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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

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Aim

Many hypertensive subjects travel to high altitudes, but little is known on ambulatory blood pressure (ABP) changes and antihypertensive drugs' efficacy under acute and prolonged exposure to hypobaric hypoxia. In particular, the efficacy of angiotensin receptor blockers in this condition is unknown. This may be clinically relevant considering that renin–angiotensin system activity changes at altitude. The HIGHCARE-HIMALAYA study assessed changes in 24 h ABP under acute and prolonged exposure to increasing altitude and blood pressure-lowering efficacy and safety of an angiotensin receptor blockade in this setting.

Methods and results

Forty-seven healthy, normotensive lowlanders were randomized to telmisartan 80 mg or placebo in a double-blind, parallel group trial. Conventional and Ambulatory BPs were measured at baseline and on treatment: after 8 weeks at sea level, and under acute exposure to 3400 and 5400 m altitude, the latter upon arrival and after 12 days (Mt. Everest base camp). Blood samples were collected for plasma catecholamines, renin, angiotensin, and aldosterone. In both groups, exposure to increasing altitude was associated with: (i) significant progressive increases in conventional and 24 h blood pressure, persisting throughout the exposure to 5400 m; (ii) increased plasma noradrenaline and suppressed renin–angiotensin–aldosterone system. Telmisartan lowered 24 h ABP at the sea level and at 3400 m (between-group difference 4.0 mmHg, 95% CI: 2.2–9.5 mmHg), but not at 5400 m.

Conclusion

Ambulatory blood pressure increases progressively with increasing altitude, remaining elevated after 3 weeks. An angiotensin receptor blockade maintains blood pressure-lowering efficacy at 3400 m but not at 5400 m.

Keywords

Blood pressure • High altitude • Angiotensin receptor blockers • Hypoxia • Ambulatory blood pressure monitoring

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Introduction

In spite of the large number of high-altitude studies,^{1–4} data on altitude-related changes in arterial blood pressure (BP) are limited and somewhat contradictory.^{2,3} Most available studies indicate that when measured with the conventional technique BP increases in response to acute high-altitude exposure.^{1–3,5–12} However, only scanty information is available on altitude-induced changes in ambulatory blood pressure (ABP),^{9–12} which provides a more sensitive estimate of the pressor effect of environmental factors and treatment. Furthermore, the effects of different altitudes on day–night BP profiles have never been systematically explored. Finally, little is known on the safety of antihypertensive drugs and on their effect on conventional BP or ABP in subjects exposed to progressively severe hypobaric hypoxia.^{9,11,13}

Because a large number of individuals, many of whom are affected by hypertension,¹⁴ are temporarily exposed to high altitude, we thought it was of interest to determine (i) the changes in conventional BP and ABP when moving from the sea level to progressively greater altitudes and (ii) whether the efficacy of antihypertensive treatment in lowering conventional BP and ABP is maintained in these conditions. The latter was done by administering an angiotensin receptor blocker because this class of BP-lowering drugs is largely used in the hypertensive population and because the activity of the renin–angiotensin system is modified at high altitude.¹⁵ These issues were investigated in the frame of the HIGH altitude Cardiovascular REsearch (HIGHCARE)-HIMALAYA study in the Mt. Everest area.

Methods

HIGHCARE-HIMALAYA was a parallel group, randomized, double-blind, trial comparing the 24 h BP effects of telmisartan 80 mg daily, and placebo at different altitudes.

Participants

The study included volunteers aged <65 years, and in good health conditions. Fifty eligible subjects were identified, of whom three withdrew their consent before the study start. Thus, 47 volunteers (32 males and 15 females) were included. Exclusion criteria were a history of cardiovascular disease or of arterial hypertension, a BP $\geq 140/90$ mmHg at repeated measurements, any chronic cardiovascular therapy, living at an altitude >500 m or repeated exposure to altitudes >3000 m above sea level in the preceding 8 months, a history of severe mountain sickness or angioedema, pregnancy, or lack of use of effective contraceptive methods in women in the fertile age range. All subjects underwent a comprehensive medical examination before the expedition, and gave written informed consent to participate. The protocol was approved by the Ethics Committee of Istituto Auxologico Italiano and the study was conducted in agreement with Declaration of Helsinki principles. The study was registered prior to the study start in EU Clinical Trials Register (www.clinicaltrialsregister.eu) with EudraCT number 2008-000540-14.

Study procedures

Subjects enrolled in the study were stratified by age and sex and randomized in blocks of four to receive either telmisartan 80 mg or placebo once daily in the morning in the 1:1 ratio. The study drugs were distributed as identical capsules containing telmisartan 40 mg or placebo. Randomization and distribution of drug containers were done by two

