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Effects of acetazolamide on central blood pressure, peripheral blood pressure, and arterial distensibility at acute high altitude exposure

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Aims We assessed the haemodynamic changes induced by exposure to high altitude hypoxia and the effects on them of acetazolamide, a drug prescribed to prevent and treat mountain sickness.

Methods and results In 42 subjects (21 males, age 36.8 ± 8.9 years) randomized to double blind acetazolamide 250 mg b.i.d. or placebo, pulse wave velocity and pulse wave parameters were assessed (PulsePen) at baseline; after 2-day treatment at sea level; within 6 h and on 3rd day of exposure to high altitude. Exposure to high altitude significantly increased diastolic ($P < 0.005$) and mean blood pressure (BP) ($P < 0.05$, after prolonged exposure) in placebo but not in the acetazolamide group. Therefore, subjects on acetazolamide showed significantly lower values of diastolic ($P < 0.005$) and mean BP ($P < 0.05$) at altitude. Furthermore, they also showed significantly lower values of systolic BP ($P < 0.05$). Pulse wave velocity did not change at high altitude, while the augmentation index, normalized for a theoretical heart rate of 75 b.p.m., significantly increased ($P < 0.05$) under placebo, but not under acetazolamide. In a multivariate model, unadjusted augmentation index at high altitude was not affected by BP changes, while significant determinants were heart rate and gender.

Conclusion Acute exposure to high altitude induced a rise in brachial BP and changes in pulse waveform-derived parameters, independent from changes in mean BP and partly counteracted by treatment with acetazolamide. The impact of acetazolamide on the haemodynamic alterations induced by hypobaric hypoxia may be considered among the beneficial effects of this drug in subjects prone to mountain sickness.

Clinical Trial Registration: EudraCT Number: 2010-019986-27.

Keywords Acetazolamide • Arterial stiffness • Blood pressure • High altitude • Hypobaric hypoxia • Pulse wave velocity

Introduction

High altitude hypobaric hypoxia is responsible for complex, acute modifications in both systemic and pulmonary circulation.[1] We previously reported that a relatively short (2–3 days) permanence at high altitude induces a significant increase in systolic and diastolic 24 h blood pressure (BP) mostly evident at night.[2] However, the high altitude-related BP effects have so far only be determined by measuring BP at the brachial artery level and no data have ever been obtained on whether peripheral BP changes correspond to changes in central BP, i.e. the BP to which vital organs are exposed, and which may respond differently from peripheral BP to environmental and pharmacological stimuli.[3] This may be the case also when considering exposure to high altitude, a condition which is accompanied by a sympathetic activation that may affect two major determinants of central BP, i.e. arterial distensibility[4,5] and pulse wave reflection via vasoconstriction.[6]

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The present study had three aims: (i) to measure the effect of acute and more prolonged exposure to high altitude not only on peripheral (i.e. brachial), but also on central (i.e. carotid) BP; (ii) to concomitantly determine the high altitude effects on large artery wall stiffness; (iii) to investigate, via a placebo (PL)-controlled study design, whether high altitude-related alterations in central BP, peripheral BP, and arterial stiffness are modified by acetazolamide (AC), a potent carbonic anhydrase inhibitor that is largely used to prevent and treat acute mountain sickness.[7–11] The effect of AC under this circumstance is ascribed to the ability of AC to increase diuresis[12,13] and bicarbonate excretion, with a resulting metabolic acidosis and chemoreceptor stimulation that reinforces ventilation.[12,14–17] A possible direct role of AC on Ca-ion release in smooth muscle cells[18,19] or on nitric oxide (NO)[20] generation has also been suggested. However, because excessive BP and heart rate (HR) increases have been regarded as possible contributors to the symptoms of acute mountain sickness,[2] haemodynamic mechanisms cannot be excluded.

