Normobaric hypoxia conditioning reduces blood pressure and normalizes nitric oxide synthesis in patients with arterial hypertension

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Objectives **Insufficient production and/or increased decomposition of the potent endogenous vasodilator nitric oxide plays an important role in development and progression of arterial hypertension and its complications. One of the most effective means of stimulating endogenous nitric oxide synthesis is controlled adaptation to hypoxia. This study examined the effect of a 20-day, intermittent, normobaric intermittent hypoxia conditioning (IHC) program on blood pressure (BP) and nitric oxide production in patients with stage 1 arterial hypertension.**

Methods **The IHC sessions consisted of four to 10 cycles of alternating 3-min hypoxia (10% FIO_2) and 3-min room air breathing. BP was monitored for 24 h before and after IHC, and nitric oxide synthesis was evaluated by 24-h urinary excretion of the stable nitric oxide metabolites nitrate and nitrite.**

Results **IHC increased nitric oxide synthesis and decreased BP in hypertensive patients to values similar to those of normotensive individuals. Significant inverse correlations were found between nitric oxide production and disease duration, SBP, and DBP. Moreover, IHC enhancement of nitric oxide synthesis was especially robust in patients with arterial hypertension of more than 5 years duration. The reduction in BP persisted for at least 3 months in 28 of 33 hypertensive patients.**

Conclusion **IHC exerted a robust, persistent therapeutic effect and can be considered as an alternative, nonpharmacological treatment for patients with stage 1 arterial hypertension. The antihypertensive action of IHC is associated with normalization of nitric oxide production.** *J Hypertens* **29:2265–2272 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; IHC, intermittent hypoxia conditioning; NO_x, nitrate with nitrite; OSA, obstructive sleep apnea; SaO_2, arterial O_2 saturation; SBP, systolic blood pressure

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Introduction

Nitric oxide is a potent endogenous regulator of vascular tone and, thus, nitric oxide impacts development and progression of many cardiovascular diseases, including arterial hypertension [1]. We showed [2] that nitric oxide production progressively decreased in patients with stage 1 arterial hypertension (140–159 mmHg SBP, 90–99 mmHg DBP), and stage 2 arterial hypertension (SBP $\geq$160 mmHg, DBP $\geq$100 mmHg) as defined by the US National Institutes of Health [3]. Insufficient production and reduced availability of nitric oxide contribute to elevation of blood pressure (BP) and also to potentially lethal complications of arterial hypertension, including stroke, myocardial infarction, and chronic renal failure [4].

Although medications are available that effectively reduce BP, many do not improve nitric oxide-dependent endothelial function [5,6]. Meerson [7] found that adaptations to stresses protect against cardiovascular and other diseases. Multiple studies have demonstrated that stresses, including exercise, emotional distress, heat, and hypoxia conditioning, stimulate nitric oxide synthesis [8–10], and some of the additional nitric oxide generated during adaptation to stress is bound to releasable nitric oxide stores in vascular walls [8,11]. This stored nitric oxide can be mobilized to reduce vascular tone during stress-free intervals. Animal experiments have shown that, among various types of adaptation, hypoxic conditioning is the most effective in stimulating nitric oxide synthesis and storage [9,12]. Beneficial effects on nitric oxide metabolism apparently underlie hypoxia-induced prevention of endothelial dysfunction and the antihypertensive effect of hypoxia observed in spontaneously hypertensive rats [10,13–15]. Thus, the present study was designed to evaluate the effect of

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normobaric intermittent hypoxia conditioning (IHC) on BP and nitric oxide production in patients with stage 1 arterial hypertension.

Methods

This study was approved by the Institutional Review Board of the Saratov Institute of Cardiology. Each volunteer provided informed consent for participation in the study and all studies adhered to the principles of the Declaration of Helsinki.

