

EFFECTS OF ADAPTATION TO INTERMITTENT NORMOBARIC HYPOXIA ON RESULTS OF 24-HOUR MONITORING OF ARTERIAL PRESSURE IN HYPERTENSIVE PATIENTS

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30 hypertensive patients of the study group received combined therapy, including adaptation to intermittent normobaric hypoxia and medicines. 32 control hypertensive patients were treated with drugs alone. 24-h monitoring of blood pressure (BP) in all the patients has shown that the study group achieved a more pronounced lowering of AP, especially of maximal AP nocturnal and diurnal rises. The combined therapy normalized 24-h AP profile, it increased the number of patients with an adequate fall of nocturnal AP, while the number and duration of high AP episodes decreased. Positive changes in a 24-h AP profile were significantly more evident in patients of the study group than in patients treated only with hypotensive drugs.

Key words: arterial hypertension, 24-h monitoring of arterial pressure, hypoxic therapy

Arterial hypertension (AH) is one of the most acute problems medical science and practice encounters today [6], because higher-than-normal arterial pressure (AP) largely increases cardiac & vascular disease incidence and mortality rates. AH is extremely wide-spread: in Russia, 39.2% of men and 41.1% of women have higher-than-normal AP [5].

Presently, there are many anti-hypertensive drugs and AH treatment methods available, but many of them have adverse effects and thus cannot adequately serve to improve patients' survival quality. In view of this, it is necessary to search and identify best-preferable non-drug AH treatment and prevention methods. Specifically, such methods include hypoxic therapy based on human adaptation to periodical exposure to gas hypoxic mixture containing 10% oxygen (GHM-10) in normobaric conditions [7, 8]. Intermittent normobaric hypoxia (INH) is typically used both for monotherapy of mild AH and within comprehensive treatment courses applied to moderate and severe AH [1, 4]. However, it is always necessary to subject hypoxic therapy effects to detailed evaluations. This can be done by way of 24-h monitoring of AP (24-MAP) allowing to maintain control over AP levels 24 hours a day, as it is required by all up-to-date approaches in monitoring of AH patients.

The purpose of this research paper was the study of the effects of adaptation to INH upon AP profile in AH patients.

Material and Methods

The examination included 62 patients with hypertension stage II. Of them, 32 patients (the main group) received a combined therapy, including INH and conventional medication (ACE inhibitors, beta-blockers, calcium antagonists and diuretics). 30 patients (the control group) received medication alone. The main-group patients had 59.3±2.7-year average age group, with their average disease duration equal to 12.2±1.9 years; the control-group patients had 52.8±4.9-year average age group, with their average disease duration equal to 9.6±2.5 years. INH was produced by inhalation, through mask attached to "ELBRUS-10A" device, of 10% oxygen and 90% nitrogen mixture. Each 3-5 minutes of GHM-10 inhalation was alternated with 3-5 minutes of atmospheric air inhalation, which made, put together, 1 cycle. Each INH session was made up of 5-10 cycles, with total GHM-10 exposure time making 25-30 minutes. The hypoxic therapy course was made up of 10-16 sessions.

All patients went through 24-MAP with use of *MEDITECH ABPM-02* Monitor (Hungary), by standard methods [2, 3, 9, 10]. The following was evaluated: 1) maximal, minimal and average systolic, diastolic and average AP (SAP, DAP and AP_{av}) and systolic rate; 2) variability of SAP and DAP (VSAP and VDAP) calculated as the mean-square deviation; 3) 24-hour index (24-I), which was equal to percentage correlation between diurnal and nocturnal average AP rates, with 10-22% assumed to be the normal rate; 4) temporal index (TI) showing the percentage share of higher-than-normal AP events (diurnal normal rate: not over 140/90 mm Hg; nocturnal normal rate: not over 120/80 mm Hg); 5) area index (AI) showing specific time spans, as within each 24 hours, when a patient had higher-than-normal AP and by how much, on the average, such too-high AP exceeded the highest limit of the normal range; 6) D and N ratios and N/D correlation rates applicable to wake- and sleep periods, respectively, as follows:

$$\frac{AP_{av} \text{ before treatment} - AP_{av} \text{ after treatment}}{AP_{av} \text{ before treatment}} \times 100\%$$

Each N/D correlation rate is characterization of the extent, to which efficacy of anti-hypertensive therapy is pronounced in night-time as compared to day-time [3].