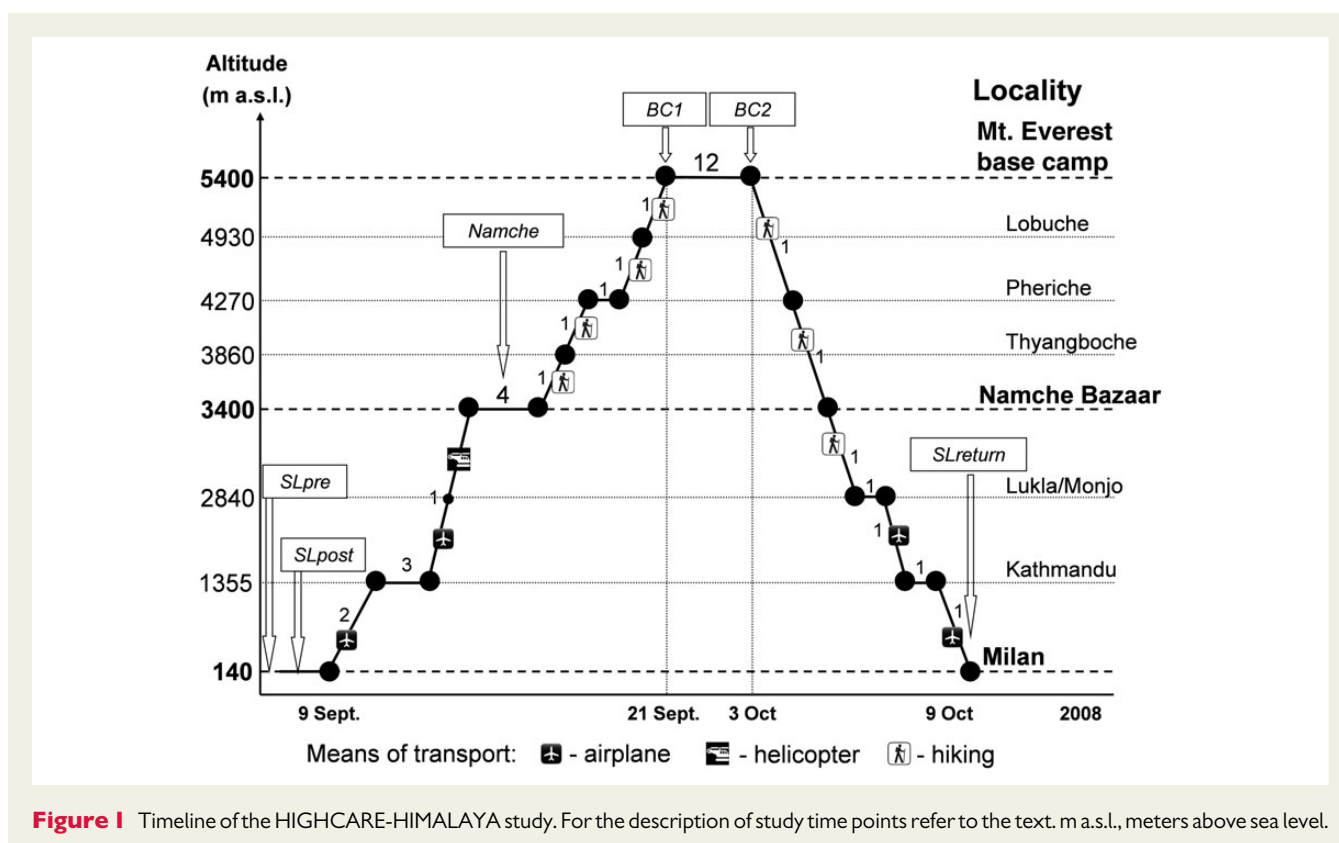
persons not otherwise involved in the study and the randomization list has not been disclosed to any of the participants or research team members throughout the study. Subjects started treatment with one morning capsule of telmisartan 40 mg or placebo, moving to two morning capsules or the corresponding placebo after 2 weeks in the absence of adverse effects or marked abnormalities in serum potassium, plasma creatinine, or sitting BP. After 8 weeks of treatment, participants travelled by air from Milan, Italy (altitude 120 m) to Kathmandu, Nepal (1355 m) where they stayed for 3 days. They were then brought by air to Namche Bazaar (3400 m), where they stayed for another 3 days. From there they hiked over 5 days to the Mt. Everest south base camp (5400 m) where they remained for 12 days before returning to Milan in a 6 day-time. During the sojourn at 3400 and at 5400 m, subjects were not allowed to perform any further ascent or strenuous physical activity. Data collection at the Mt. Everest base camp was performed in tents under conditions of comfortable temperature, while at Namche Bazaar it was performed in a heated lodge. Participants were asked to take the study drugs until completion of all measurements (see below) after return to the sea level. No other drug was allowed during the expedition, including pharmacological prevention of acute mountain sickness (AMS). When necessary, however, subjects received medical treatment for this condition, never lasting >3 days.

Measurements

Conventional BP (two measurements taken 1–2 min apart) and heart rate (HR) were obtained by a validated oscillometric device (Microlife A100plus, Microlife, Windau, Switzerland) in the morning hours with the subject resting in the sitting position for 5 min. 24 h ABP monitoring was performed by validated oscillometric devices (Spacelabs 90207 and 90217, Spacelabs Healthcare, Issaquah, WA, USA), the device cuff being applied to the non-dominant arm in the morning and removed after 24 h. Subjects were instructed to remain still during each measurement and to attend the scheduled daily activities while avoiding major physical efforts during the recording. Measurements were programmed every 15 min during day-time (7–23 h) and every 20 min at night (23–7 h). Mean values were computed for systolic (S) BP, diastolic (D) BP, and HR over the 24 h, day- and night-time as defined by subject's diary. Nocturnal BP fall was calculated as per cent reduction of night BP vs. the day-time value. Only recordings with at least 70% of the expected readings rated as valid by pre-defined criteria¹⁶ were considered. Transcutaneous oxygen saturation (SpO₂) was measured with pulse oximeter (Life Scope, Nihon Kohden, Tokyo, Japan). Plasma noradrenaline and adrenaline (high-performance liquid chromatography), renin (LIAISON Direct Renin CLIA, DiaSorin, Italy), serum angiotensin (RIA, Buhmann Laboratories, Switzerland), aldosterone (RIA, DiaSorin, Italy), and haematocrit were assessed in a morning blood sample taken after 15 min in a seated position. All measurements were performed at sea level before treatment (*SLpre*), at sea level after 8 weeks on-treatment (*SLpost*); during acute (Day 1–3) exposure to the altitude of 3400 m (*Namche*); during acute (Day 1–3, *BC1*) and prolonged (Day 9–12, *BC2*) exposure to the altitude of 5400 m and immediately after return to sea level (*SLreturn*) (Figure 1). Measurements included also the assessment of acute mountain sickness symptoms by the Lake Louise Score¹⁷ and of self-reported quality of sleep during the stay at high altitude.

