Ambulatory Blood Pressure in Untreated and Treated Hypertensive Patients at High Altitude

The High Altitude Cardiovascular Research–Andes Study

Grzegorz Bilo, Francisco C. Villafuerte, Andrea Faini, Cecilia Anza-Ramírez, Miriam Revera, Andrea Giuliano, Sergio Caravita, Francesca Gregorini, Carolina Lombardi, Elisabetta Salvioni, Jose Luis Macarlupu, Deborah Ossoli, Leah Landaveri, Morin Lang, Piergiuseppe Agostoni, José Manuel Sosa, Giuseppe Mancia, Gianfranco Parati

Abstract—Blood pressure increases during acute exposure to high altitude in healthy humans. However, little is known on altitude effects in hypertensive subjects or on the treatment efficacy in this condition. Objectives of High Altitude Cardiovascular Research (HIGHCARE)–Andes Lowlanders Study were to investigate the effects of acute high-altitude exposure on 24-hour ambulatory blood pressure in hypertensive subjects and to assess antihypertensive treatment efficacy in this setting. One hundred untreated subjects with mild hypertension (screening blood pressure, 144.1±9.8 mm Hg systolic, 92.0±7.5 mm Hg diastolic) were randomized to double-blind placebo or to telmisartan 80 mg+modified release nifedipine 30 mg combination. Twenty-four–hour ambulatory blood pressure monitoring was performed off-treatment, after 6 weeks of treatment at sea level, on treatment during acute exposure to high altitude (3260 m) and immediately after return to sea level. Eighty-nine patients completed the study (age, 56.4±17.6 years; 52 men/37 women; body mass index, 28.2±3.5 kg/m^2). Twenty-four–hour systolic blood pressure increased at high altitude in both groups (placebo, 11.0±9 mm Hg; P<0.001 and active treatment, 8.1±10.4 mm Hg; P<0.001). Active treatment reduced 24-hour systolic blood pressure both at sea level and at high altitude (147.9±11.1 versus 132.6±12.4 mm Hg for placebo versus treated; P<0.001; 95% confidence interval of the difference 10.9–19.9 mm Hg) and was well tolerated. Similar results were obtained for diastolic, for daytime blood pressure, and for nighttime blood pressure. Treatment was well tolerated in all conditions. Our study demonstrates that (1) 24-hour blood pressure increases significantly during acute high-altitude exposure in hypertensive subjects and (2) treatment with angiotensin receptor blocker-calcium channel blocker combination is effective and safe in this condition.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01830530.

(*Hypertension*. 2015;65:1266-1272. DOI: 10.1161/HYPERTENSIONAHA.114.05003.) • **Online Data Supplement**

Key Words: altitude ■ anoxia ■ antihypertensive agents ■ blood pressure ■ blood pressure monitoring, ambulatory

Acute exposure to high-altitude hypoxia induces important changes in cardiovascular regulation,[1–4] including an increase in blood pressure (BP) and heart rate (HR).[2,5–8] Millions of subjects travel for relatively short periods of time to high altitude either for work or for leisure including many affected by hypertension[9] in whom the pressor effect of high altitude may be relevant. Limited information is available, however, on the acute BP effects of high altitude in hypertensive subjects,[10] and on the effectiveness and tolerability of antihypertensive drugs under these circumstances. As a result, the few recommendations published on the management of hypertensive subjects planning to spend time at high altitude for either leisure or work are largely based on experts' opinion rather than on evidence.[2,11–14]

Both angiotensin receptor blockers (ARBs) and dihydropyridine calcium antagonists are widely used for the monotherapy of hypertension, and their combination has been included among the preferred therapeutic choices by recent

Received December 4, 2014; first decision December 21, 2014; revision accepted March 27, 2015.

From the Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano, Milan, Italy (G.B., A.F., M.R., A.G., S.C., F.G., C.L., D.O., G.M., G.P.); Laboratorio de Fisiologia Comparada, Departamento de Ciencias Biológicas y Fisiológicas, Universidad Peruana Cayetano Heredia, Lima, Peru (F.C.V., C.A.-R., J.L.M., L.L., J.M.S.); Department of Health Sciences, Università di Milano-Bicocca, Milan, Italy (S.C., G.M., G.P.); Heart Failure Unit, Centro Cardiologico Monzino, IRCCS, Milan, Italy (E.S., P.A.); Departamento De Ciencias De La Rehabilitación Y Movimiento Humano, Universidad de Antofagasta, Antofagasta, Chile (M.L.); and Department of Clinical Sciences and Community Health, Cardiovascular Section, Università degli Studi di Milano, Milan, Italy (P.A.).

This article was sent to Takayoshi Ohkubo, Guest Editor, for review by expert referees, editorial decision, and final disposition.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi: 10.1161/HYPERTENSIONAHA.114.05003/-/DC1.

Correspondence to Gianfranco Parati, Istituto Auxologico Italiano, Ospedale San Luca, Piazzale Brescia 20, Milan, Italy. E-mail gianfranco.parati@unimib.it

guidelines.[15,16] Furthermore, the calcium antagonist nifedipine lowers pulmonary pressure typically elevated at high altitude and is used in prevention and treatment of high-altitude pulmonary edema.[4]

Aims of the present study were to extend the information on the acute effects of high altitude on conventional and 24-hour BP obtained in previous studies in normotensive volunteers[8,17] to hypertensive subjects residing at sea level, and to determine whether the efficacy of antihypertensive treatment with the combination of an ARB (telmisartan) and a slow release calcium antagonist (nifedipine gastrointestinal therapeutic system [GITS]) is maintained at high altitude.