24-MAP was performed twice: before the treatment course and after it.

Results obtained and comments

24-MAP results obtained for patients of the main group and the control group are shown in Table 1 and 2. Patients, who received medications alone, did not have, after the treatment course was over, any evidence of reduction of their average diurnal DAP, or maximal diurnal DAP and AP_{av} rates, or maximal nocturnal DAP and AP_{av} rates. In the main-group patients, after the hypoxic therapy course combined with drugs, all the said parameters were evidently reduced.

After the INH course, as compared to the medications-alone group, INH-treated patients had more reduced minimal rates of their average 24-h SAP, DAP and AP_{av} (by 14.6 and 11.7, 17.6 and 9.7 and 15.4 and 14.4% respectively). The main group had a more pronounced increase of 24-I (by 85.3 and 31.5% respectively for SAD and by 61.5 AND 21% for DAP). In both groups, 24-I rates were normalized, which, apparently, evidenced restoration of circadian rhythms. The main group had a greater reduction of AI (by 76% for SAP and by 78.2% for DAP, as compared to 56.2% for SAP and 65.7% for DAP in the control group), which evidenced a reduction in pressure-load duration. No evident changes in VAP, in either group, was reported.

In day time, INH-therapy patients had their maximal AP_{av} reduced to a greater extent, than it was with the control-group patients (by 7.3 and 5.3% respectively). As it was with the average 24-h rates, the INH therapy was followed by a greater reduction in minimal diurnal rates of SAP, DAP and AP_{av} (by 17, 16 and 23% respectively, as compared to 9.5, 14 and 12.3% in the control group). The INH-group had a greater reduction in their AI, SAP, DAP and AP_{av} (by 80.2, 78.1 and 80.9% respectively, as compared to 65.3, 51.1 and 61.6% in the control group).

In night time, the main group had a more pronounced reduction in maximal rates of SAP, DAP and AP_{av} (by 12.4, 7 and 10.2% respectively, as compared to 9.2, 6.3 and 7% in the control group). The extent of reduction in minimal AP rates, both in the main group and in the control group, was practically similar (by 19.2 and 14.6% for SAP, by 17.2 and 18% for DAP and by 17.2 and 16.6% for AP_{av} respectively). AI was more pronouncedly reduced in the main group (by 77.5, 90.9 and 87.5%, respectively, for SAP, DAP and AP_{av} , as compared to 73.3, 65.3 and 72.7% respectively in the control group).

TABLE 1. Dynamics of 24-h AP profile in AH patients before and after INH therapy (M±m)