Study variables

The primary variable of interest was 24 h average SBP. Secondary variables were 24 h DBP and HR; day- and night-time SBP, DBP, and HR; nocturnal SBP, DBP, and HR falls and conventional SBP, DBP, and HR values. Other variables were subjects' demographic and clinical characteristics, i.e. age, gender, body mass index (BMI), haematocrit, SpO₂, plasma



noradrenaline and adrenaline, plasma renin, serum angiotensin II, and aldosterone, self-reported sleep quality. The Lake Louise Score and the occurrence of adverse events were considered as safety variables.

Sample size

Assuming a standard deviation (SD) of 9 mmHg, we estimated that 20 subjects in each of the two treatment groups were needed to detect a 6 mmHg difference in 24 h average SBP between the sea level and the high-altitude condition, with a power of 80% and an alpha of 0.05 in a two-sided *t*-test.

Statistical analysis

All analyses were performed using R software Version 2.15.3 (R Foundation for Statistical Computing). Continuous variables are reported as means \pm SD or (in adjusted models) as least square means \pm standard error. To assess the effect of the altitude level and the treatment group, we used the linear mixed-effects models package (nlme, linear, and non-linear mixed-effects models) accounting for repeated measurements, with a compound symmetry covariance structure fitting the models by maximizing the restricted log-likelihood. Baseline (*SLpre*) values were included as a 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 algorithm which controls the expected rate of false-positive results for all positive results (false discovery rate; FDR).¹⁸ An α level of 0.05 was used for all hypothesis tests.

Results

Two of the 47 participants (both in the telmisartan group) were excluded from analysis because of non-adherence with the study

procedures. Two additional subjects randomized to active treatment stopped drug intake early in the study, but because they completed all study procedures, they were considered as belonging to the placebo group for data analysis (Figure 2). Their exclusion in a safety analysis did not change the principal findings of the study. The placebo ($n = 25$) and telmisartan ($n = 20$) groups did not differ for age, gender distribution (18 males/7 females vs. 13 males/7 females), BMI, or baseline BP values (Figure 3 and Table 1). The study took place in the second half of year 2008.

Effects of high altitude on conventional and ambulatory blood pressure

In the placebo group, exposure to 3400 and 5400 m above sea level was associated with a progressive increase in either conventional and ambulatory SBP and DBP, which persisted after prolonged sojourn at the higher altitude, falling to the initially lower values when subjects returned to the sea level (Figure 3; Supplementary material online, Table S1). The ABP increase was greater than the conventional BP increase and, at the highest altitude reached, particularly marked during the night-time (Figures 3 and 4) with thus a reduction in nocturnal dipping (Figure 5). Exposure to the two high-altitude levels was associated with a progressive and persistent increase in either conventional or ambulatory HR, as well (Figure 6). The Lake Louise Score was ≥ 3 (considered as indicative of AMS) in 9 subjects at Namche, in 22 subjects at CB1, and in 3 subjects at CB2. There were no differences in terms of pressor response to altitude (defined as increase in 24 h, day-time or night-time BP compared with *SLpost*) or in terms of nocturnal BP fall size

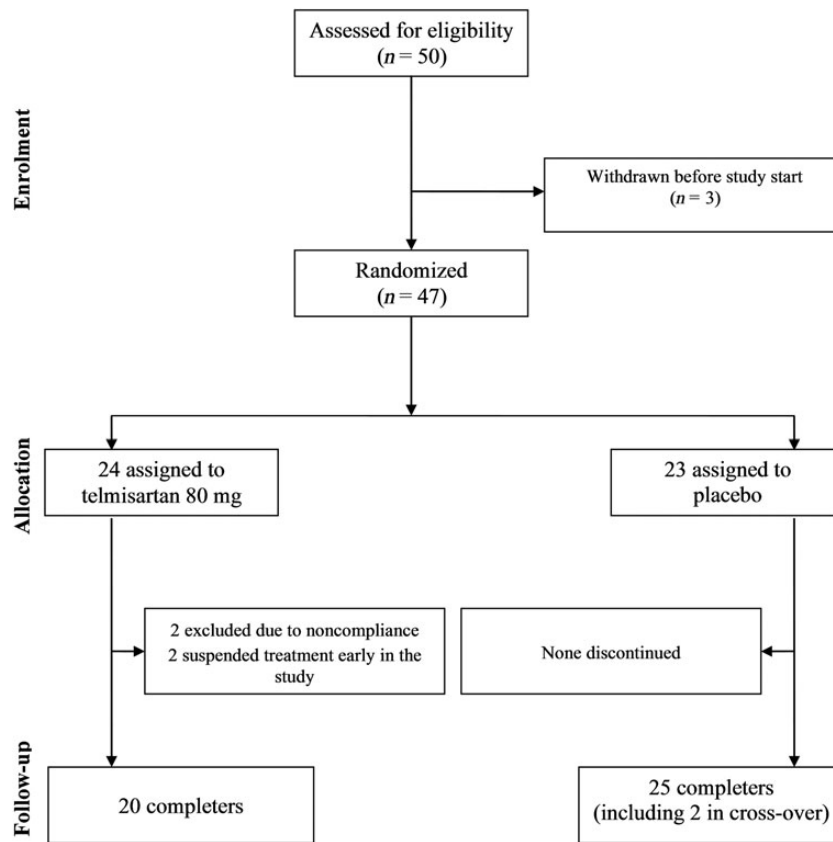


Figure 2 Flow of subjects in the study.

between subjects with or without AMS. In a sensitivity analysis, BP increase at altitude of 5400 m was particularly pronounced in subjects aged over 50 years (increase in 24 h SBP at BC1 24.6 vs. 15.2 mmHg in younger subjects; at BC2 22.9 vs. 12.1 mmHg, respectively, $P < 0.01$ for both), but the overall statistical model of BP in the study did not change substantially after including age as covariate.