Participants

Young white men (~32 years of age), with stage 1 hypertension (3–10-year duration) as confirmed by their BP measured during physical examination were initially recruited to undergo IHC. In this examination, BP was measured in duplicate after 20-min quiet rest, with the participant in the seated position. These pressures were measured in the supported, dominant arm by standard mercury sphygmomanometry. All participants had stable body weight with BMI between 20.0 and 24.9. None of the participants had abnormal blood count, blood chemistry, or urinalysis. Participants who had occasionally taken short-acting antihypertensive agents, such as captopril, were included at this stage of the recruitment, but participants who regularly took any antihypertensive medication were excluded from participation in the study. Also excluded from the study were participants with histories of malignant and symptomatic arterial hypertension, ischemic heart disease, cancer, metabolic or endocrine disorders, or any chronic inflammatory disease. Participants who had been recently exposed to hyperthermia or intensive solar radiation, including cosmetic tanning, were also excluded. Forty-nine participants met these study criteria; all antihypertensive drugs were withheld from these participants for the remainder of the study.

Before IHC, hypertensive participants underwent clinical evaluation as recommended for hypertensive patients (2007 European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension). This evaluation included a physical examination, 24-h BP monitoring, 12-lead ECG, ultrasonic and Doppler cardiography, chest radiography, ultrasound examination of kidneys, blood count, blood chemistry, and urinalysis, which included tests for microalbuminuria, bacteriuria, and leukocyturia. This clinical evaluation was repeated 1 day and 3 months after completion of the IHC regimen. Aside from stage 1 arterial hypertension, no abnormal findings were detected in any of the participants.

A control, non-IHC group consisted of 20 normotensive participants without apparent disease, aged 35.1 ± 4.6 years. BP and urinary nitric oxide excretion were measured in these control participants.

Blood pressure monitoring

All hypertensive and normotensive participants underwent outpatient BP monitoring for 24 h (TM-2421 monitor; A & D, Tokyo, Japan) during which BP was recorded at 30-min intervals during daytime and at 60-min intervals at night. From these data, mean 24-h BP was computed, and mean daytime and night-time SBP and DBP were computed. For the hypertensive participants, 24-h BP monitoring was performed before a 20-day IHC program and again on the next day following IHC.

Initial hypoxic test

Prior to IHC, the 49 hypertensive participants underwent a preliminary 5-min hypoxic test to determine their hypoxia tolerance and to acquire information needed to adjust individually the hypoxic intensity of the subsequent IHC regimen. For 4 days prior to this test, the hypertensive participants consumed a low-nitrate diet, which excluded sausage, canned food, raw root vegetables, and cabbage. For 24 h prior to the hypoxic test, each participant's entire urine output was collected. During the hypoxic test, the participants inhaled a gas mixture in which the O_2 concentration was gradually decreased from 18 to 10% O_2 as BP, arterial O_2 saturation (SaO_2), ECG, heart rate, and respiratory rate were monitored. BP was measured by sphygmomanometry, as in the initial evaluation, and SaO_2 was measured by a pulse oximeter (Sensor Medics, Homestead, Florida, USA). The protocol for this hypoxic test required that the test be stopped if any of the following conditions were observed: SaO_2 80% or less, BP equal to or greater than 160/100 mmHg, greater than 10% increase in heart rate, any ECG signs of myocardial ischemia, respiration rate more than 40 breaths/min, or participant-reported shortness of breath, dizziness, or headache. Three participants aborted the test due to mask discomfort or other reasons not associated with clinical or physiological signs. All of the other 46 participants who completed this hypoxic test breathed 10% O_2 for 5 min with no adverse effects and were enrolled in the IHC study.

Intermittent hypoxia conditioning

Normobaric IHC was performed for 20 consecutive daily sessions with a Hypoxicator-10M (Hypoxia Medical Ltd, Moscow, Russia). The participants inspired alternately moderately hypoxic air (10% O_2) or normal atmospheric air, each for 3 min, for four to 10 cycles daily.

Of the 46 participants who began IHC, 37 completed the conditioning and the subsequent measurements of BP and nitric oxide production. No participant experienced physiological or psychological distress during IHC. Of the nine participants who did not complete IHC, four withdrew for personal reasons and five were switched to drug therapy. The decision to switch patients to drug therapy was based on the following rationale. Preliminary

experiments had demonstrated that IHC produced an antihypertensive effect evident in most participants by 7 days (N.P. Lyamina, unpublished observations). In the current study, if no antihypertensive effect was observed by 7 days, IHC was discontinued, and that participant was switched to drug therapy.