Parameter	Before treatment			After treatment		
	24 hours	Day time	Night time	24 hours	Day time	Night time
SAP _{av} , mm Hg	133,4 ± 6,8	137,5 ± 8,2	125,2 ± 4,3	120,7 ± 2,5*	126,0 ± 3,2*	107,7 ± 1,8*
DAP _{av} , mm Hg	78,2 ± 5,9	84,5 ± 6,9	72,9 ± 2,2	70,9 ± 3,0*	76,4 ± 3,1	61,1 ± 3,2*
AP _{av} , mm Hg	96,7 ± 6,1	102,6 ± 7,3	90,6 ± 2,6	87,5 ± 2,6*	92,9 ± 3,0*	78,9 ± 3,7
SAP max., mm Hg	166,8 ± 6,6	169,3 ± 8,7	148,1 ± 9,5	153,0 ± 3,9*	156,8 ± 4,3*	129,7 ± 1,2*
DAP max., mm Hg	100,0 ± 3,1	104,3 ± 6,6	85,5 ± 6,8	94,3 ± 1,8*	98,8 ± 4,6*	79,5 ± 2,8
AP _{av} max., mm Hg	120,0 ± 6,2	124,0 ± 7,2	106,2 ± 3,8	111,3 ± 4,3*	115,0 ± 4,6	95,4 ± 2,9*
SAP min., mm Hg	104,4 ± 6,6	110,6 ± 2,8	107,0 ± 2,9	89,2 ± 1,8*	94,0 ± 3,7*	89,0 ± 5,1*
DAP min., mm Hg	53,5 ± 5,2	62,0 ± 2,1	57,2 ± 3,8	44,1 ± 1,4*	52,1 ± 2,9	46,2 ± 4,1*
AP _{av} min., mm Hg	71,5 ± 2,7	79,2 ± 7,4	74,6 ± 3,5	60,5 ± 1,3*	66,8 ± 1,5*	61,8 ± 3,9*
VSAP, mm Hg	13,3 ± 0,6	14,6 ± 0,6	10,8 ± 1,0	15,3 ± 3,0	14,1 ± 0,6	11,8 ± 1,1
VDAP, mm Hg	10,3 ± 1,2	10,0 ± 0,3	8,4 ± 0,5	12,0 ± 3,8	11,1 ± 0,6	10,2 ± 0,8
VAP _{av} , mm Hg	10,7 ± 0,7	11,0 ± 0,3	8,7 ± 0,6	11,7 ± 7,6	11,5 ± 0,6	10,3 ± 0,9
SAP TI, %%	31,2 ± 2,6	34,5 ± 6,8	35,3 ± 3,2	19,4 ± 2,8*	17,8 ± 9,1*	25,7 ± 4,1*
DAP TI, %%	23,0 ± 3,2	24,9 ± 4,2	23,5 ± 6,8	13,6 ± 1,1*	15,6 ± 3,8*	8,1 ± 3,2*
AP _{av} TI, %%	24,7 ± 4,3	26,6 ± 2,3	28,7 ± 6,1	14,3 ± 3,7*	15,7 ± 4,1*	13,0 ± 5,1*
SAP 24-I, %%	6,8 ± 2,1	-	-	12,6 ± 3,4*	-	-
DAP 24-I, %%	10,4 ± 2,8	-	-	16,8 ± 3,2*	-	-
AP _{av} 24-I, %%	9,0 ± 1,8	-	-	14,7 ± 2,6*	-	-
SAP AI, mm Hg/h	203,1 ± 30,1	234,7 ± 141,0	330,7 ± 60,3	48,8 ± 6,2*	46,4 ± 16,6*	73,8 ± 10,8
DAP AI, mm Hg/h	123,6 ± 21,2	166,5 ± 111,1	148,6 ± 44,2	26,9 ± 3,9*	36,4 ± 18,2*	13,4 ± 2,1*
AP _{av} AI, mm Hg/h	143,1 ± 14,3	181,6 ± 30,1	23,4 ± 82,3	28,3 ± 12,8*	34,7 ± 20,1*	25,0 ± 6,9

Note. Herein above and in Table 2: * means $p < 0.05$ as compared to pre-treatment rates; VAP_{av} means variability of AP_{av}; max. means maximal, min. – minimal and av. – average rates.

TABLE 2. Dynamics of 24-h AP profile in AH patients before and after drug treatment (M±m)