Effects of angiotensin receptor blockade on the blood pressure effects of high altitude

Telmisartan did not have a significant lowering effect on conventional BP while it caused a significant ABP reduction at sea level and at the altitude of 3400 m (between-group difference in 24 h systolic BP 4.0 mmHg, 95% CI: 2.2–9.5 mmHg), without preventing the pressor response to high altitude (Figure 3; Supplementary material online, Table S1). At 5400 m, however, the BP-lowering effect of the drug was no longer evident upon arrival (-1.1 mmHg, 95% CI: -3.2 to 1.1 mmHg) and after 12 days of permanence at this altitude (1.9 mmHg, 95% CI: -0.5 to 4.4 mmHg) with only some recovery of treatment effect on night-time DBP and after returning to sea level (Figures 3 and 4). Telmisartan had no significant effect on HR both at sea level and at high altitudes (Figure 6).

Other findings

As shown in Figure 7, in the placebo group noradrenaline showed a marked progressive increase with exposure to the 3400 and 5400 m altitude, with a tendency to return to baseline values upon return to sea level. No changes in adrenaline levels were observed. In contrast, renin, angiotensin II, and aldosterone were reduced at high altitude and the changes were significant ($P < 0.05$ for all) at 5400 m. Altitude exposure was also associated with a progressive increase in haematocrit ($41.1 \pm 3.9\%$ at *SLpost*, $43.9 \pm 4.9\%$ at *Namche*, $50.1 \pm 5.5\%$ at *BC1*, $53.5 \pm 5.6\%$ at *BC2*, and 43.8 ± 4.68 at *SLreturn* again with no differences between untreated and treated subjects. Reduced nocturnal BP dipping appeared to be present only in subjects with reduced quality of sleep but not in those who reported optimal quality although the interaction was only significant for SBP at BC2 (Supplementary material online, Figure S1).

Few adverse events were reported during the study. In the telmisartan group, one subject reported facial oedema after a few days of treatment, leading to drug suspension. Another subject had symptomatic hypotension at the base camp, which disappeared after halving the drug dose.

There were no between-group differences at high altitude in either SpO_2 (90.6 ± 2.6 vs. $91.0 \pm 2.8\%$ at *Namche*, 77.7 ± 5.5 vs. $77.5 \pm 5.9\%$ at *BC1*, 85.9 ± 3.3 vs. $85.7 \pm 4.3\%$ at *BC2*, respectively) and in the Lake Louise Score.