On the day following completion of IHC, 24-h BP monitoring and urine collection were initiated. The clinical effect of IHC was evaluated using the following criteria: full response, achieving average 24-h BP of less than 140/90 mmHg; partial response, reducing average 24-h BP by 10% or more from the pretreatment value, but with posttreatment average 24-h BP of more than 140/90 mmHg. In addition, arterial BP was measured at 3 months after IHC in 33 of the participants that had arterial hypertension prior to IHC. BP values below 140/90 mmHg were taken to indicate persistent antihypertensive effects of IHC in these participants.

Nitric oxide production

Nitric oxide production was evaluated by the 24-h urinary excretion of the stable nitric oxide metabolites, nitrite and nitrate (collectively, NO_x), prior to IHC and on the next day after completion of IHC. Nitrate was reduced to nitrite with cadmium and measured spectrophotometrically following the Griess reaction [16]. Results were expressed as micromole NO_x excreted per day.

Statistical analyses

Data are presented as means ± SEM. Paired *t*-tests were used to identify statistically significant differences before and after IHC within the same participants. Unpaired *t*-tests were used to identify statistically significant differences between findings in control and hypertensive participants. Linear correlation analysis was used to examine the effect of BP on urinary excretion of NO_x. *P* values below 0.05 were taken to indicate statistically significant differences.

Results

The principal findings of this study were that IHC reduced BP and increased nitric oxide production in participants with stage 1 arterial hypertension. After the IHC treatment, a full antihypertensive response was observed in 34 of the 37 (92%) previously hypertensive participants. The other three participants had a partial response to IHC. The clinical condition of the participants also improved after the IHC treatment: three of five patients reported less sleep disorders, five of seven patients reported fewer or less severe headaches, and four of six patients reported less dizziness. The patients also reported that their ability to work increased after the IHC program.

Table 1 shows 24-h BP data for 20 control participants and for 37 hypertensive participants before and after IHC. The duration of arterial hypertension did not affect these diurnal variations in BP. SBP and DBP during both daytime and night-time were significantly greater in arterial hypertension participants than in control participants. BP values of arterial hypertension participants were significantly lower after completion of IHC. SBP and DBP values fell similarly by 15 and 17%, respectively. The greatest change observed was in night-time DBP, which fell by 27%. Figure 1 shows that the BP values did not differ significantly between participants with arterial hypertension duration of 5 years or less vs. more prolonged arterial hypertension. However, IHC tended to decrease DBP to a greater extent in the former (14.4%) than the latter (9.0%) subgroup. The three participants who showed only a partial antihypertensive response to IHC had arterial hypertension of more than 5 years.

Table 1 Effect of intermittent hypoxia conditioning on daytime and night-time arterial blood pressures in participants with stage 1 arterial hypertension

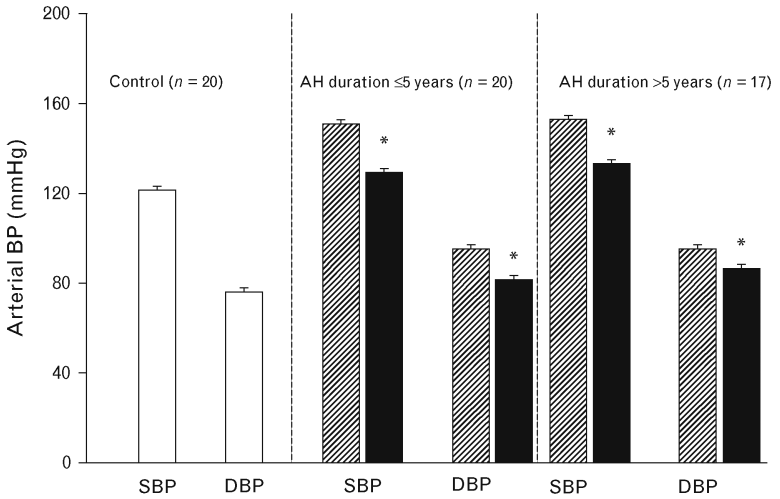
		Participants with stage 1 arterial hypertension ($n = 37$)	
	Control ($n = 20$)	Pre-IHC	Post-IHC
SBP (mmHg)			
Average	121.4 ± 1.2	151.4 ± 1.4*	129.4 ± 1.0†
Daytime	125.3 ± 1.3	154.3 ± 1.5*	135.6 ± 1.1†
Night-time	115.3 ± 1.4	131.3 ± 1.2*	118.3 ± 1.0†
DBP (mmHg)			
Average	76.1 ± 0.8	95.1 ± 0.7*	78.5 ± 0.7†
Daytime	84.9 ± 1.1	95.9 ± 0.8*	88.2 ± 0.7†
Night-time	67.7 ± 0.7	94.7 ± 0.6*	69.6 ± 0.6†