The study was conducted in the frame of the High Altitude Cardiovascular Research (HIGHCARE)–Andes Lowlanders Study.

Methods

This was a single-center, parallel-group, randomized, double-blind, controlled trial comparing the 24-hour BP effects of telmisartan 80 mg combined with nifedipine gastrointestinal therapeutic system 30 mg against placebo at sea level and at an altitude of 3260 m.

Participants

Subjects with known or suspected arterial hypertension, residing permanently in the metropolitan area of Lima, Peru (altitude <500 m), were screened. Subjects were included if they fulfilled the following criteria: age between 18 and 65 years; permanent residence at low (<500 m) altitude; conventional systolic BP (SBP) between 140 and 159 mm Hg or conventional diastolic BP (DBP) between 90 and 99 mm Hg and mean daytime BP: 135≤SBP<150 mm Hg or 85≤DBP<95 mm Hg in the absence of antihypertensive treatment (see below); written informed consent was obtained to participate in the study. We excluded subjects who would likely have BP in moderate to severe range after washout, those with contraindications to either study drug, with history of serious mountain sickness, recently exposed to high altitude, with secondary hypertension or other relevant diseases, severe obesity and pregnant women (detailed criteria are available in Box S1 in the online-only Data Supplement).

All subjects underwent a general health check before the expedition. The protocol was approved by the Ethics Committees of participating institutions in Italy and Peru and by Peruvian Drug Agency. The study was conducted in agreement with Declaration of Helsinki principles.

Study Organization

Subjects' eligibility criteria were assessed at the screening visit at sea level (visit 0). A baseline sea level visit (visit 1) was then performed (after 4 weeks washout in treated subjects), after which eligible subjects were randomized to placebo or active treatment group and remained on the assigned treatment until study end. Two sea level visits were then performed: visit 2 (safety visit, 2 weeks) and visit 3 (6 weeks) when study assessments were repeated. Two to 10 days after visit 3, the participants were brought by car to high altitude (Huancayo, Peru, 3260 m) where they stayed for 3 days (2 nights) during which study assessments were repeated (visit 4). On the morning of the first or second day after the return to sea level, visit 5 took place during which conventional BP was measured and the ambulatory BP monitor was placed. The details on the design of the study are shown in Figure 1 and Figure S1 in the online-only Data Supplement.

Study Drugs

Commercially available tablets of nifedipine gastrointestinal therapeutic system 30 mg and telmisartan 80 mg were used in the active treatment arm, whereas sucrose was used as placebo. Active medications and placebo were placed in identical capsules to be taken in a single morning administration. Throughout the study, the use of other antihypertensive medication or of drugs aimed at preventing high-altitude sickness was not allowed. In case of acute mountain sickness symptoms, an appropriate medical therapy was allowed.

Randomization and Blinding

A randomization list was generated before the study start. Randomization was performed within blocks including between 4 and 8 participants, without stratification. At inclusion, each participant received consecutive identification code associated with one of the treatment groups. Throughout the study, all subjects and investigators were blind to the treatment administered.

Measurements

Information collected during the study included clinical history, symptoms and adverse events, conventional BP and HR, 24-hour ambulatory BP and HR, respiratory rate, body height and weight, waist circumference, blood oxygen saturation (SpO_2), Lake Louise Score of acute mountain sickness,[18] and other variables, not discussed in this article.

Conventional BP and HR were obtained as the average of 2 seated measurements performed 1 to 2 minutes apart after at least 5 minutes of rest on the nondominant arm using a validated oscillometric device (UA-767 Plus; AND, Tokyo, Japan).[19] Twenty-four–hour ambulatory BP monitoring was performed using validated oscillometric devices (TM-2430; AND, Tokya, Japan),[20] applied to the nondominant arm in the morning and removed after 24 hours. At high altitude (visit 4), the device was always placed in the morning of the first day after the arrival, that is, after 13 to 17 hours of permanence (Figure S1). The subjects were instructed to attend at their usual activities during the monitoring period, while avoiding strenuous exercise. Measurements were programmed every 15 minutes during daytime (7–23 hours) and every 20 minutes at nighttime (23–7 hours). Mean values were computed for SBP, DBP, and HR over 24 hours, daytime, and nighttime (defined based on subjects' activity logbook). Nocturnal BP fall was calculated as percent reduction of mean BP at nighttime from the mean daytime value. Only recordings with at least 70% of expected

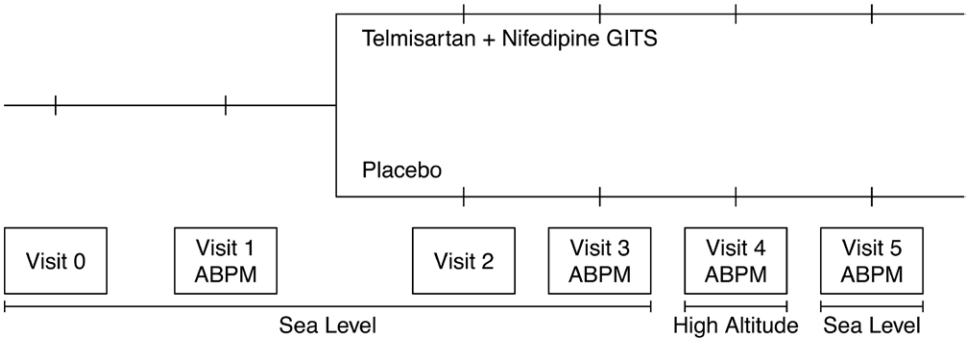

Figure 1. Study design and visits. ABPM indicates ambulatory blood pressure monitoring.

readings rated as valid were considered.[21] Spot measurement of transcutaneous blood oxygen saturation (SpO_2) was performed during sea level visits and on day 1 (evening of the arrival day), day 2, and day 3 (both in the morning) of high-altitude permanence with pulse oximeter (RAD-5; Masimo Corp, Irvine, CA).