Methods

Study design and protocol

This was a randomized, double blind, parallel group, PL-controlled study. Healthy lowlanders without known cardiovascular disease, no chronic cardiovascular therapy, no history of severe mountain sickness, no recent exposure to altitudes >2000 m, and no contraindications to AC were included in the study, provided that an exercise test immediately prior to the inclusion did not show evidence of myocardial ischaemia. On the basis of the wide literature available, we have assumed that 20 subjects/group were sufficient to demonstrate with $P < 0.05$ and a power of 0.8 a difference in PWV of 1 m/s, in a population aged from 25 to 45 years old, characterized by mean PWV ± SD of 6.74 ± 1.13 m/s. We also hypothesized a total number of drop-outs = 4 (20%). Based on these considerations, we thus recruited 22 subjects/group. Subjects were randomly assigned to receive PL or AC, 250 mg b.i.d.[21,22] for 3 days at sea level and again during the entire duration of the permanence at high altitude starting from the day of the departure. Ascent from Milan (122 m a.s.l.) to the high altitude laboratory (Capanna Regina Margherita, Monte Rosa, 4559 m a.s.l.) was completed in <28 h. Capanna Margherita was reached from Alagna Valsesia (altitude 1130 m) with subjects ascending first by cable-car up to Punta Indren (3200 m) and then on foot to the Gnifetti hut (altitude 3647 m). After an overnight stay, the hike was continued up to Capanna Regina Margherita.

In all subjects a spontaneous respiratory rate at rest in stable conditions, arterial blood oxygen saturation, and 24-h diuresis were measured every day. Oxygen saturation was derived through a finger pulse oximeter (Ohmeda Tuff Sat with sensor OxyTip Finger 6051-0000-160, GE Healthcare-Finland). After the first night at high altitude, arterial blood samples were collected and immediately analysed with the use of an i-STAT System blood gas analyzer (Abbott Laboratories, Abbott Park, Illinois, USA); PaO_2, $PaCO_2$, pH, and bicarbonate concentration were assessed.

Measurements

To avoid interference by the physical activity involved in the ascent to the high altitude laboratory, data collection was started at least 4 h after reaching the Capanna Regina Margherita and was continued over the 4-day permanence in this shelter without any physical activity. Data were always collected in rooms kept at the stable air temperature of 19–20°C. A standardized questionnaire for the clinical assessment of acute mountain sickness (Lake Louise score[23]) was completed daily.

Measurements were obtained in four conditions: (i) at sea level, off-treatment (SL-pre); (ii) at sea level, after 2 days of the 3 day double-blind treatment (SL-post); (iii) on treatment, at high altitude, within 4–6 h after arrival to Capanna Regina Margherita (HA1), and (iv) on-treatment after two full days of permanence at high altitude (HA2). In each condition peripheral BP and HR were measured three times, at brachial artery level, in the supine position with a validated oscillometric device (AND UA-767PC, AND Company Ltd, Tokyo, Japan). Measurements were spaced by 3 min intervals.

Arterial stiffness

Arterial stiffness was derived from the measurement of carotid-femoral pulse wave velocity (aortic-PWV) using a validated high-fidelity PulsePen device[24,25] (DiaTecne srl, Milano, Italy). As described in detail previously,[25] the PulsePen consists of an applanation tonometer and an integrated ECG unit. Pulse wave velocity was measured by recording carotid and femoral waveforms in rapid succession. Pulse wave velocity was defined as the distance between the measuring sites divided by the difference between the delayed rise of the distal pulse wave from the R-wave belonging to the immediately preceding ECG qRs complex, and the delayed rise of the proximal pulse wave from the R-wave belonging to the immediately preceding ECG qRs complex. The pulse wave delay is assessed by calculating the time elapsed from the peak of the R-wave and the 'foot' of the immediately following pressure pulse contour. The distance of the pulse wave transit represents the difference between the distance from the supra-sternal notch to the femoral point of application of the tonometer and the distance from the carotid point of tonometer application and the supra-sternal notch. The device did not validate measurements if BP or HR differences between the carotid and femoral artery recordings were >10%. In each patient PWV measurements were repeated twice and their mean was used for the analysis. The examination was usually completed in 10 min.

Central blood pressure

The PulsePen applanation tonometer was also used to directly record at the common carotid artery site the pulse waveform and central BP values.[25] The augmentation index (AIx) was defined as the difference between the second and first systolic peaks and expressed as a percentage of central pulse pressure.[26] Because AIx is affected by HR, which is increased during hypobaric hypoxia exposure at altitude, AIx values were normalized for a theoretical HR of 75 b.p.m. (AIx@75) via a conventional formula.[27]

Statistical analysis

All data were analysed by means of SAS version 9.1. Continuous variables are reported as means ± SD. The effects of the study condition and treatment were subjected to analysis of variance (repeated measures ANOVA). Two-sided *t*-test analysis was performed with Bonferroni's correction when required. Adjusted regression estimates were obtained by mixed models procedure of SAS (proc mixed) accounting for repeated measurements of arterial properties variables with a compound symmetry covariance structure. As in our data, it was not necessary to model fixed and random effects simultaneously, random effects were not specified. An α level of 0.05 was used for all hypotheses tested. Age, sex, height, HR, mean arterial pressure (MAP), O_2 saturation, and respiratory rate were used as covariates.