Data were obtained by 24-h monitoring of arterial blood pressure (BP). Values are mean ± SEM. IHC, intermittent hypoxia conditioning. * $P < 0.001$ vs. normotensive control values. † $P < 0.05$ vs. value before IHC.

Arterial BP was measured 3 months later in 33 of the arterial hypertension participants who completed IHC. A persistent reduction in arterial BP was seen in 28 of these participants in which SBP was 131.6 ± 2.3 mmHg and DBP was 82.1 ± 1.5 mmHg. These participants remained normotensive without medications. Arterial hypertension recurred in the other five participants: SBP was 149.6 ± 6.7 mmHg and DBP was 93.6 ± 3.5 mmHg. These participants had been prescribed medications to treat their hypertension. Thus, the antihypertensive effects of a 20-day IHC program persisted for at least 3 months in 85% of participants with stage 1 arterial hypertension.

Urinary excretion of NO_x inversely correlated with both DBP and SBP of hypertensive participants prior to IHC ($r = -0.43$ and $r = -0.51$, respectively; $P < 0.001$ for both pressures). Figure 2 shows urinary excretion of nitrite with nitrate, that is, NO_x, an index of nitric oxide production, for control and hypertensive participants before and after IHC. Hypertensive participants excreted significantly less NO_x than control participants before treatment with IHC (46 ± 4 vs. 63 ± 5 μmol/day). After IHC, the excretion of NO_x of these participants increased significantly by 29% to a rate (59 ± 5 μmol/day) not

Fig. 1



Effect of intermittent hypoxia conditioning on blood pressure in patients with different durations of stage 1 hypertension. Open bars, normotensive participants; hatched bars, pre-IHC; solid bars, post-IHC. Values are mean ± SEM. AH, arterial hypertension; IHC, intermittent hypoxia conditioning. $^{*}P < 0.01$ vs. pre-IHC value.

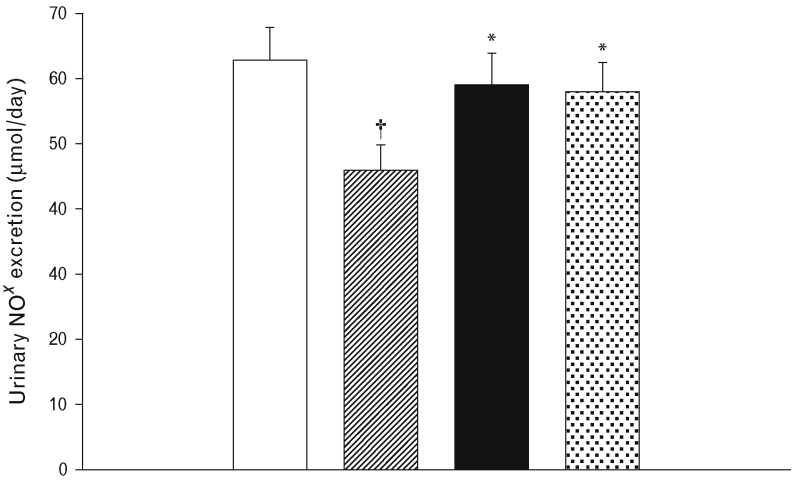
significantly different from that of the control participants. Furthermore, a statistically significant increase in urinary NO_x excretion persisted for at least 3 months after IHC treatment of the hypertensive participants (58 ± 5 μmol/day).

Figure 3 shows that participants with arterial hypertension for more than 5 years excreted less NO_x before IHC than did participants with arterial hypertension of shorter duration. Both groups had significant increases in urinary excretion of NO_x after IHC. A significantly greater post-IHC increase in NO_x excretion was observed in those participants with more than 5 years arterial hypertension duration, 27% compared with 15% in participants with arterial hypertension for 5 years or less duration. The increases in NO_x excretion persisted for 3 months in both subgroups.