Study Variables

Twenty-four–hour ambulatory mean SBP at V4 was the primary efficacy variable. Secondary efficacy variables included: 24-hour DBP, daytime, and nighttime mean SBP and DBP at high altitude (V4), 24-hour, daytime, and nighttime mean SBP and DBP at sea level (V3); nocturnal fall of SBP and DBP at high altitude (V4) and at sea level (V3); conventional SBP and DBP at high altitude (V4) and at sea level (V3).

Safety variables included adverse events, vital signs, routine laboratory blood tests performed during treatment and, at high altitude, additionally Lake Louise Score and SpO_2.

Sample Size

On the basis of data from previous studies,[8,17] we estimated that the primary efficacy variable (24-hour ambulatory SBP at high altitude) would have a SD of 12 mm Hg within each group. On the basis of this estimate, 84 patients (42 per each of the 2 treatment groups) were needed to identify an 8 mm Hg difference in the primary efficacy variable between the study groups with a power of 80% and type I error rate of 0.05, assuming a 10% patient dropout. To account for a possible imprecision in the estimate of SD (based on studies in normotensive subjects) and of dropout rate, we decided to recruit a total of 50 subjects per group.

Statistical Analysis

The primary efficacy analysis was performed per protocol, ie, in subjects who had completed all study visits and showed no major protocol deviations. The safety analysis was performed in subjects in whom at least 1 dose of study medication was administered.

R software version 2.15.3 (R Foundation for Statistical Computing) was used. Continuous variables are reported as mean±SD or (in adjusted models) as least square mean±SE. Differences between groups at baseline were assessed for categorical variables with χ^2 test and for continuous variables with unpaired 2-tailed Student *t* test.

To assess the combined effect of altitude level and treatment group, we used the linear mixed-effects models package (nlme, linear, and nonlinear mixed-effects models) accounting for repeated measurements, with a compound symmetry covariance structure, fitting the models by maximizing the restricted log-likelihood. Visit 1 values were included as fixed effect in the linear mixed-effects models to reduce the error variance by accounting for individual differences in responses. For multiple post hoc comparisons, we used the Holm algorithm.[22] An α level of 0.05 was used for all hypothesis tests.

Table 1. Baseline Characteristics of Subjects Included in Per-Protocol Analysis

Variable	All (n=89)	T/N (n=47)	PL (n=42)	*P* Value (T/N vs PL)
Age, y	51.7±8.9	51.5±8.4	52.1±9.5	> 0.20
Sex (M/F)	50/39	27/20	23/19	> 0.20
Height, cm	163.5±8.4	162.4±8.8	164.8±8.0	0.19
Weight, kg	76.1±13.7	73.5±13.9	79.1±13.0	0.05
BMI, kg/m^2	28.3±3.6	27.7±3.5	29.0±3.5	0.08
Current smokers, n (%)	20 (22)	10 (21)	9 (21)	> 0.20
History of dyslipidemia, n (%)	41 (46)	21 (45)	20 (48)	> 0.20
Previous antihypertensive treatment, n (%)	25 (28)	14 (30)	11 (26)	> 0.20

BMI indicates body mass index; F, female; M, male; PL, placebo; and T/N, telmisartan/nifedipine gastrointestinal therapeutic system.

Results

Of 332 screened subjects, 100 fulfilled selection criteria and were randomized (age, 55.7±17.2 years; 59 men/41 women). Of those, 89 completed the study and were considered in the per-protocol analysis (Figure S2). There were no significant between-group differences at baseline except for a somewhat higher body weight (*P*=0.05) and body mass index (*P*=0.08) in the placebo group (Table 1).

Effects of High-Altitude in Untreated Subjects

Compared with prealtitude (visit 3) values, conventional and 24-hour SBP and DBP were significantly higher at high altitude (Figure 2). This increase tended to be more pronounced for ambulatory than for conventional BP (*P* for difference >0.10). The increase was greater during the night than during the daytime (SBP, 9.3 versus 14.0 mm Hg; *P*<0.02 and DBP, 4.4 versus 7.5 mm Hg; *P*<0.01), with a marked reduction in the size of the nocturnal BP fall (for SBP from 15.5±7.4% to 11.5±8%; *P*<0.05; Figure S3). The BP changes were accompanied by a significant increase in 24-hour, daytime, and nighttime mean HR, with an attenuation of the nocturnal bradycardia. Increase in BP and HR occurring at altitude largely disappeared on return to sea level (visit 5) although 24-hour, daytime, and nighttime SBP values remained higher after than before altitude exposure (visit 3). Detailed information on BP and HR behavior is shown in Table 2 and Table S1.