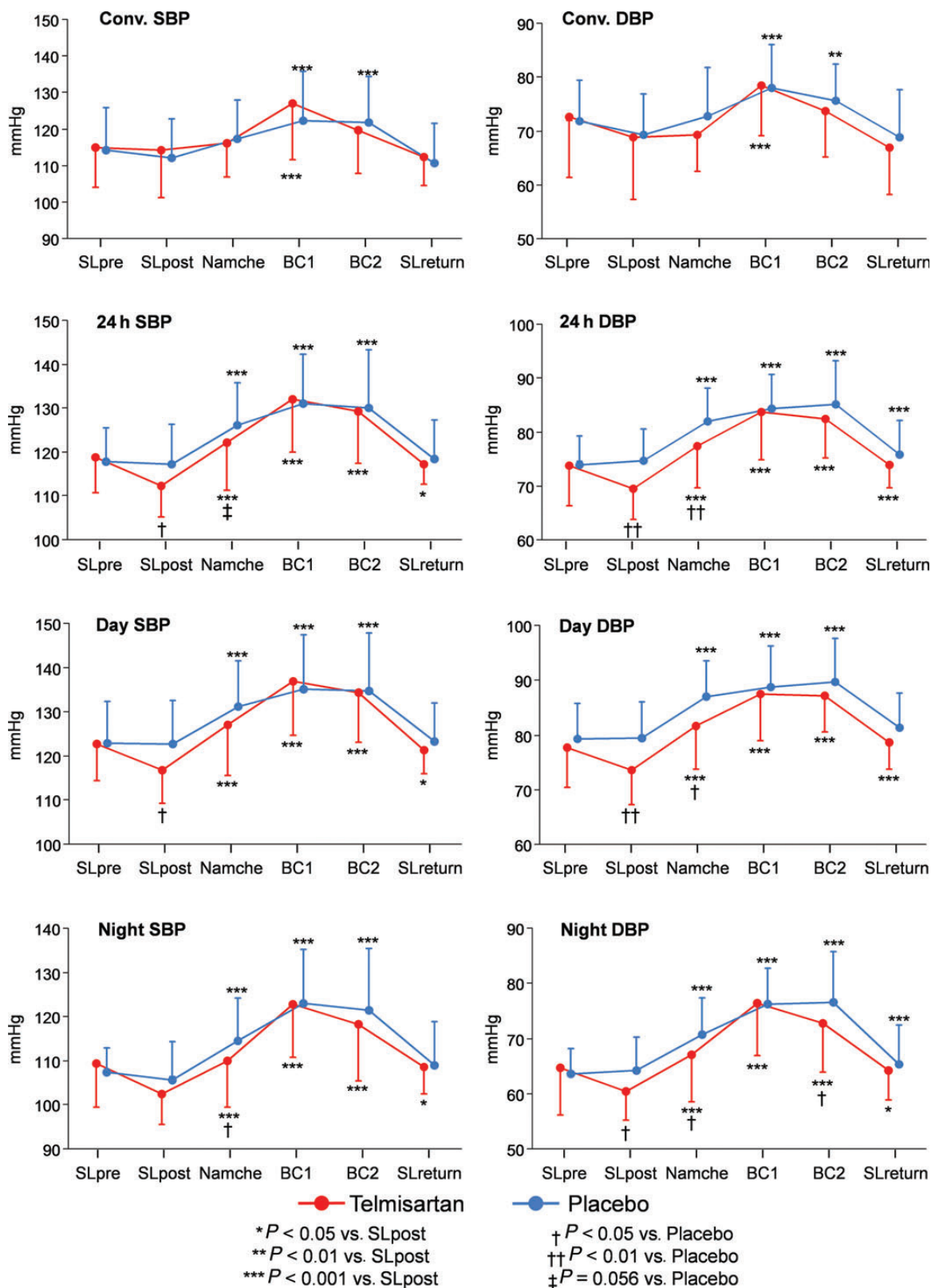


Figure 3 Conventional, 24 h, day-time and night-time systolic blood pressure and diastolic blood pressure for the different study conditions in placebo (blue lines) and telmisartan (red lines) treated subjects. Data are separately shown at sea level pre-treatment (SLpre), at sea level post-treatment (SLpost), at 3400 m (Namche), at the Mt. Everest base camp, 5400 m, during first 3 days (BC1) and after 11–12 days (BC2), and immediately after return to sea level (SLreturn). Different symbols indicate the level of statistical significance between-groups and among different altitudes. Conv, conventional BP values.

Table 1 Baseline characteristics of study participants

	Telmisartan, n = 20	Placebo, n = 25	All, n = 45
Age (years)	40.3 ± 10.8	39.3 ± 9.8	39.7 ± 10.1
Sex (M/F)	13/7	18/7	31/14
BMI (kg/m ²)	23.4 ± 2.8	22.2 ± 2.9	22.7 ± 2.9
SBP			
24 h (mmHg)	118.7 ± 8.1	117.7 ± 7.8	118.2 ± 7.9
Day-time (mmHg)	122.8 ± 8.3	122.2 ± 8.7	122.5 ± 8.5
Night-time (mmHg)	109.4 ± 10.0	107.2 ± 5.6	108.2 ± 7.9
Nocturnal dip (%)	10.9 ± 5.9	12.1 ± 3.9	11.6 ± 4.9
DBP			
24 h (mmHg)	73.8 ± 7.4	73.9 ± 5.4	73.9 ± 6.3
Day-time (mmHg)	77.7 ± 7.4	78.7 ± 5.8	78.3 ± 6.5
Night-time (mmHg)	64.7 ± 8.5	63.4 ± 4.6	64.0 ± 6.6
Nocturnal dip (%)	16.9 ± 6.4	19.2 ± 5.4	18.1 ± 5.9
HR			
24 h (mmHg)	63.7 ± 9.2	67.7 ± 8.3	65.9 ± 8.8
Day-time (mmHg)	67.1 ± 9.2	71.4 ± 9.6	69.4 ± 9.6
Night-time (mmHg)	56.1 ± 9.9	59.2 ± 7.3	57.7 ± 8.6

Discussion

Our paper provides several new observations on the effects of high altitude on ABP in subjects without and with antihypertensive drug treatment. These observations will be discussed separately.

Effects of high altitude on ambulatory blood pressure

In our subjects, exposure to progressively higher altitude was associated with a progressive, marked increase of systolic and diastolic ABP. The increase (i) occurred immediately after the high altitude was reached; (ii) persisted during prolonged altitude exposure; (iii) involved the day-time ABP values but was particularly pronounced for the night-time ones, with a consequent reduction of the nocturnal dipping phenomenon at the higher altitude; and (iv) disappeared after return to sea level. Following the somewhat inconsistent results of the few studies that have addressed this issue in the past,^{9–12} this provides solid evidence that high altitude has an acute and persistent, albeit reversible, pressor effect on daily life BP, with a similarly acute, persistent, and reversible alteration of its circadian pattern.

High altitude and antihypertensive drug treatment

Only two previous studies have addressed the effect of antihypertensive drugs on the 24 h ABP values at high altitude, both of them showing a limited ability of beta-adrenergic receptor blockers to prevent the BP increase that occurs in this circumstance.^{9,11} In our subjects, the BP-lowering effect of telmisartan observed at the sea level was preserved at an altitude of 3400 m but disappeared when the altitude of 5400 m was reached. At variance from what observed with beta-blockers, the administration of which was accompanied by a lower SpO₂ and worse exercise capacity and tolerability,^{11,13}

administration of telmisartan at high altitude was well tolerated with no negative impact on SpO₂ or AMS severity. This provides the first demonstration that the efficacy of one of the most common treatments of hypertension, i.e. that based on a blockade of angiotensin II receptors, is preserved during acute exposure to moderate altitudes, but is impaired when subjects move to very high altitudes. At a practical level this implies that, in subjects already under angiotensin II receptor blockade, treatment efficacy will likely be maintained up to 3400 m, that is at altitudes that can be reached by trekkers, climbers, skiers, or workers, although we cannot be certain that this extends to some hypertensive subjects at older age in whom renin–angiotensin system activity is different already at sea level. In contrast, patients should be warned that the antihypertensive effect of an angiotensin II receptor blockade will likely be lost at very high altitudes, at which they will probably move from a controlled to an uncontrolled BP state.