Discussion

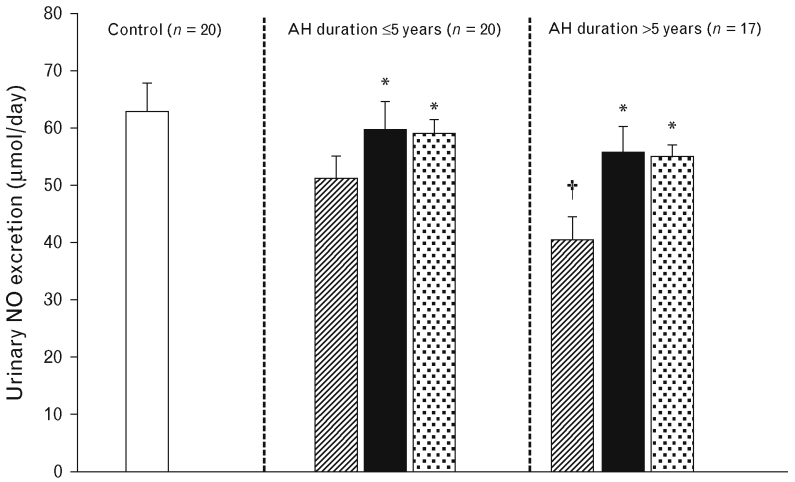
This study demonstrates for the first time that IHC exerts an antihypertensive effect associated with improvement

Fig. 2



Effect of intermittent hypoxia conditioning on 24-h urinary excretion of nitrite and nitrate by participants with stage 1 hypertension. Open bar, normotensive participants; hatched bar, pre-IHC; solid bar, post-IHC; stippled bar, 3 months after IHC. Values are mean ± SEM. IHC, intermittent hypoxia conditioning. $^{*}P < 0.05$ vs. pre-IHC; $^{\dagger}P < 0.05$ vs. normotensive control.

Fig. 3



Effect of intermittent hypoxia conditioning on urinary excretion of nitrite and nitrate in participants with different durations of stage 1 hypertension. Open bar, normotensive controls; hatched bars, pre-IHC; solid bars, post-IHC; stippled bar, 3 months after IHC. Values are mean ± SEM. AH, arterial hypertension; IHC, intermittent hypoxia conditioning. $^{*}P < 0.05$ vs. respective pre-IHC; $^{\dagger}P < 0.05$ vs. pretreatment value for arterial hypertension duration for 5 years or less. As shown in Fig. 2 pre-IHC values were significantly less than normotensive control values, $P < 0.05$.

of nitric oxide production in patients with arterial hypertension. The hallmarks of adaptation to intermittent hypoxia implicate nitric oxide-dependent mechanisms in the development of IHC protective effects. Specifically, adaptation to hypoxia produces an antihypertensive effect and improves endothelium-dependent relaxation of blood vessels in stroke-prone spontaneously hypertensive rats [13,14]. Mashina *et al.* [17] showed that adaptation to intermittent hypobaric hypoxia prevented endothelial dysfunction of cerebral blood vessels in experimental Alzheimer's disease. This protection apparently stems from stimulation of nitric oxide synthesis and formation of releasable nitric oxide stores in vascular walls, which not only bind excessive nitric oxide, thereby preventing its toxic effects, but also may function as an additional source of free nitric oxide under conditions of nitric oxide shortage [11].

Several investigators have used IHC for the treatment of cardiovascular diseases [7,18,19], and we have successfully applied this approach for the treatment of heart arrhythmias in patients [20]. On the basis of these studies, we tested the possibility that adaptation to normobaric IHC produces chronic reductions in BP in hypertensive patients, and that this adaptation is associated with normalization of nitric oxide production.