Effects of Treatment

After 6 weeks of treatment at sea level, office and ambulatory BP showed, respectively, a small reduction and no reduction at all in the placebo group, whereas in the active treatment group, all BP values were significantly reduced. The 24-hour mean SBP value (primary efficacy variable) was thus lower with active treatment than with placebo at sea level (visit 3) and remained significantly lower at high altitude (visit 4; 147.9±11.1 mm Hg for placebo; 132.6±12.4 mm Hg for active treatment; *P*<0.001; 95% confidence interval of the difference: 10.9–19.9 mm Hg). Similar results were obtained for conventional SBP and DBP, for 24-hour DBP, and for daytime and night-time BP taken separately (Table 2; Figure 2; Table S1). The increase in conventional and 24-hour SBP at high altitude tended to be smaller in the active treatment group, but the difference was not significant (conventional, 2.5±15.0 versus 7.8±15.2 mm Hg; *P*=0.10; 24-hour, 8.1±10.4 versus 11.0±9.0 mm Hg; *P*=0.17 for active treatment and placebo, respectively). No differences in HR were observed between study groups. No sex-related differences were observed in the outcomes.

Safety Results

At sea level, adverse events occurred in 27 subjects: 18 in the active treatment and 9 in the placebo group. None of the adverse events were classified as serious except transient neurological symptoms, which developed in 1 subject in placebo

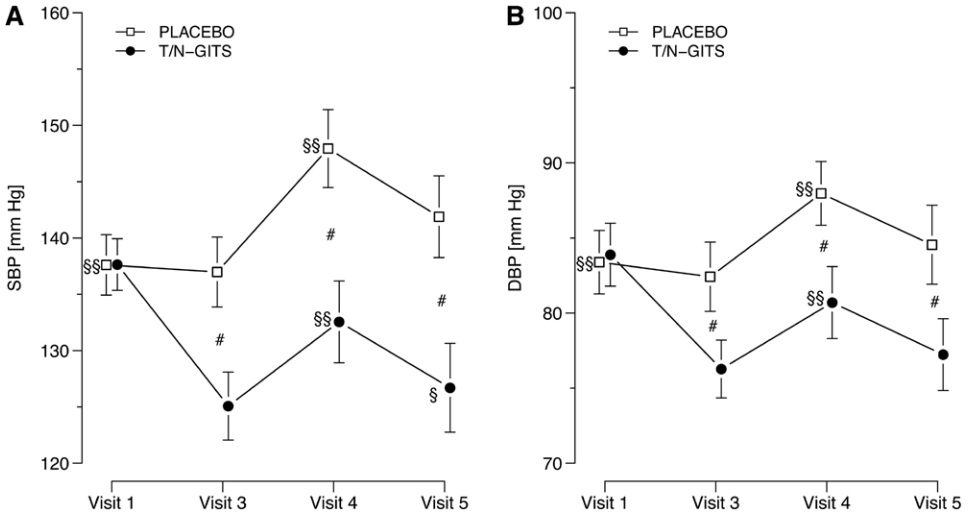

Figure 2. Mean 24-hour systolic blood pressure (SBP; primary outcome) and diastolic blood pressure (DBP) at 4 study visits in participants receiving active treatment (black circles) or placebo (open squares). Comparisons vs visit 3 (sea level, on treatment): §§P<0.001, §P<0.01. Comparisons active vs placebo: #P<0.001.

group, subsequently withdrawn from the study. The details on adverse events are shown in Table S2.

At high-altitude, there were no differences between groups in Lake Louise Score (median for both groups: first day: 1; second day: 2; and third day: 1), while SpO_2 was higher in the active treatment than in placebo group (Figure 3).

Discussion

Our study shows for the first time that in hypertensive patients living at sea level under acute exposure to high altitude (1) a marked increase occurs in conventional and ambulatory BP, accompanied by a reduction in nocturnal BP fall; (2) the combination of 2 antihypertensive drugs (a blocker of the renin–angiotensin system and a long-acting calcium antagonist) although not able to abolish the pressor response to high-altitude exposure, continues to exert a BP-lowering effect as it does at the sea level, with no tolerability and safety problems.

Except for very short exposures to hypoxia (where hypoxia-dependent vasodilation may prevail), studies in animals and healthy normotensive individuals have repeatedly documented that conventional BP undergoes a marked increase during acute exposures to altitudes of ≥3000 m.[23–27] In healthy normotensive subjects, an increase in ambulatory BP was also shown,[17,28,29] which becomes progressively more marked as the altitude increases, with a concomitant reduction, at high altitudes, of the nocturnal BP dipping.[17] The present study shows that similar changes occur in hypertensive subjects, regardless of the presence of antihypertensive treatment. In several subjects in our study, 24-hour SBP increased at high altitude by >25 mm Hg with average daytime values exceeding 160 mm Hg. Although in our subjects with low risk at baseline, this was not associated with immediate safety issues, in individuals at higher cardiovascular risk, the resulting marked increase in left ventricle afterload might be clinically relevant and could contribute to the increased risk of sudden death reported in skiers with pre-existing hypertension acutely exposed to high altitude.[30]

In the present study (in line with what observed in normotensive subjects[17]) under acute exposure to high altitude: (1) ambulatory BP increased more than conventional BP; this implies that studies relying on the traditional BP measurement method may underestimate the pressor effects of high altitude; (2) the BP increase was particularly marked during the night, presumably because at high altitude there is a further critical reduction in SpO_2 during sleep,[31] leading to further sympathetic activation that opposes the sleep-induced hypotension.

