse effects can significantly reduce the HTNT efficiency [16]. Only one (perindopril A and indapamide) of the two antihypertensive combinations used in our study wa beneficial regarding the properties of peripheral arteries.

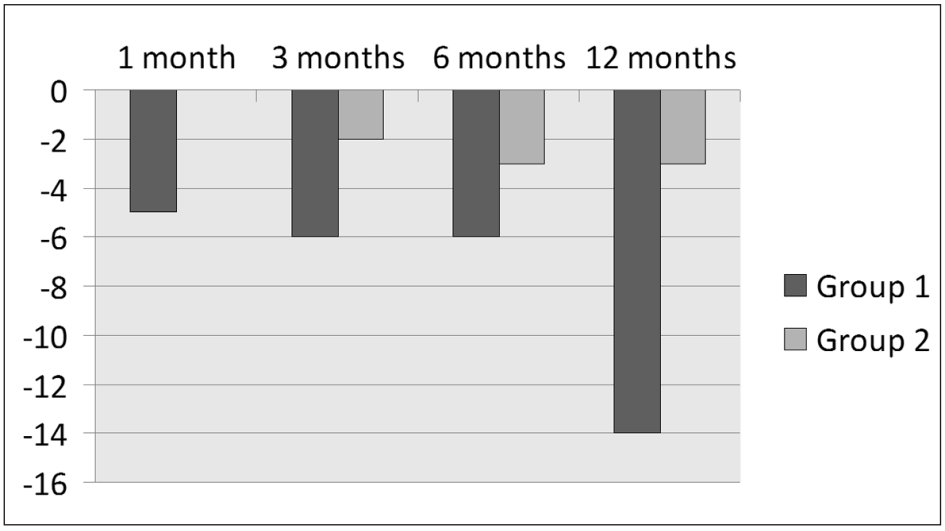
Its benefits can be attributed to the structural and functional properties of the peripheral vasculature. The walls of small arteries, arterioles and venules

Figure 5. The changes of reflection index during follow-up



Note: the change of each parameter is expressed as percentages (Δ %) in relation to the baseline value of the parameter in each group, taken as 100 %; * — significant differences between the groups $p \leq 0.05$.

Figure 6. The changes of peripheral vascular age during follow-up



Note: the change of each parameter is expressed as percentage (Δ %) in relation to the baseline value of the parameter in each group, taken as 100 %; * — significant differences between the groups $p \leq 0.05$.

contain a significant number of smooth muscle cells [17], which are subject to the impact of humoral vasodilator and vasoconstrictor factors produced by the endothelium. Currently, endothelial dysfunction is considered one of the key mechanisms for HTN development and aggravation. It is accompanied by the increased production of vasoconstrictor factors (endothelins) causing the increased tone of smooth muscle cells which is an additional factor leading to vascular remodeling.

Therefore, the favourable peripheral vasoprotective effects in group 1 can be explained by a proven influence of perindopril A and indapamide on the endothelial function recovery in HTN patients [18, 19].

Conclusions

The used HTNT modes provide improvement of the properties of the vascular walls of the aorta and main arteries, however, the fixed combination of perindopril A and indapamide

demonstrates a relatively earlier and more significant vasoprotective effect.

Peripheral vasoprotective effects were observed only in HTN patients treated with the fixed combination of perindopril A and indapamide (group 1).

The fixed combination of perindopril A and indapamide vs. the fixed combination of enalapril and hydrochlorothiazide has vasoprotective benefits on the arterial wall stiffness of various regions of the vascular bed.

Conflict of interest

The authors declare no conflict of interest.

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