An antihypertensive effect of IHC might seem surprising in light of the well documented hypertensive response to the intermittent hypoxia of obstructive sleep apnea (OSA) [21]. As noted by Bernardi [22], the intensity, cycle duration and frequency, duration of the hypoxic conditioning regimen, and cumulative exposure to hypoxia are important determinants of whether the result will be detrimental or beneficial. Hypoxia of OSA is intensive, with arterial hemoglobin oxygen saturation often falling below 80%. Although these intensive hypoxic stresses are brief, less than 1 min, they are frequently repeated for many hours each night, often interrupting sleep. As expiration is blocked in OSA, arterial CO_2 rises, causing respiratory acidosis and activation of the muscle metaboreflex [14]. These intermittent hypoxic and hypercapnic episodes impose oxidative stress, systemic inflammation, and sympathetic excitation, which are further aggravated by arousal [23]. In addition, circulating endothelin, catecholamines, and other vasoactive hormones are increased [24]. In contrast, the IHC employed in this study and in others that demonstrated beneficial effects of intermittent hypoxia [14] was less intensive, extended for 3 min per exposure, and limited to four to 10 exposures per day for only 20 days. Participants experienced mild hyperventilation, but no physiological or psychological distress during IHC. The more moderate oxidative stress of IHC has been reported to be protective in numerous tissues [14]. IHC increases parasympathetic function and induces synthesis of erythropoietin [25,26], which has cardioprotective [25,27], neuroprotective [28], and anti-inflammatory actions [29]. As the present study demonstrated, IHC improves nitric oxide production and storage, consistent with its antihypertensive action. Although the determinants of intermittent hypoxia's pro-hypertensive vs. antihypertensive character are generally understood, further investigation is required to optimize the antihypertensive actions of IHC.

Nitric oxide is rapidly oxidized *in vivo* to NO_x, the major nitric oxide metabolites, by oxygenated hemoglobin,

molecular oxygen, and superoxide anions. Measurement of urinary NO_x excretion is generally accepted as a facile indicator of total body nitric oxide synthesis [30]. However, this measurement may be confounded by the contribution of dietary nitrate to plasma NO_x. Some studies have suggested that NO_x can be used as an index of the endogenous formation of nitric oxide, provided that the oral intake of nitrate is restricted for at least 48 h [31] or even up to 4 days [32]. Accordingly, in this study we minimized the impact of dietary nitrate and nitrite on the urinary NO_x measurement by collecting the urine after a 4-day low-nitrite/nitrate diet.

Adaptive stimulation of nitric oxide synthesis by IHC may involve a direct hypoxic activation of endothelial nitric oxide synthase and/or increased expression of this enzyme [10], which could account for the increased excretion of nitric oxide metabolites observed in IHC-treated patients in our study. Another possible mechanism of increased nitric oxide production in IHC may be activation of antioxidant enzymes by adaptation to hypoxia [33,34]. Previously, we observed increased activity of lipid peroxidation and decreased antioxidant activity not only in hypertensive patients but also in participants with high-normal BP [2]. This finding is concordant with current ideas on the role of reactive oxygen species in the impairment of nitric oxide production and endothelial dysfunction associated with hypertension [35]. Published studies have demonstrated that free radical processes can be reversed and antioxidant status normalized by successful antihypertensive treatment [36,37]. Therefore, IHC may prevent excessive generation of reactive oxygen species and improve the nitric oxide availability by enhancing endogenous antioxidant defenses.

Stimulation of nitric oxide synthesis is not the only potential mechanism for IHC's antihypertensive effect. The results of multiple studies on protective effects of intermittent hypoxia suggest other mechanisms, including improved O_2 delivery and utilization in tissues [38], IHC-induced increases in sodium and water excretion [7], increased parasympathetic [39] and decreased sympathetic nervous activity [40–42], reduction of peripheral vascular resistance [43], potentiation of antioxidant defense due to increased activity of antioxidant enzymes [44], and prevention of vessel rarefaction, especially in brain and skeletal muscles [45,46], due to increased expression of vascular endothelial growth factor [47]. As any long-term, effective antihypertensive treatment can improve endothelial function, including enhancement of eNOS activity [48,49], the reduction of BP induced by these antihypertensive mechanisms may by itself serve to normalize nitric oxide metabolism.

Earlier, we showed that IHC produced robust antiarrhythmic and antianginal effects in patients with ischemic heart disease [50]. These effects persisted for 3 months after IHC therapy in 88% of patients and for 6 months in 80% of patients. Patients receiving a maintenance course of IHC (10–15 sessions) had further improvement in arrhythmic status 9 months later. In patients not receiving the maintenance course, the antiarrhythmic effect gradually subsided at 9 months after IHC.