Our study was not designed to investigate the mechanisms of BP increase at high altitude in hypertensive subjects. However, we think that it is reasonable to extrapolate the information obtained in normotensive subjects and showing that (1) vasoconstriction causes by chemoreflex-mediated sympathetic activation seems the single most important mechanism involved; (2) other pressor mechanisms, which may play a role, include increased arterial stiffness, endothelin secretion, and blood viscosity; (3) renin–angiotensin–aldosterone system is not likely to be activated.[4,17] Apart from hypoxia, other factors associated with high-altitude environment may have contributed to the observed BP changes. Daytime ambient temperature was lower by about 6°C at high altitude than at sea level; however, based on the results of previous studies,[32,33] its contribution to BP increase in our study probably did not exceed 2 mm Hg. Psychological stress related to change of environment could have some relevance, too. Sleep quality and duration might affect nighttime BP but we observed no such relationship. Other potentially relevant factors could include the occurrence of sleep apneas, degree of physical activity, and previous exposures to high altitude.

Interestingly, we observed a marked reduction of nocturnal BP dipping at about 3300 m in hypertensive subjects, whereas in the normotensive participants of the HIGHCARE-HIMALAYA study, a clear-cut blunting of the nighttime BP fall was only observed at a higher altitude of 5400 m.[17] Such a discrepant behavior may have 2 possible explanations: (1) SpO_2 decrease at night is larger in hypertensive than in normotensive subjects or (2) hypertensive subjects have greater chemoreflex sensitivity.[34]

Another novel and clinically relevant contribution of our study is the information on the BP effects at high altitude

Table 2. BP and HR Variables Derived From Conventional Measurements and From 24-Hour Ambulatory BP Monitoring in Telmisartan/Nifedipine GITS (n=47) and Placebo Group (n=42)

Variable	Group	Baseline (V1)	Sea Level on Treatment (V3)	High Altitude (V4)	Return to Sea Level (V5)
SBP					
Conv., mm Hg	Placebo	141.4±12.1	137.9±14.5	145.8±13.7*	137.7±12.8
	Active	141.0±12.7†	123.3±14.1	125.8±11.8	123.6±15.5
	P value	>0.20	<0.001	<0.001	<0.001
24 h, mm Hg	Placebo	137.6±8.6	137.0±10.0	147.9±11.1†	141.9±11.6*
	Active	137.6±7.8†	125.1±10.1	132.6±12.4†	126.7±13.1
	P value	>0.20	<0.001	<0.001	<0.001
Day, mm Hg	Placebo	144.1±7.8	143.9±8.6	153.3±10.3†	148.2±10.9‡
	Active	143.6±7.5†	132.0±10.0	138.0±11.1†	133.3±13.6
	P value	>0.20	<0.001	<0.001	<0.001
Night, mm Hg	Placebo	122.7±13.4	121.7±14.5	135.7±15.9†	128.4±16.6*
	Active	123.5±11.4†	110.4±11.9	119.8±18.1†	111.3±14.6
	P value	>0.20	<0.001	<0.001	<0.001
Dip, %	Placebo	14.9±6.6	15.5±7.4	11.5±8.0‡	13.4±8.5
	Active	14.1±6.0	16.3±6.4	13.3±8.8.0	16.6±7.6
	P value	>0.20	>0.20	>0.20	>0.20
DBP					
Conv., mm Hg	Placebo	90.9±8.1	88.9±10.7	92.2±10.5	87.9±11.2
	Active	91.0±8.2†	80.6±10.4	83.5±9.2	79.1±9.7
	P value	>0.20	<0.001	<0.001	<0.001
24 h, mm Hg	Placebo	83.4±6.8	82.4±7.4	88.0±6.8†	84.6±8.4
	Active	83.9±7.1†	76.3±6.4	80.7±8.2†	77.2±7.9
	P value	>0.20	<0.001	<0.001	<0.001
Day, mm Hg	Placebo	87.6±6.8	86.9±7.0	91.3±6.9†	88.8±8.3
	Active	87.8±7.4†	80.4±6.5	83.7±7.9*	81.4±8.4
	P value	>0.20	<0.001	<0.001	<0.001
Night, mm Hg	Placebo	73.7±9.1	72.7±9.9	80.2±9.4†	75.2±10.3
	Active	74.6±8.6†	67.3±7.7	73.5±10.6†	67.5±8.3
	P value	>0.20	0.023	0.004	<0.001
Dip, %	Placebo	15.7±8.7	16.4±8.9	12.1±8.5‡	15.4±8.5
	Active	15.0±7.0	16.2±7.5	12.1±8.2‡	17.0±7.5
	P value	>0.20	>0.20	>0.20	>0.20
HR					
24 h, bpm	Placebo	75.6±8.6	78.1±7.8	86.5±8.5†	75.0±8.2‡
	Active	74.1±7.6	77.0±7.3	85.3±9.2†	76.8±8.2
	P value	>0.20	>0.20	>0.20	>0.20
Day, bpm	Placebo	80.0±8.8	82.8±7.7	89.9±8.4†	78.6±8.1*
	Active	78.2±7.9‡	81.7±7.5	88.8±9.2†	81.0±8.6
	P value	>0.20	>0.20	>0.20	>0.20
Night, bpm	Placebo	66.1±9.6	67.8±9.4	79.2±10.5†	66.9±9.5
	Active	64.3±8.1	67.1±8.2	76.9±10.3†	66.7±8.1
	P value	>0.20	>0.20	>0.20	>0.20
Dip, %	Placebo	17.4±7.4	18.2±7.7	12.0±7.4†	15.1±6.9
	Active	17.7±7.0	17.8±7.2	13.2±6.9*	17.2±7.2
	P value	>0.20	>0.20	>0.20	>0.20

Ambulatory BP data are separately shown for 24 hours, daytime, nighttime, as well as for nocturnal fall (dip, shown as percentage of daytime mean level). Data are shown as mean±SD. *P* values in the table refer to contrasts between groups for each condition. DBP indicates diastolic blood pressure; GITS, gastrointestinal therapeutic system; HR, heart rate; and SBP, systolic blood pressure.