The study protocol was approved by the Ethical Committee of the Istituto Auxologico Italiano, Milan, Italy. All subjects gave their written informed consent to the study procedures.

Results

Twenty-two subjects were randomized to AC and 22 subjects to PL. Three subjects were not included in the analysis because of their need to be treated with dexamethasone for acute mountain sickness symptoms (two subjects on PL and one subject on AC). One subject in the AC group did not ascend to the high altitude shelter for personal reasons and another subject from the same group was not compliant with the prescribed treatment. Thus, data analysis was performed from 19 subjects on AC and 20 subjects on PL. At baseline there was no significant difference between the demographic, metabolic, and haemodynamic characteristics of the two groups (Table 1). In either group haemoglobin oxygen saturation was significantly reduced after acute exposure to high altitude and showed a later progressive recovery. The oxygen desaturation was always significantly greater in the PL than in the AC-treated patients (*Figure 1*). In a subgroup of 26 subjects (12 PL and 14 AC) arterial blood gas analysis was carried out after one night stay at 4559 m a.s.l. Subjects treated with AC had lower pH values (7.37 ± 0.02 vs. 7.46 ± 0.03, $P < 0.001$), higher pO_2 (50.97 ± 6.1 vs. 44.07 ± 3.6 mmHg, $P < 0.001$), lower pCO_2 (25.01 ± 2.23 vs. 27.75 ± 2.73 mmHg, $P = 0.01$) and bicarbonate concentration (14.53 ± 1.4 vs. 19.96 ± 1.82 mmol/L, $P < 0.001$), and a higher urinary volume (1795.75 ± 581.4 vs. 1404.5 ± 552.12 L/day, $P = 0.04$) when compared with the PL group, with no significant differences in the respiratory rate.

The effects of high altitude on BP in the two groups are shown in *Figure 2*. In the PL group either the peripheral systolic blood pressure (SBP) and the central SBP did not change significantly from sea level (115.0 ± 12.1 mmHg; 103.7 ± 10.7 mmHg) to acute high altitude exposure (115.9 ± 8.8 and 105.2 ± 6.9 mmHg), with a weak and statistically not significant increase when the high altitude exposure was prolonged (119.6 ± 9.9 and 108.8 ± 8.0 mmHg, respectively). In the AC treated group peripheral SBP significantly fell with treatment both at SL and when arriving at high altitude (from 115.9 ± 13.2 to 109.9 ± 12.5 mmHg at SL-post, $P = 0.030$ and to 108.1 ± 9.4 mmHg at HA1, $P = 0.038$). After prolonged stay at altitude the peripheral SBP returned towards baseline values (113.8 ± 11.5 mmHg). Comparing the two treatment groups, the peripheral SBP was lower in AC only under acute exposure to high altitude ($P = 0.011$). The reduction in the central SBP was weaker and statistically not significant.

In the PL group, diastolic blood pressure (DBP) significantly raised from sea level to acute high altitude exposure (from 72.1 ± 6.5 to 70.0 ± 6.8 mmHg at SL-post, to 77.1 ± 6.8 mmHg at HA1, $P = 0.003$), with a further increase when the high altitude exposure was prolonged (79.7 ± 9.0 mmHg, $P = 0.003$). As expected, the trend was similar for MAP, that increased from sea level to acute high altitude exposure (86.4 ± 7.7 mmHg at SL-pre, 85.0 ± 7.8 mmHg at SL-post and 90.0 ± 6.2 mmHg at HA1), with a further and statistically significant increase after stay at altitude (93.0 ± 8.6 mmHg, $P = 0.040$ compared with SL-pre).

In the group treated with AC, no significant change in DBP and MAP was recorded in comparison with baseline values (DBP: 70.9 ± 8.6 mmHg at SL-pre, 68.3 ± 6.2 mmHg at SL-post, 70.4 ± 5.3 mmHg at HA1, and 74.5 ± 7.3 mmHg at HA2; MAP: 85.9 ± 9.4, 82.2 ± 7.8, 82.9 ± 5.6, and 87.6 ± 7.8 mmHg, respectively). At arrival at high altitude, MAP and DBP values were significantly lower in the AC group than in the PL group ($P < 0.001$ and $P = 0.0015$, respectively); after permanence at high altitude MAP and DBP remain significantly slightly lower in the AC group ($P = 0.047$ and $P = 0.049$, respectively).