Mechanisms

Previous studies have shown that exposure to high altitudes is accompanied by sympathetic activation^{19–21} due to stimulation of chemoreceptors by hypoxia.² This is likely to be the primary reason for the pressor response to high altitude seen in our subjects because plasma noradrenaline (but not adrenaline) levels showed a progressive increase at progressively higher altitude in parallel with both the ABP increase and the SpO₂ reduction in line with previous reports.⁹ On the other hand, our results do not support the hypothesis that BP increase was due to stress related to AMS, as no relationship was found between BP changes and AMS occurrence. The pressor effect of high altitude may not just have a single responsible mechanism, however, and factors such as blood viscosity and endothelin-1 levels (both of which have been shown to increase at high altitude)^{22,23} are also likely to be involved. Our data provide indirect

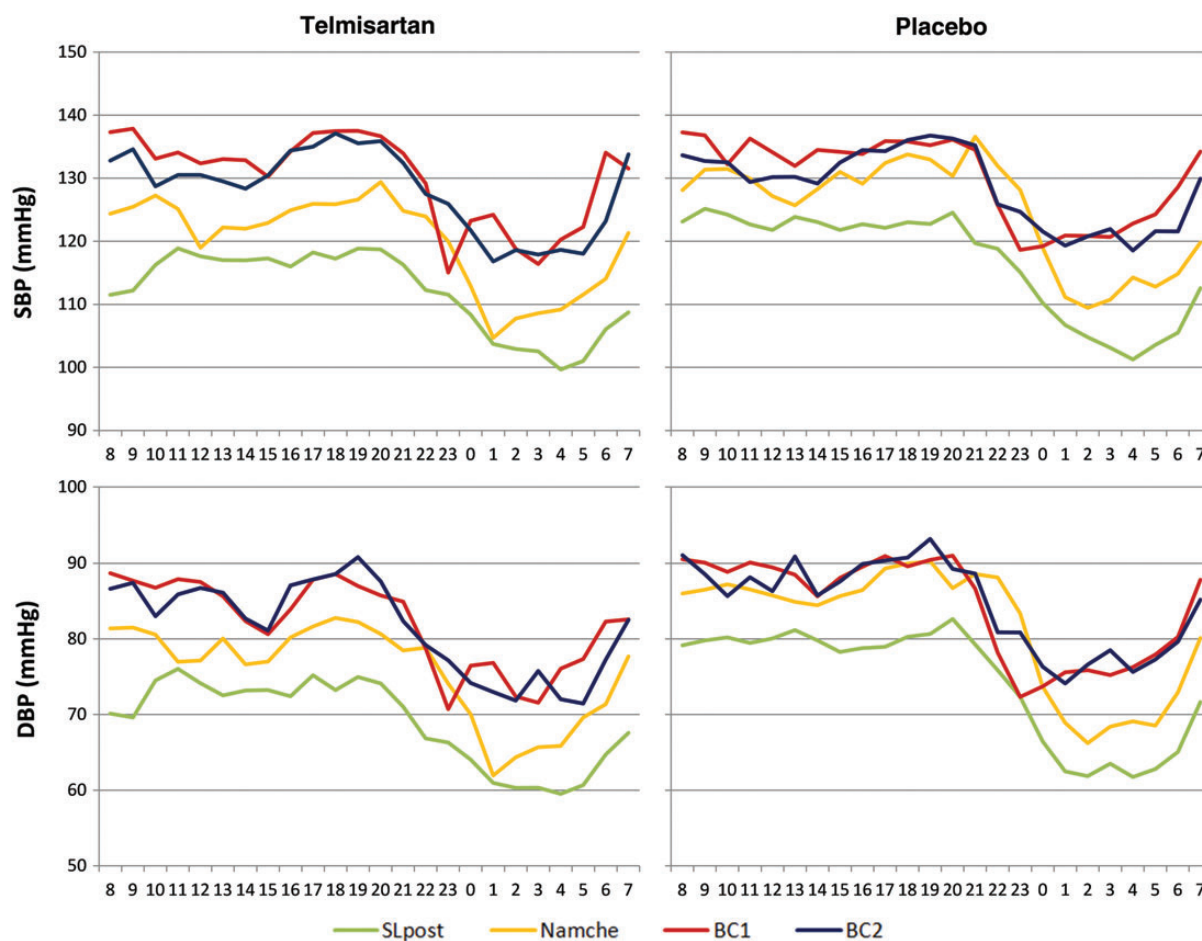


Figure 4 Averaged 24 h systolic and diastolic blood pressure profiles in both treatment groups. Data are shown separately at sea level post-treatment (SLpost, green lines), at 3400 m (Namche, yellow lines), at the Mt. Everest base camp, 5400 m, during the first 3 days (BC1, red lines) and after 11–12 days (BC2, blue lines). Altitude exposure was associated with a progressive upwards shift in 24 h BP profiles, more evident for nocturnal blood pressure.

support to a contribution of blood viscosity because at high-altitude subjects exhibited an increase in haematocrit. More importantly, they provide clear evidence that no contribution to the pressor effect could have come from the renin–angiotensin–aldosterone system, the activity of which was suppressed at very high altitude (5400 m), in line with the results of previous studies.^{24–26} This suppression presumably explains the concomitant reduction of the antihypertensive effect of telmisartan, as supported by a tendency of telmisartan to partially recover its efficacy after almost 2 weeks of permanence at 5400 m (BC2), in parallel with a partial recovery of the RAAS activity. Indeed, at BC2 the activity of the renin–angiotensin–aldosterone system tended to increase again, probably due to adaptation to hypoxia and to progressive reduction of volaemia, typical of prolonged high-altitude permanence. It seems reasonable to speculate that not only angiotensin receptor antagonists, but also all renin–angiotensin–aldosterone system antagonists (ACE inhibitors, anti-aldosterone drugs, and renin inhibitors) are less or not at all effective at very high altitudes.

