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Blood pressure response to six-minute walk test in hypertensive subjects exposed to high altitude: effects of antihypertensive combination treatment

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ABSTRACT

Background: Limited evidence exists on blood pressure (BP) responses to exercise in hypertensive subjects exposed to high altitude, and on the effects of antihypertensive treatment in this setting.
We aimed to asses BP response to submaximal exercise in hypertensive lowlanders acutely exposed to high altitude, and the effects of a calcium antagonist–angiotensin receptor blocker combination in this condition.
Methods: 89 mild-hypertensive participants in HIGHCARE-ANDES study performed a six-minute walk test in 3 conditions: at sea-level off-treatment; at sea-level after 6 weeks of double-blind treatment with telmisartan 80mg + slow release nifedipine 30 mg or with placebo; on the first full day of permanence at 3260 m altitude under randomized treatment.
Results: The distance walked in 6 min was reduced by about 10% at high altitude in both groups ($p < 0.001$) without treatment-related differences. Systolic BP increased at altitude in both groups, remaining lower on telmisartan/nifedipine than on placebo both before and after exercise ($p < 0.001$).The exercise-induced increase in systolic BP at altitude was blunted by active treatment as compared to placebo ($+32.0 \pm 19.8$ vs $+41.9 \pm 23.3$ mm Hg, $p < 0.05$). Diastolic BP was unchanged from sea-level to altitude in both groups, showing lower values on telmisartan/nifedipine than on placebo before and after exercise ($p < 0.01$). Oxygen saturation was similarly reduced in both groups before exercise at altitude, but after exercise it was higher on telmisartan/nifedipine than on placebo.
Conclusions: In mild hypertensives, acute exposure to high altitude enhances the BP response to exercise. Such an enhanced response is effectively reduced by telmisartan/nifedipine combination therapy, without affecting exercise performance.

1. Introduction

There is worldwide an increase of leisure or professional activities at high altitude [1]. As a result of this, a growing number of sea level residents, including subjects with pre-existing cardiovascular conditions such as arterial hypertension, are acutely exposed to high altitude without previous experience nor preparation, unaware of the potential risks carried by high altitude hypobaric hypoxia exposure [2–7].

Blood pressure (BP) has been shown to increase during acute exposure to high altitude, both in healthy subjects and in patients affected by arterial hypertension [6,8,9]. However, scarce information is available on the BP response to physical activity required by daily life, in particular when considering hypertensive lowlanders acutely exposed to altitude.

Six-minute walk test (6MWT) is a simple and inexpensive test, widely applied in several clinical settings to evaluate functional status and hemodynamic responses to submaximal exercise [10–14]. The few studies in which the 6MWT was applied at altitude have reported

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a good safety profile of the test [15,16], thus supporting its use as an easily applicable tool to assess physical capacity and hemodynamic responses in hypoxic conditions.

When considering antihypertensive treatment at altitude, we had previously demonstrated the efficacy of the combination of the angiotensin receptor blocker telmisartan with the calcium channel blocker nifedipine (commonly used to prevent pulmonary edema at altitude) in counteracting the BP rise over 24 h in hypertensive lowlanders acutely exposed to an altitude of 3260 m a.s.l. [9].

The aims of this study were to explore the BP response to submaximal exercise of mild hypertensive lowlanders acutely exposed to high altitude, and to assess the effects of telmisartan 80 mg with nifedipine Gastro-Intestinal Therapeutic System (GITS) 30 mg combination treatment on their exercise capacity and on their exercise-related BP response.

2. Methods

2.1. Participants

This study was performed within the frame of the HIGH altitude CArdiovascular REsearch ANDES (HIGHCARE-ANDES) Lowlanders study. Complete information on study methods was previously published [9] and protocol information can be found in the clinicaltrials.gov database under the identifier NCT01830530.

In brief, we enrolled 100 individuals with grade I essential hypertension and no significant comorbidities who were either untreated or had previously stopped antihypertensive therapy for four weeks. The study protocol was approved by the Ethics Committee of Istituto Auxologico Italiano (Milan, Italy) and Universidad Peruana Cayetano Heredia (Lima, Peru), and conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent to participate. The participants were randomized to receive double-blind treatment with either a fixed-dose combination of Telmisartan 80 mg/nifedipine-GITS 30 mg or with placebo, and underwent repeated testing at sea level in Lima (Peru), and at high altitude (3260 m a.s.l., Huancayo, Peru).

The 6MWT was performed in three occasions:

1. At sea-level (Lima, Peru) off-treatment;
2. Again at sea level after 6 weeks of double-blind treatment with telmisartan/nifedipine-GITS or placebo;
3. On the 1st full day of permanence at 3260 m altitude (Huancayo, Peru), under the same randomized treatment.