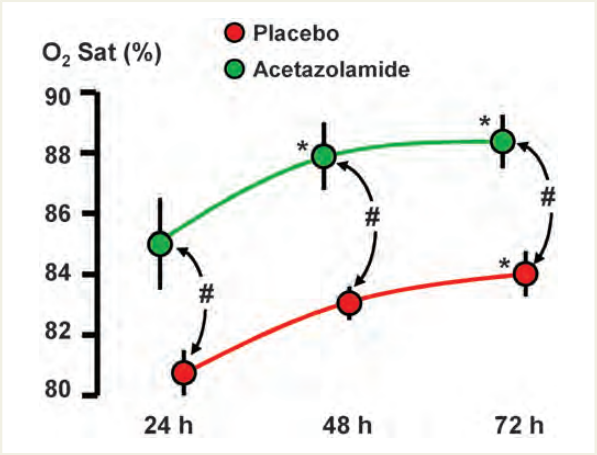

Figure 1 Arterial oxygen saturation (O_2 Sat, pulse oximetry) during exposure to high altitude (Days 1, 2, and 3) in the acetazolamide group and the placebo-treated group. *$P < 0.05$ vs. 24 h values of the same group; #$P < 0.05$ vs. placebo group at same step.

Table 1 Basal values of clinical, haemodynamic, and anthropometric parameters of all participants

	Placebo	Acetazolamide
Sex (M/F)	10/10	9/10
Age (years)	37.0 ± 9.5	35.6 ± 7.1
Height (cm)	172.2 ± 9.8	171.8 ± 8.8
Weight (kg)	66.5 ± 13.2	63.3 ± 12.3
BSA (m^2)	1.78 ± 0.22	1.74 ± 0.20
BMI (kg/m^2)	22.3 ± 2.7	21.3 ± 2.7
Brachial SBP (mmHg)	115.1 ± 11.8	115.9 ± 13.2
Carotid SBP (mmHg)	103.6 ± 9.7	104.3 ± 12.9
Brachial PP (mmHg)	43.0 ± 8.4	45.0 ± 9.6
Carotid PP (mmHg)	31.5 ± 6.4	33.4 ± 9.0
MAP (mmHg)	86.4 ± 7.7	85.9 ± 9.4
DBP (mmHg)	72.1 ± 6.5	70.9 ± 8.6
Heart rate (b.p.m.)	59.2 ± 6.7	63.9 ± 9.1
AIx (%)	−1.5 ± 14.1	−4.4 ± 13.8
AIx@75 (%)	−7.6 ± 13.9	−8.7 ± 13.6
Aortic PWV (m/s)	6.3 ± 1.2	6.4 ± 1.3

AIx, augmentation index; AIx@75, augmentation index normalized for a theoretical heart rate of 75 b.p.m.; BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