The reasons behind the observed reduction in nocturnal dipping at altitude of 5400 m are less clear. While our data do not fully explain

this phenomenon, we may still propose several plausible mechanisms. One, at least during prolonged exposure to high altitude, poor sleep quality seemed to play an important role. Two, while we found no direct relationship with sleep breathing disorders, it is possible that nocturnal SpO₂ reduction contributed to the disproportionate increase in nocturnal BP values. In fact SpO₂ was lower during the night than the day, presumably leading to a greater nighttime hypoxic chemoreceptor stimulation.²⁷ Three, baroreflex function may also be altered at high altitude as reported previously by some authors.^{28,29} Such alteration may have affected BP responses to posture changes and sleep in a similar way as in subjects with disease-related autonomic dysfunction (e.g. diabetic autonomic neuropathy and parkinsonism), where a non-dipping pattern is also common.

In summary, BP increase at high altitude appears to depend primarily on chemoreflex-induced increase in sympathetic activity. Other factors, such as increased blood viscosity and endothelin-1 levels may contribute as well. The observed more pronounced increase in nocturnal BP at 5400 m could be due to poor sleep quality, reduced blood oxygenation at night

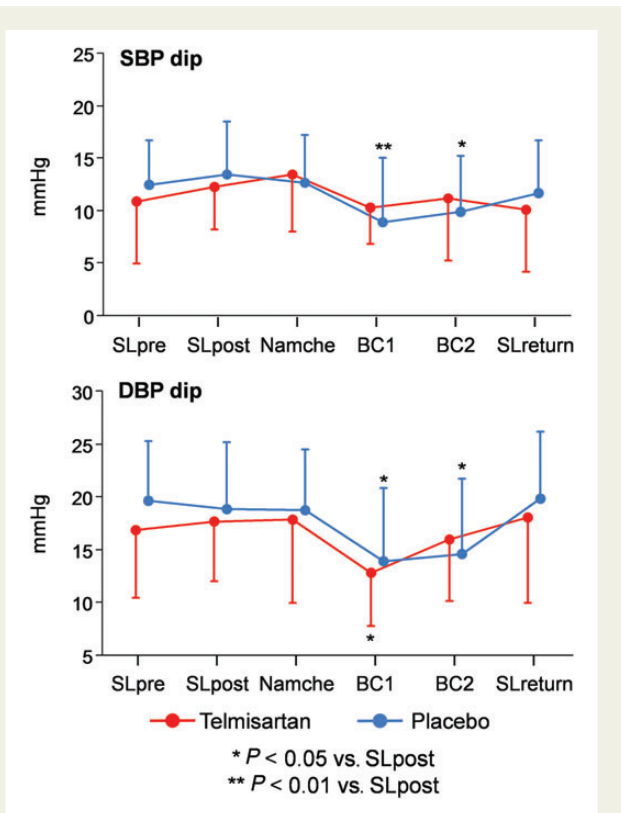


Figure 5 Changes in the size of nocturnal blood pressure dipping (reduction of blood pressure at night expressed as percentage of day-time average) in both treatment groups throughout the study. For abbreviations and symbols see Figures 2 and 3.

and/or to altered arterial baroreflex function. Renin–angiotensin–aldosterone system suppression at very high altitude seems to affect the BP lowering efficacy of the antagonists of this system.

Strengths and limitations

Our study has a number of strengths, including a sample size larger than in most available studies at high altitude, a controlled design by which the effect of antihypertensive treatment was assessed, the quality of the ABP measurements and data collection at multiple points, including the one after return to the sea level. There are, however, also some inevitable limitations. One, although an effort was made to standardize subjects’ activities, we cannot exclude that the pressor effect of high altitude on ABP might have been affected by behavioural modifications. However, we have previously observed that high-altitude exposure (4500 m above sea level) increased ABP and reduced night-time dipping also in subjects confined in an alpine shelter, with behavioural activities that were kept similar to those at the sea level.¹¹ Furthermore, behavioural changes were not responsible for the loss of the effect of antihypertensive drug treatment at very high altitude because, based on their diary, there were no behavioural differences between placebo and telmisartan-treated patients. Thus, even if potentially involved, the ‘behavioural’ factors cannot entirely explain our findings. Two, for obvious reasons, our study could only include healthy volunteers in a good physical shape. While it seems reasonable to extrapolate the results to hypertensive subjects, direct evidence is needed to confirm that the pressor response to high altitude and the changes in the efficacy of antihypertensive treatment occur to a similar degree also in this group.