Parameter	Before treatment			After treatment		
	24 hours	Day time	Night time	24 hours	Day time	Night time
SAP _{av} , mm Hg	137,7 ± 3,6	140,7 ± 3,6	127,6 ± 3,8	124,8 ± 3,3*	128,7 ± 3,6*	112,2 ± 1,8*
DAP _{av} , mm Hg	81,5 ± 3,9	83,8 ± 3,8	73,5 ± 4,3	72,5 ± 4,2*	75,5 ± 4,3	62,3 ± 3,0*
AP _{av} , mm Hg	100,2 ± 3,6	102,8 ± 3,5	91,5 ± 3,9	89,9 ± 3,5*	93,2 ± 3,7*	78,9 ± 2,4*
SAP max., mm Hg	174,4 ± 6,1	174,2 ± 3,4	149,3 ± 6,1	161,2 ± 2,9*	161,2 ± 4,2*	135,5 ± 2,2*
DAP max., mm Hg	105,2 ± 2,2	105,2 ± 6,1	87,1 ± 3,7	96,1 ± 2,9*	97,0 ± 3,0	81,6 ± 5,2
AP _{av} max., mm Hg	123,3 ± 2,9	123,3 ± 3,9	106,1 ± 3,4	105,6 ± 6,1*	116,8 ± 3,6	98,7 ± 4,4
SAP min., mm Hg	104,8 ± 2,6	108,0 ± 2,8	110,1 ± 3,5	92,5 ± 3,1*	98,5 ± 3,1*	94,0 ± 3,7*
DAP min., mm Hg	56,8 ± 3,4	60,7 ± 2,2	59,5 ± 4,2	46,6 ± 2,8*	52,2 ± 3,1*	48,8 ± 2,9*
AP _{av} min., mm Hg	74,1 ± 3,2	78,0 ± 3,0	77,9 ± 4,1	63,4 ± 2,5*	68,4 ± 3,1*	65,0 ± 2,8*
VSAP, mm Hg	14,7 ± 0,8	13,5 ± 0,6	11,6 ± 1,8	15,1 ± 0,8	13,6 ± 0,7	12,2 ± 1,5
VDAP, mm Hg	11,2 ± 0,5	9,9 ± 0,4	8,1 ± 1,1	11,5 ± 0,6	10,6 ± 0,5	9,4 ± 1,2
VAP _{av} , mm Hg	10,6 ± 0,9	10,6 ± 0,4	8,5 ± 1,3	9,6 ± 1,1	10,6 ± 0,6	10,0 ± 1,3
SAP TI, %%	59,1 ± 8,0	56,2 ± 12,1	67,4 ± 11,4	25,2 ± 1,7*	24,8 ± 11,2*	28,0 ± 4,6*
DAP TI, %%	39,1 ± 8,5	41,1 ± 10,1	41,7 ± 12,2	16,6 ± 1,6*	18,5 ± 3,3*	10,1 ± 4,0*
AP _{av} TI, %%	49,9 ± 9,0	48,5 ± 11,4	54,8 ± 11,6	17,3 ± 7,0*	17,5 ± 8,2*	15,2 ± 5,7*
SAP 24-I, %%	9,5 ± 1,4	-	-	12,5 ± 1,5	-	-
DAP 24-I, %%	13,8 ± 2,1	-	-	16,7 ± 2,7	-	-
AP _{av} 24-I, %%	11,8 ± 1,6	-	-	14,8 ± 2,1	-	-
SAP AI, mm Hg/	205,3 ± 39,3	181,1 ± 33,9	334,0 ± 89,8	68,2 ± 10,1*	62,9 ± 21,6*	89,3 ± 3,7*
DAP AI, mm Hg/h	81,8 ± 16,1	88,2 ± 21,6	66,9 ± 27,7	35,8 ± 2,1*	43,1 ± 6,8*	23,2 ± 6,0*
AP _{av} AI, mm Hg/h	106,5 ± 22,6	104 ± 30,2	113,9 ± 41,2	36,5 ± 18,3	40,1 ± 10,1*	31,1 ± 6,8*

The great extent of reduction in maximal nocturnal AP rates in INH group is evidenced with N/D ratio: it made 1.64±0.06 and 1.72±0.08 for SAP and DAP, as compared to 1.38±0.07 and 1.5±0.05 respectively in the control group ($p<0.05$).