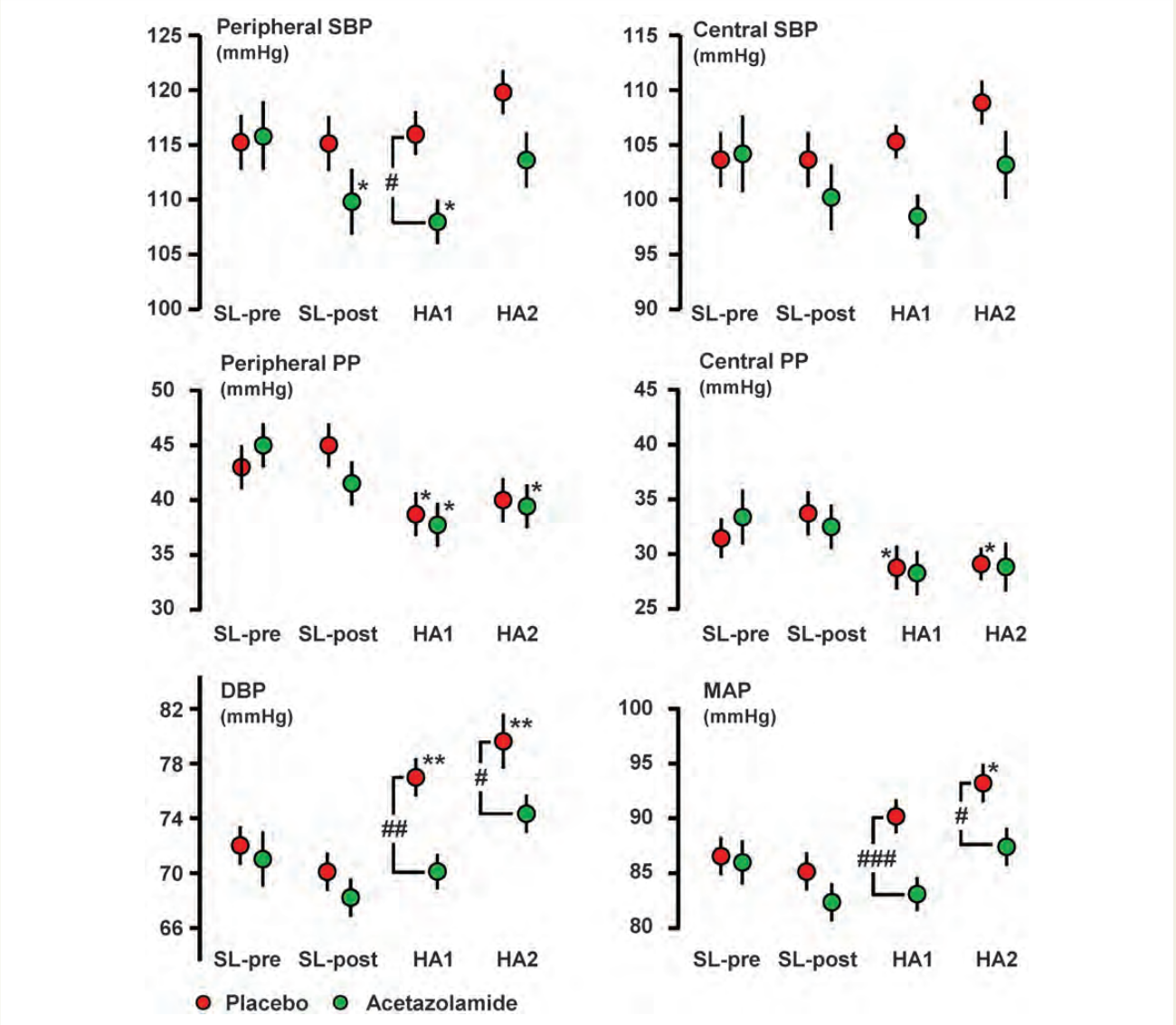

Figure 2 The behaviour of blood pressure values in the placebo group and the acetazolamide group at the different steps of the study. The central blood pressure was measured at the common carotid artery; the peripheral blood pressure was measured at the brachial artery. Data are expressed as mean ± SE. *$P < 0.05$, **$P < 0.005$ vs. sea level basal values of the same group; #$P < 0.05$, ##$P < 0.005$, ###$P < 0.001$ acetazolamide vs. placebo group at same step. SBP, systolic blood pressure; PP, pulse pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SL-pre, sea level, off treatment; SL-post, sea level, on treatment; HA1, high altitude, within 4–6 h after arrival to 4559 m a.s.l.; HA2, after two full days of permanence at high altitude.

Because DBP increased more than SBP, acute exposure to high altitude was associated with a reduction in the peripheral pulse pressure (from 45 ± 9.2 to 38.8 ± 8.9 mmHg, $P = 0.005$ in the PL group and from 41.6 ± 8.5 to 37.7 ± 8.8 mmHg, $P = 0.03$ in the AC group) and the central pulse pressure (from 33.7 ± 8.2 to 28.1 ± 7.1 mmHg, $P = 0.005$ in the PL group, and from 32.3 ± 7.4 to 28.4 ± 7.6 mmHg, $P = 0.0014$ in the AC group), compared with SL-post, in this case with no significant between-group difference.

No significant linear correlation was found between oxygen saturation and DBP ($r^2 = 0.010$) or MAP ($r^2 = 0.146$) as well as between respiratory rate and DBP ($r^2 = 0.013$) or MAP ($r^2 = 0.006$).

The effects of high altitude on HR are shown in *Figure 3*, upper panel. In the PL group, HR increased markedly after acute high altitude exposure (from 59.2 ± 6.7 to 84.1 ± 9.7 b.p.m., $P < 0.001$). The trend was similar in the AC-treated group (from 59.8 ± 9.3 at SL-post to 77.4 ± 9.7 b.p.m. at HA1) in which, however, the acute increase was significantly less pronounced, with a return towards sea level values after 36 h.