Symbols of statistical significance refer to contrasts between visit 3 versus remaining study conditions: *$P<0.01$, †$P<0.001$, ‡$P<0.05$.

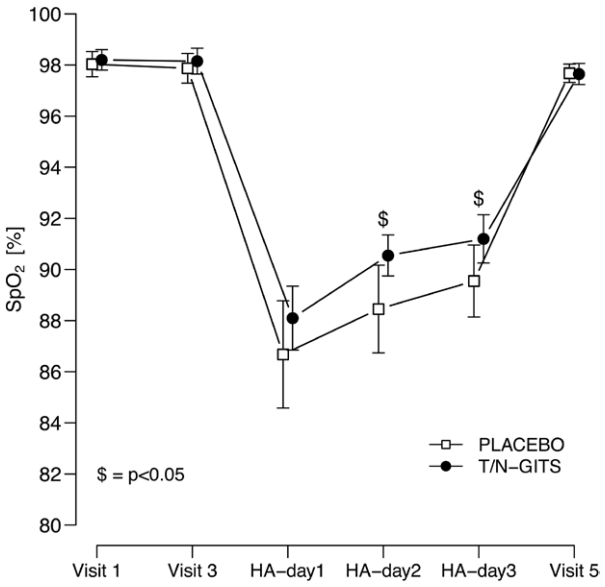

Figure 3. Oxygen saturation in spot measurements at sea level and on the first, second, and third day at high altitude in subjects on active treatment (black circles) or placebo (open squares). All measurements were performed in the morning except for the first day at high altitude (HA), when they were performed in the evening. Comparisons active treatment vs placebo: $*P*<0.05.

of a commonly used and guideline-supported combination treatment between an ARB and a slow release calcium antagonist.[16,17] Two previous studies reported that β-blockers have a limited effect in preventing the 24-hour BP increase that occurs at high altitude,[8,28] and their use (particularly of carvedilol) is associated with lower SpO_2, worse tolerability, and exercise capacity.[8,35] In the healthy participants of HIGHCARE-HIMALAYA, we observed that BP-lowering effect of telmisartan monotherapy was maintained ≤3400 m but not at higher altitudes (5400 m), with no tolerability issues.[17] In the hypertensive participants of the present study, the combined treatment with telmisartan and nifedipine was effective and safe at an altitude (3260 m) similar to the lower altitude reached in HIGHCARE-HIMALAYA, with BP values that remained lower than in placebo-treated subjects, as it occurred at sea level. Moreover, the active treatment group had higher SpO_2 at high altitude (possibly because of the dilatory effect of nifedipine on pulmonary vasculature leading to improved ventilation:perfusion ratio), even if no differences in acute mountain sickness were found between treatment groups.

Our study has several elements of strengths including: (1) adequate sample size, (2) controlled double-blind design, and (3) assessment of the BP effect of high altitude and treatment by ambulatory BP monitoring, an approach that is prognostically superior to conventional BP measurements[16] and that better reflects the high altitude–related BP alterations.[17] The study also has some inevitable limitations. First, for practical reasons, we could not assess whether the pressor effect of high altitude and the efficacy of antihypertensive treatment in this setting are maintained over longer time periods. Second, because of safety concerns, we could not verify the possibility of a loss or decrease of treatment efficacy at higher altitudes, an observation we previously made in normotensive patients under ARB administration.[17] However, our study reflects a common real-life situation (skiing, hiking, work-, or tourism-related trips) in which patients with hypertension are exposed to altitudes of 2500 to 3500 m for up to a few days. Third, our subjects were sampled from the local population, which means that the results cannot be easily generalized to other populations, whose different genetic background might determine different responses to hypoxia and BP-lowering drugs. However, our patients were of mixed ethnic origin and they lived permanently at sea level, with thus no high-altitude adaptation. Furthermore, native Andean populations show a lower degree of genetic adaptation to high-altitude environment when compared, for example, with Tibetans, ie, ethnic groups characterized by a longer history of altitude exposure.[36] Therefore, we think that the genetic background of our population had no relevant impact on the results. Finally, the accuracy of oscillometric devices at high altitude is largely unknown although our yet unpublished data indicate that it is not meaningfully affected.

Perspectives

Our findings support the recommendation that hypertensive subjects with low baseline cardiovascular risk may be safely exposed to moderately high altitude for short periods of time if properly treated. Combination of a calcium antagonist and an ARB seems safe and effective in this setting.

Major knowledge gaps still remain in this area and further studies are needed (1) to assess the safety of high-altitude exposure in controlled hypertensive subjects in higher risk categories; (2) to assess safety and efficacy of other classes of cardiovascular drugs at high altitude, also considering different altitudes and longer duration of exposure.

Sources of Funding

High Altitude Cardiovascular Research (HIGHCARE)–Andes project was supported by a grant from Bayer Healthcare, Germany. Ambulatory blood pressure monitoring devices were supplied by AND, Tokyo, Japan, and Intermed, Italy.