Comparison of after-treatment 24-MAP rates, as in the main group and in the control group, showed the following results. The main group had evident ($p<0.05$) reduction of maximal SAP rates within 24 hours, and SAP TI, DAP TI and SAP AI in day time, and average and maximal rates of SAP, SAP AI and DAP AI in night time.

Before treatment, 50% of the main-group patients had non-dipper 24-h curve, 18.8% - over-dipper 24-h curve, 12.4% - night-peaker 24-h curve, and only 18.8% of them had dipper 24-h curve. After INH therapy, night-peaker was not recorded any more at all, while the share of dipper curves grew up to 40.6%; the share of over-dipper curves did not change at all, while that of non-dipper curves was reduced (see Table 3).

TABLE 3. Dynamics of per-type changes in 24-h AP profile curve in AH patients, as exposed to INH

Curve type	Number of patients			
	Before treatment		After treatment	
	Absolute number	%%	Absolute number	%%
Dipper	6	18.8	13	40.6
Non-dipper	16	50	13	40.6
Over-dipper	6	18.8	6	18.8
Night-peaker	4	12.4	0	0

In medication-treatment group, after the treatment course, there were no more night-peaker curves any more either; the share of non-dipper profiles was also reduced through a growth in the share of dipper profiles. At the same time, the share of over-dipper curves was also reported as increased (from 10 up to 30%, see Table 4).

TABLE 4. Dynamics of per-type changes in 24-h AP profile curve in AH patients, as exposed to medication therapy

Curve type	Number of patients			
	Before treatment		After treatment	
	Absolute number	%%	Absolute number	%%
Dipper	15	50	15	50
Non-dipper	9	30	6	20
Over-dipper	3	10	9	30
Night-peaker	3	10	0	0

Therefore, the effected treatment yielded positive results both in the main and in the control patient group. The most pronounced reduction of maximal SAP-, DAP- and AP_{av} rates, nocturnally and diurnally, was reported during combined drug- and INH treatment. This is an evidence of a more pronounced effect of the combined treatment upon episodes of increased AP, which is vitally important for prevention of AH vascular complications. Exponentiation of the hypotensive effect of the drugs and INH showed also a major reduction of minimal rates of average 24-h AP. The main-group patients had a greater increase of 24-h AP 24-h profile normalization was accompanied with a growth in the number of patients, who had an adequate AP reduction in night time. Patients treated with INH had a more pronounced, as compared with the drug-treatment group, reduction in the duration of AP growth episodes.

The main group had a more pronounced reduction of SAP maximal peaks through each 24 hours and an evident, unlike that of the control group, reduction of diurnal average DAP and reduction of maximal DAP (diurnally and nocturnally). The combined therapy lead, to a reduction of the hypertensive load (less than 25%) and to a reduction in AP growth episode duration, to a greater extent than the drug treatment did.

Both groups had a reduction in the share of non-dipper curves through an increase in the dipper share; night-peaker curves were not registered any more at all. This is an evidence of an improvement in AP fluctuation circadian rhythms accompanied with restoration of periods of nocturnal reduction and full elimination of AP growth peaks during nocturnal sleeping. At the same time, there was a growth in the number of patients with over-dipper AP 24-h profile type in the drug-treatment group. Excessive nocturnal AP reduction can entail a reduction in cerebral and coronary blood flows, which extends the risk of a myocardial infarction- or insult development. Adaptation to INH, apparently, has a protective effect against excessive nocturnal AP reduction.

Conclusions

1. If hypoxic therapy and drug therapy are combined, the hypotensive effect grows – especially in so far as maximal AP increase (both nocturnal and diurnal) is concerned.
2. The combined INH & drug therapy leads to normalization of 24-h AP profile, and to a greater number of patients having an adequate nocturnal AP reduction, and to a lesser number and a lesser duration of AP growth episodes.
3. Long-term changes in 24-h AP profile are evidently more pronounced in patients treated with combined therapy, as compared to patients treated conventionally, with use of anti-hypertensive drugs alone.

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