Acute and prolonged exposure to high altitude were associated with a significant increase in the AIx@75 (*Figure 3*, lower panel) in the PL group (from −7.6 ± 13.9 to −0.15 ± 13.6 at HA1 and −0.23 ± 14.6% at HA2, $P = 0.049$), but not in the AC group (from −12.6 ± 11.3 at SL-post to −7.2 ± 12.3% at HA1 and −6.5 ± 11.0% at HA2).

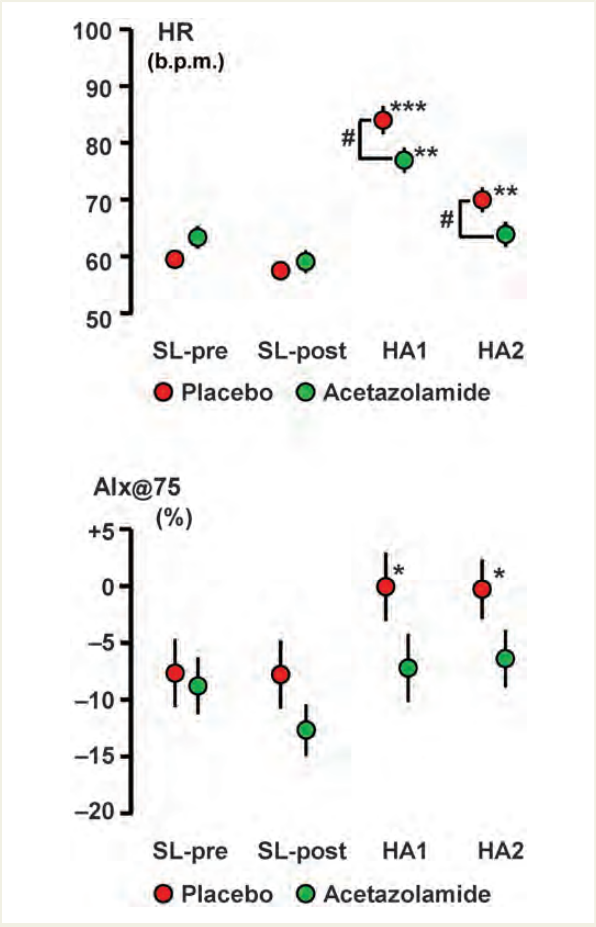

Figure 3 The behaviour of the heart rate (HR, upper panel) and of the augmentation index normalized for a theoretical heart rate of 75 b.p.m. (AIx@75, lower panel), in the placebo group and the acetazolamide group at the different steps of the study. Data are expressed as mean ± SE. $*P < 0.05$, $**P < 0.001$ vs. sea level basal values of the same group; $\#P < 0.05$ acetazolamide vs. placebo group at same step. SL-pre, sea level off treatment; SL-post, sea level on treatment; HA1, high altitude, within 4–6 h after arrival to 4559 m a.s.l.; HA2, after two full days of permanence at high altitude.

In a multivariate analysis, significant determinants of AIx values at high altitude were HR ($P = 0.030$; $\beta = -0.45$) and gender ($P = 0.016$; $\beta = 9.92$) with higher values in females, and with no significant contribution of other parameters which showed alterations at high altitude (MAP, respiratory rate, arterial O_2 saturation).

Figure 4 shows the changes in central pulse waveform induced by high altitude and the effects of AC. Blood pressure waveform significantly changed at high altitude, but only in PL subjects. Subjects in the AC group had constantly BP and AIx values lower than PL subjects.

As shown in *Figure 5*, no significant change in PWV values was recorded at high altitude in the two groups, even after adjustment for confounding variables (HR, MAP, and age).

Twenty subjects had a Lake Louise Acute Mountain Sickness Score >3 at high altitude (47.6% of all participants); 14 of these were in the PL group (63.6%), and 6 in the AC group (30.0%). The difference was statistically significant (Pearson's χ^2 test, $P = 0.019$). No differences in terms of haemodynamic parameters were observed in subjects with or without symptoms of acute mountain sickness, as quantified by the LLS score, while oxygen saturation was slightly lower in the group with when compared with the group without acute mountain sickness symptoms (80.1 ± 5.1 vs. 83.3 ± 5.0%, $P = 0.046$).