Disclosures

Dr Parati received speaker's fee or consultation fee from Bayer Healthcare, Daiichi Sankyo, Menarini, CVRx, Pfizer Inc, Servier. G. Bilo received speaker's fee from Bayer Healthcare. P. Agostoni is a consultant for Menarini Int. and Bayer Healthcare and received Speaker's fee from Novartis, Daiichi Sankyo, and Servier. G. Mancia received speaker's fee, consultation fee or research grants from Boehringer Ingelheim, CVRx, Daiichi Sankyo, Medtronic Vascular Inc, Menarini Int, Merck Serono, Novartis, Pfizer Inc, Recordati, Servier, Siron, and Takeda. The other authors report no conflicts.

References

1. Hainsworth R, Drinkhill MJ. Cardiovascular adjustments for life at high altitude. *Respir Physiol Neurobiol*. 2007;158:204–211. doi: 10.1016/j.resp.2007.05.006.
2. Mieske K, Flaherty G, O'Brien T. Journeys to high altitude–risks and recommendations for travelers with preexisting medical conditions. *J Travel Med*. 2010;17:48–62. doi: 10.1111/j.1708-8305.2009.00369.x.
3. Bärtsch P, Swenson ER. Clinical practice: acute high-altitude illnesses. *N Engl J Med*. 2013;368:2294–2302. doi: 10.1056/NEJMcp1214870.
4. Bärtsch P, Gibbs JS. Effect of altitude on the heart and the lungs. *Circulation*. 2007;116:2191–2202. doi: 10.1161/CIRCULATIONAHA.106.650796.
5. Duplain H, Vollenweider L, Delabays A, Nicod P, Bärtsch P, Scherrer U. Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. *Circulation*. 1999;99:1713–1718.