Long-lasting antihypertensive effects of IHC were demonstrated earlier in some Russian clinical reports. Vorob'ev *et al.* [51] examined the antihypertensive effects of IHC in patients with stages 1 and 2 essential hypertension. IHC reduced BP, improved the patients' health status and physical performance, and normalized O_2 consumption and transport. The antihypertensive effect persisted for 6 months in 80% and 1 year in 43% of the patients. Seventy-nine percent of these patients were able to discontinue medications after IHC. No unfavorable effects were observed. Mukharliamov *et al.* [52] used a 10-day IHC program [10 cycles/day of 5 min hypoxia (10–14% O_2) interspersed with 5-min normoxia] in patients with stages 1 and 2 hypertension. In that study, IHC reduced both SBP and DBP, heart rate, and peripheral resistance. The persistence of these favorable effects prompted the suggestion that administering IHC courses one to two times a year would be sufficient to maintain the reduced BP in hypertensive patients.

The current study is the first to show that the persistence of the antihypertensive effect of IHC is associated with chronically enhanced nitric oxide production in patients with stage 1 arterial hypertension. Earlier, we compared changes in plasma NO_x in patients with different stages of hypertension [2] and found that nitric oxide production was significantly increased in young participants with BP at the upper end of the normal range. At the prehypertensive and early hypertensive stages, the increased nitric oxide production may dampen increases in BP. Nitric oxide production tended to decrease with protracted high-normal BP, and eventually fell in patients with definitive hypertension. We observed that the presence of risk factors for hypertension, such as smoking and obesity in individuals with high-normal BP, provoked the transition from increased nitric oxide production to nitric oxide shortage. Chronic activation of nitric oxide synthesis due to increased expression of nitric oxide synthase protein may be a pivotal mechanism underlying the long-standing antihypertensive effect of IHC.

The limitations of this study must be acknowledged. The study was limited to young adults with stage 1 arterial hypertension, and it is unknown whether the favorable effects of IHC demonstrated here would occur in older patients and/or those with more severe hypertension. The possibility that combining IHC with antihypertensive medications would be more effective than either treatment alone was not examined. In this study, nitric

oxide production was assessed from urinary excretion of nitric oxide metabolites. Although this noninvasive approach is a well accepted method to monitor nitric oxide production, it does not identify the specific sites of nitric oxide formation or permit quantification of internal nitric oxide stores [8,11]. A sham-conditioned group of hypertensive patients was not studied, although it would not be expected that such patients would experience appreciable reductions in BP as observed in the IHC patients.

Although the finding that IHC had an antihypertensive effect is consistent with previous studies [14], we must acknowledge that in the current study, five participants did not respond by 7 days and were switched to drug therapy, as it would have been medically improper to have continued IHC while withholding drug therapy. This subgroup of nonresponding participants may have been refractory to IHC treatment or have required a longer IHC program to produce an effect. Even if the five nonresponders had completed the 20-day IHC protocol with unchanged BP and were included for calculation of post-IHC BP (132 ± 1 mmHg, $n = 42$), there still would have been a statistically significant IHC-induced reduction in mean BP compared with the pre-IHC value (151 ± 2 mmHg, $n = 42$).

Perspectives

This investigation demonstrates that IHC is an effective, nonpharmacological therapy for patients with stage 1 arterial hypertension, and this therapy normalizes nitric oxide production. It remains to be determined whether IHC is effective in patients with more severe hypertension and whether IHC can reduce requirements for antihypertensive medications in these patients.

In conclusion, this study demonstrates impaired production of the vasodilator nitric oxide in patients with stage 1 arterial hypertension vs. normotensive participants. Urinary excretion of NO_x, an index of nitric oxide production, inversely correlates with duration and severity of arterial hypertension as well as SBP and DBP. However, adaptation to intermittent normobaric hypoxia evoked by a 20-day IHC regimen stimulates nitric oxide synthesis and reduces both SBP and DBP in patients with stage 1 arterial hypertension. None of the participants reported untoward effects of hypoxia over the course of the IHC program. In most patients, the antihypertensive effects of IHC persisted for at least 3 months, as did the increased nitric oxide formation.

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Conflicts of interest

There are no conflicts of interest.

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