2.2. Six-minute walk test

The 6MWT was performed according to the American Thoracic Society protocol [10]. The test was conducted by trained personnel in an indoor corridor of 30 m length. Heart rate (HR), blood oxygen saturation (SpO_2), systolic and diastolic BP (SBP and DBP) were repeatedly measured in the sitting position after 10 min rest before starting the test, immediately after completing the 6MWT, and after 3 and 5 min of recovery. The quantitative assessment of dyspnea and fatigue through the Borg scale was concomitantly performed. SpO_2 and HR were measured on a subject's index finger with a pulse oxymeter (Tuffsat, GE Healthcare, USA). BP was measured with a validated oscillometric device (AND UA-767Plus, AND, Japan). The total distance walked over 6 min (6MWD) was recorded at the end of the test.

2.3. Statistical analysis

Descriptive data are reported as mean ± standard deviations for continuous variable. The Linear Mixed-Effects Models with contrasts a posteriori and a compound symmetry covariance structure was used, fitting the models by maximizing the restricted log-likelihood. For the SpO_2 and Borg scale a Friedman rank sum test was used with pairwise Wilcoxon rank sum test as post-hoc. For multiple comparisons, the algorithm which controls the expected rate of false-positive results for all positive results (false discovery rate) was used [17]. An α level of 0.05 was used for all hypothesis tests. All data analyses were performed using R Core Team (2015), Vienna, Austria.

3. Results

3.1. General characteristics

Data from 89 subjects who completed the study were included in the final analysis (age 52.2 ± 9.7; 39F/50M; BMI 28.3 ± 3.5 kg/m^2; n = 47 on telmisartan/nifedipine-GITS, n = 42 on placebo). There were no significant differences between groups at baseline, except for a higher weight ($p = 0.021$) in placebo group (Table 1).

3.2. Assessment at rest: heart rate, blood pressure, oxygen saturation

Table 2 shows resting SBP/DBP and HR values in the different study conditions at rest. There were no significant differences between groups at sea level before treatment. On treatment, subjects on telmisartan/nifedipine-GITS had lower SBP/DBP values than the placebo group both at sea level and at high altitude (Table 2). A marked SBP increase at rest was observed at altitude in the placebo group ($p < 0.001$), but not in telmisartan/nifedipine-GITS group, while no significant changes were observed for DBP.

HR before exercise was not different between telmisartan/nifedipine-GITS and placebo at sea level both off-treatment (72.4 ± 9.9 vs 72.6 ± 9.1 bpm) and on-treatment (72.3 ± 10.1 vs 73.0 ± 8.8 bpm). Shifting from sea level to high altitude, resting HR increased significantly ($p < 0.001$) without treatment-related differences (83.7 ± 11.4 bpm on telmisartan/nifedipine-GITS vs 80.1 ± 8.7 bpm on placebo).

At altitude, SpO_2 was significantly reduced (from 97.9 ± 1.3 to 89.6 ± 4.1%; $p < 0.001$) without treatment-related differences.

3.3. Six-minute walk test distance

All the subjects completed the 6MWT in the absence of adverse events. 6MWD was similar in both groups at sea level off treatment. We found a small but significant increase by about 3% in 6MWD at sea level on treatment as compared to sea level off treatment in both groups, probably because of a learning effect, without treatment-related differences. Mean walked distances at sea level on treatment were 596.3 ± 57.2 m (range 497–750 m) in telmisartan/nifedipine-GITS, and 594.1 ± 64.3 m (range 434–720 m) in the placebo group. A significant reduction of about 10% in 6MWD was observed in both groups on going from sea level to high altitude ($p < 0.001$), without treatment-related differences (Fig. 1).

3.4. Blood pressure response to exercise

SBP at the end of the exercise was lower ($p < 0.05$) on telmisartan/nifedipine-GITS than on placebo at sea level on treatment, and this difference was maintained after 3 and 5 min of recovery.

Table 1
Demographic characteristics of study participants. T/N-GITS = telmisartan 80 mg + nifedipine gastro-intestinal therapeutic system 30 mg; BMI, body mass index.

	All	T-N/GITS	Placebo
N (males, %)	89 (50, 56.2%)	47 (27, 57.4%)	42 (23, 54.8%)
Age [y/o]	52.2 ± 9.5	52.8 ± 8.6	51.4 ± 10.4
Weight [Kg]	76.1 ± 13.7	73.5 ± 13.9	79.2 ± 13.0
Height [cm]	163.5 ± 8.4	162.4 ± 8.8	164.8 ± 8.0
BMI [Kg/m^2]	28.3 ± 3.6	27.7 ± 3.6	29.0 ± 3.5