6. Hansen J, Sander M. Sympathetic neural overactivity in healthy humans after prolonged exposure to hypobaric hypoxia. *J Physiol*. 2003;546(Pt 3):921–929.
7. Higgins JP, Tuttle T, Higgins JA. Altitude and the heart: is going high safe for your cardiac patient? *Am Heart J*. 2010;159:25–32. doi: 10.1016/j.ahj.2009.10.028.
8. Bilo G, Caldara G, Styczkiewicz K, Revera M, Lombardi C, Giglio A, Zambon A, Corrao G, Faini A, Valentini M, Mancia G, Parati G. Effects of selective and nonselective beta-blockade on 24-h ambulatory blood pressure under hypobaric hypoxia at altitude. *J Hypertens*. 2011;29:380–387. doi: 10.1097/HJH.0b013e3283409014.
9. Moore LG. Altitude-aggravated illness: examples from pregnancy and prenatal life. *Ann Emerg Med*. 1987;16:965–973.
10. Savonitto S, Cardellino G, Doveri G, Pernpruner S, Bronzini R, Milloz N, Colombo MD, Sardina M, Nassi G, Marraccini P. Effects of acute exposure to altitude (3,460 m) on blood pressure response to dynamic and isometric exercise in men with systemic hypertension. *Am J Cardiol*. 1992;70:1493–1497.
11. Donegani E, Hillebrandt D, Windsor J, Gieseler U, Rodway G, Schöffl V, Küpper T. Pre-existing cardiovascular conditions and high altitude travel. Consensus statement of the Medical Commission of the Union Internationale des Associations d'Alpinisme (UIAA MedCom) Travel Medicine and Infectious Disease. *Travel Med Infect Dis*. 2014;12:237–252. doi: 10.1016/j.tmaid.2014.02.004.
12. Rimoldi SF, Sartori C, Seiler C, Delacrétaz E, Mattle HP, Scherrer U, Allemann Y. High-altitude exposure in patients with cardiovascular disease: risk assessment and practical recommendations. *Prog Cardiovasc Dis*. 2010;52:512–524. doi: 10.1016/j.pcad.2010.03.005.
13. Luks AM. Should travelers with hypertension adjust their medications when traveling to high altitude? *High Alt Med Biol*. 2009;10:11–15. doi: 10.1089/ham.2008.1076.
14. Agostoni P. Considerations on safety and treatment of patients with chronic heart failure at high altitude. *High Alt Med Biol*. 2013;14:96–100. doi: 10.1089/ham.2012.1117.
15. Mancia G, Fagard R, Narkiewicz K, et al.; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357. doi: 10.1097/01.hjh.0000431740.32696.cc.
16. Mancia G, Parati G, Bilo G, Choi J, Kilama MO, Ruilope LM; TALENT investigators. Blood pressure control by the nifedipine GITS-telmisartan combination in patients at high cardiovascular risk: the TALENT study. *J Hypertens*. 2011;29:600–609. doi: 10.1097/HJH.0b013e328342ef04.
17. Parati G, Bilo G, Faini A, Bilo B, Revera M, Giuliano A, Lombardi C, Caldara G, Gregorini F, Styczkiewicz K, Zambon A, Piperno A, Modesti PA, Agostoni P, Mancia G. Changes in 24 h ambulatory blood pressure and effects of angiotensin II receptor blockade during acute and prolonged high-altitude exposure: a randomized clinical trial. *Eur Heart J*. 2014;35:3113–3122. doi: 10.1093/eurheartj/ehu275.
18. Roach C, Bartsch P, Hackett PH, Oelz O. The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and Molecular Medicine: Proceedings of the 8th International Hypoxia Symposium*. Burlington, VT: Queen city Printers; 1993:272–274.
19. Verdecchia P, Angeli F, Poeta F, Reboldi GP, Borgioni C, Pittavini L, Porcellati C. Validation of the A&D UA-774 (UA-767Plus) device for self-measurement of blood pressure. *Blood Press Monit*. 2004;9:225–229.
20. Palatini P, Frigo G, Bertolo O, Roman E, Da Cortà R, Winnicki M. Validation of the A&D TM-2430 device for ambulatory blood pressure monitoring and evaluation of performance according to subjects' characteristics. *Blood Press Monit*. 1998;3:255–260.
21. Parati G, Omboni S, Palatini P, Rizzoni D, Bilo G, Valentini M, Rosei EA, Mancia G. Italian society of hypertension guidelines for conventional and automated blood pressure measurement in the office, at home and over 24 hours. *High Blood Press Cardiovasc Prev*. 2008;15:283–310. doi: 10.2165/0151642-200815040-00008.
22. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979;6:65–70.
23. Reeves JT, Mazzeo RS, Wolfel EE, Young AJ. Increased arterial pressure after acclimatization to 4300 m: possible role of norepinephrine. *Int J Sports Med*. 1992;13 Suppl 1:S18–S21. doi: 10.1055/s-2007-1024581.
24. Vogel JA, Harris CW. Cardiopulmonary responses of resting man during early exposure to high altitude. *J Appl Physiol*. 1967;22:1124–1128.
25. Bärtsch P, Shaw S, Franciolli M, Gnädinger MP, Weidmann P. Atrial natriuretic peptide in acute mountain sickness. *J Appl Physiol (1985)*. 1988;65:1929–1937.
26. Modesti PA, Vanni S, Morabito M, Modesti A, Marchetta M, Gamberi T, Sofi F, Savia G, Mancia G, Gensini GF, Parati G. Role of endothelin-1 in exposure to high altitude: Acute Mountain Sickness and Endothelin-1 (ACME-1) study. *Circulation*. 2006;114:1410–1416. doi: 10.1161/CIRCULATIONAHA.105.605527.
27. Kaufmann PA, Schirlo C, Pavlicek V, Berthold T, Burger C, von Schulthess GK, Koller EA, Buck A. Increased myocardial blood flow during acute exposure to simulated altitudes. *J Nucl Cardiol*. 2001;8:158–164. doi: 10.1067/mnc.2001.112537.
28. Wolfel EE, Selland MA, Mazzeo RS, Reeves JT. Systemic hypertension at 4,300 m is related to sympathoadrenal activity. *J Appl Physiol (1985)*. 1994;76:1643–1650.
29. Veglio M, Maule S, Cametti G, Cogo A, Lussiana L, Madrigale G, Pecchio O. The effects of exposure to moderate altitude on cardiovascular autonomic function in normal subjects. *Clin Auton Res*. 1999;9:123–127.
30. Burtscher M. Risk of cardiovascular events during mountain activities. *Adv Exp Med Biol*. 2007;618:1–11.
31. Caravita S, Faini A, Lombardi C, Valentini M, Gregorini F, Rossi J, Meriggi P, Di Rienzo M, Bilo G, Agostoni P, Parati G. Sex and acetazolamide effects on chemoreflex and periodic breathing during sleep at altitude. *Chest*. 2015;147:120–131. doi: 10.1378/chest.14-0317.
32. Barnett AG, Sans S, Salomaa V, Kuulasmaa K, Dobson AJ; WHO MONICA Project. The effect of temperature on systolic blood pressure. *Blood Press Monit*. 2007;12:195–203. doi: 10.1097/MBP.0b013e3280b083f4.
33. Halonen JI, Zanobetti A, Sparrow D, Vokonas PS, Schwartz J. Relationship between outdoor temperature and blood pressure. *Occup Environ Med*. 2011;68:296–301. doi: 10.1136/oem.2010.056507.
34. Somers VK, Mark AL, Abboud FM. Potentiation of sympathetic nerve responses to hypoxia in borderline hypertensive subjects. *Hypertension*. 1988;11(6 Pt 2):608–612.
35. Valentini M, Revera M, Bilo G, Caldara G, Savia G, Styczkiewicz K, Parati S, Gregorini F, Faini A, Branzi G, Malfatto G, Magrì D, Agostoni P, Parati G. Effects of beta-blockade on exercise performance at high altitude: a randomized, placebo-controlled trial comparing the efficacy of nebivolol versus carvedilol in healthy subjects. *Cardiovasc Ther*. 2012;30:240–248. doi: 10.1111/j.1755-5922.2011.00261.x.
36. Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. *Circulation*. 2007;115:1132–1146. doi: 10.1161/CIRCULATIONAHA.106.624544.

Novelty and Significance

What Is New?

- The direct demonstration of changes in 24-hour blood pressure in hypertensive subjects exposed to high altitude. The demonstration of antihypertensive treatment efficacy in this setting.

What Is Relevant?

- Demonstration that nifedipine gastrointestinal therapeutic system/telmisartan combination is safe and maintains its BP-lowering effect in hypertensive subjects acutely exposed to high altitude, even if it does not prevent an increase in blood pressure.

Summary

Hypertensive patients who plan brief permanence at high altitude may expect blood pressure to increase. If they receive treatment with dihydropyridine calcium antagonist and angiotensin receptor blocker, its efficacy should be maintained.