Discussion

Our study provides several new results. (i) Exposure to high altitude is accompanied by significant increases in DBP and MAP that occur immediately after the arrival at high altitude and persist virtually unchanged over the following 3 days in the same environmental condition; (ii) acute and prolonged exposure to high altitude also cause a persistent change in central pulse waveform and in AIx values; (iii) all the above changes are attenuated by AC whose beneficial effects in acute mountain sickness are thus not limited to ventilation but importantly extend to high altitude-induced haemodynamic phenomena.

The pressure effect of high altitude is traditionally regarded as being the final result of the double action of hypoxia on the cardiovascular system.[1] More specifically, the direct vasodilating effect of hypoxia is outbalanced by hypoxia-dependent stimulation of peripheral and central chemoreceptors, leading to systemic vasoconstriction and to an increase in ventilation that transforms the bradycardic effect of chemoreceptor stimulation into tachycardia.[1,28,29] Our present results allow to complete the high altitude-dependent haemodynamic pattern by showing that the peripheral BP response is not dissociated but in line with a similar behaviour of central BP, i.e. a BP that is regarded as having an important prognostic significance.[30] The stimulating effects of high altitude on the sympathetic nervous system are likely to play a role because sympathetic activation leads to vasoconstriction.[31] The resulting increase in systemic vascular resistance contributes to the increase in brachial DBP and MAP. Together with changes in timing and amplitude of reflected waves, it is also a major determinant of central BP waveform modifications.

In the control group, at high altitude we observed an increase in MAP and DBP.

We can exclude any effect of physical exercise, because early data collection at arrival at high altitude always started at least 4 h after reaching the high altitude laboratory, and no physical activity was allowed during permanence in the high altitude shelter. Moreover, we can also exclude any interference by ambient air temperature, because all studies were carried out inside the Capanna Regina Margherita Laboratories, at stable temperatures ~19–20°C. In untreated subjects, in the early phase of exposure to high altitude hypoxia, vasodilatation tends to override sympathetic vasoconstriction in the systemic circulation. Thus, an increase in BP values may become more evident and significant after some days of permanence at high altitude, a phenomenon which could be explored in our study because data collection was continued over 4 days at altitude.

We previously reported that in healthy young or middle-aged individuals a relatively short (2–3 days) permanence at high