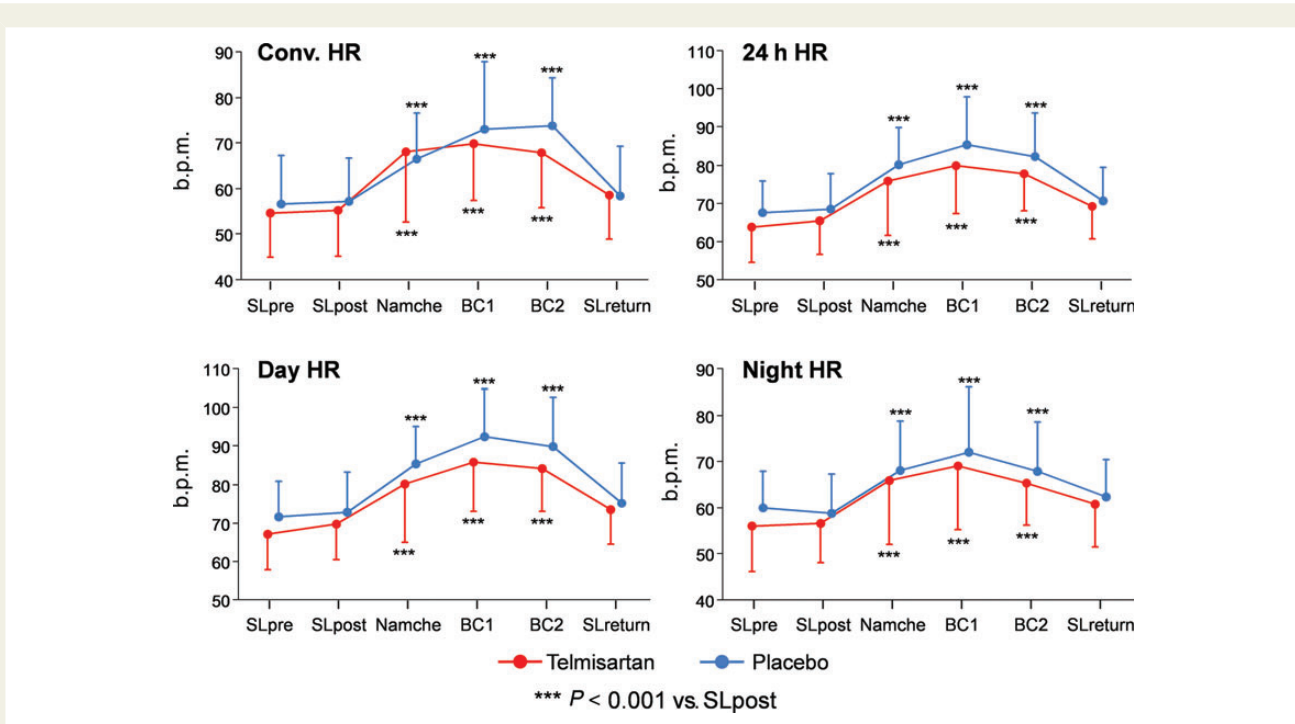


Figure 6 Changes in conventional, 24 h, day-time and night-time heart rate in both treatment groups throughout the study. Data for the placebo group are shown in blue, while those for the telmisartan group in red. For other abbreviations see Figures 2 and 3.

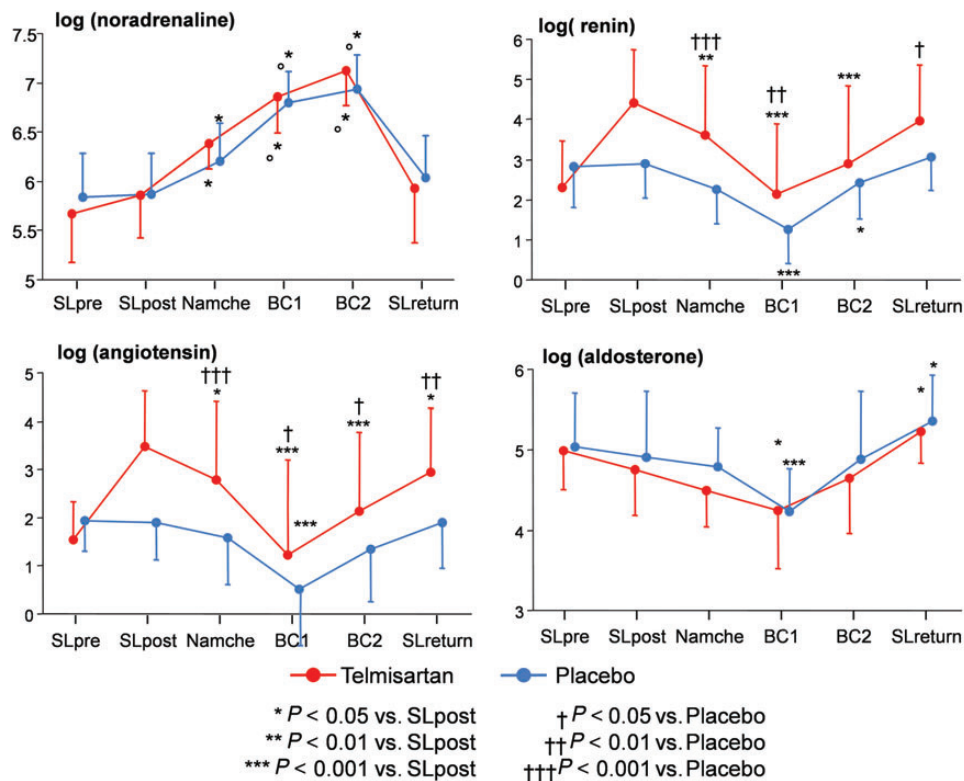


Figure 7 Plasma noradrenaline (log[ng/L]) and renin (log[mU/L]), serum angiotensin (log[pg/mL]) and aldosterone (log[ng/L]) levels in both treatment groups throughout the study. Data for the placebo group are shown in blue, while those for the telmisartan group in red. For other abbreviations see Figures 2 and 3.

A final contribution of our study deserves to be mentioned. In our subjects, the pressor effect of high altitude was more visible on ABP than on conventional BP. Furthermore, only ABP showed the antihypertensive effect of telmisartan and its modification above sea level. This offers another example of the superiority of ABP monitoring over conventional BP measurements.³⁰ This may be particularly the case when unusual environmental conditions affecting BP, such as high altitude, are studied.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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