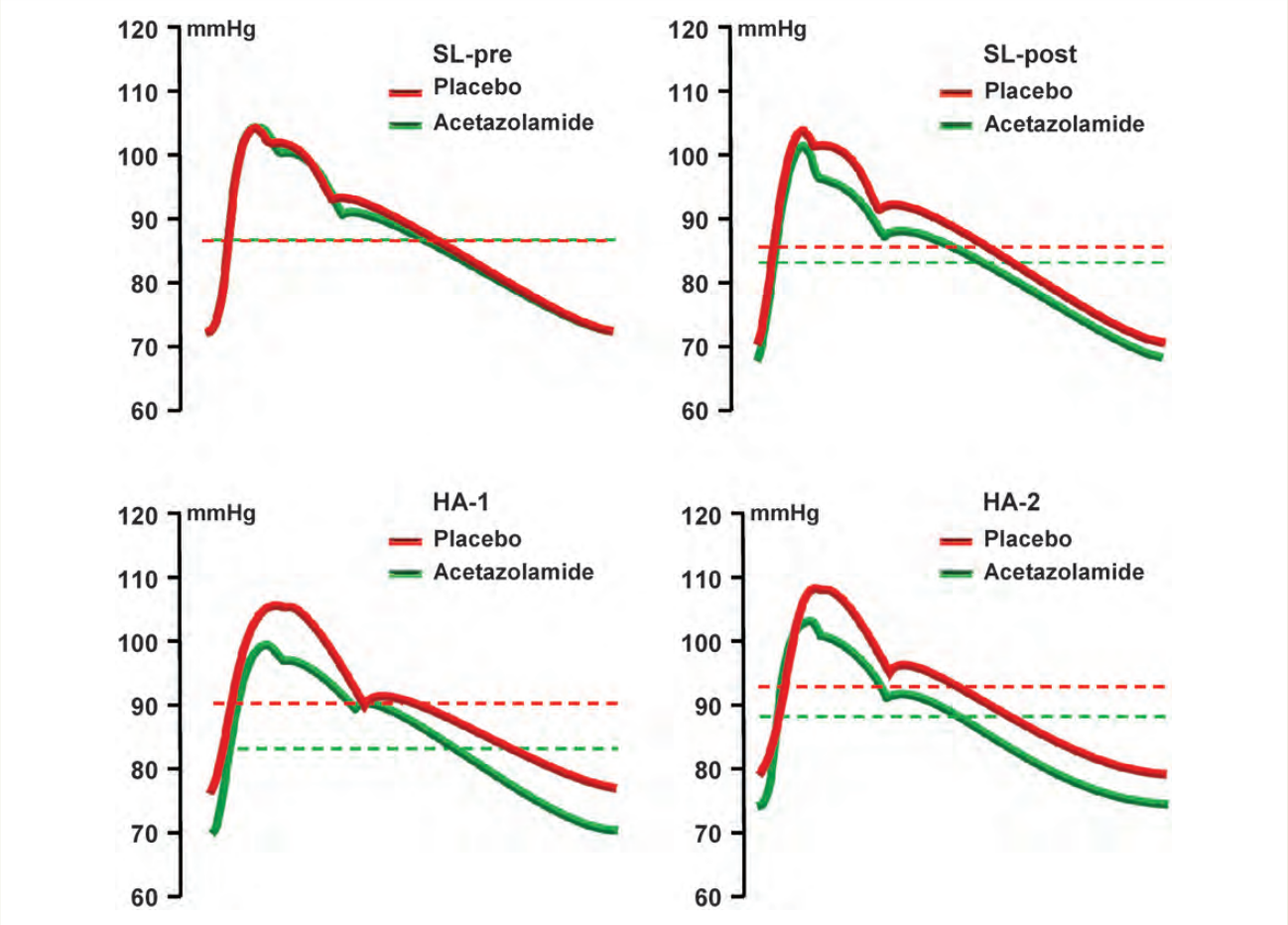

Figure 4 Changes in central pulse waveform in the placebo group (red line) and the acetazolamide group (green line) at the different steps of the study. Waveform analysis was performed on the ensemble-averaged waveforms of all participants, analysed for each step and group. The horizontal dotted line shows the values of the mean arterial pressure. SL-pre, sea level off treatment; SL-post, sea level on treatment; HA1, high altitude, within 4–6 h after arrival to 4559 m a.s.l.; HA2, after two full days of permanence at high altitude.

altitude significantly increased 24 h and night time ambulatory systolic and diastolic BP, with only minor changes in daytime BP.[2] In the same study, we found no significant differences in conventional BP between sea level and high altitude. This observation is in line with our present data, the well known limitations of spot BP measurements being likely responsible for our inability to find significant increases in systolic BP from sea level to high altitude using spot BP measurements. Moreover, here we reported BP measured immediately before arterial stiffness parameters collection, which was done in supine position, a condition that cannot be compared with ambulatory or conventional seated BP.

For the first time, this study also provides information on the behaviour of arterial wall properties at different times of exposure to hypobaric hypoxia at altitude. Actually, the more specific marker of arterial stiffness, i.e. aortic PWV (carotid-femoral PWV) did not change, at least after acute exposure to altitude. The viscoelastic properties of aorta are in relationship with structural changes of the arterial wall, and only weakly sensitive to the functional factors.[26] Thus acute exposure at high altitude did not affect significantly mechanical properties of large arteries.

A very interesting finding of our study is the increase in the AIx shown at high altitude in the control group, whose determinants were gender differences and the increase in HR. Our data are at variance from what reported by AJ Thomson *et al.* who showed a reduction in the AIx as an effect of short-term isocapnic hypoxia.[32] In this study, eight healthy men were exposed to 1-h period of hypoxia (mean peripheral O_2 saturation: $82.6 \pm 0.3\%$) in a laboratory environment. The AIx fell markedly during hypoxia (mean $-10.7 \pm 1.1\%$, $P < 0.001$). Taken together, these data seem to confirm that at the time of first exposure to hypoxia, the prominent effect is a direct vasodilatation of systemic arterioles. However, hypoxic vasodilatation prevails over sympathetic vasoconstriction in the systemic circulation[1] only during the first few hours of exposure. Indeed, after this short transient phase, the sympathetically mediated vasoconstriction prevails over the directly induced systemic vasodilatation. Even if the AIx is commonly considered and used as a marker of arterial stiffness, it is known to be influenced by both the timing and intensity of reflected BP waves returning to the proximal aorta. Change in small artery tone affects wave reflection: vasodilatation reduces the AIx,

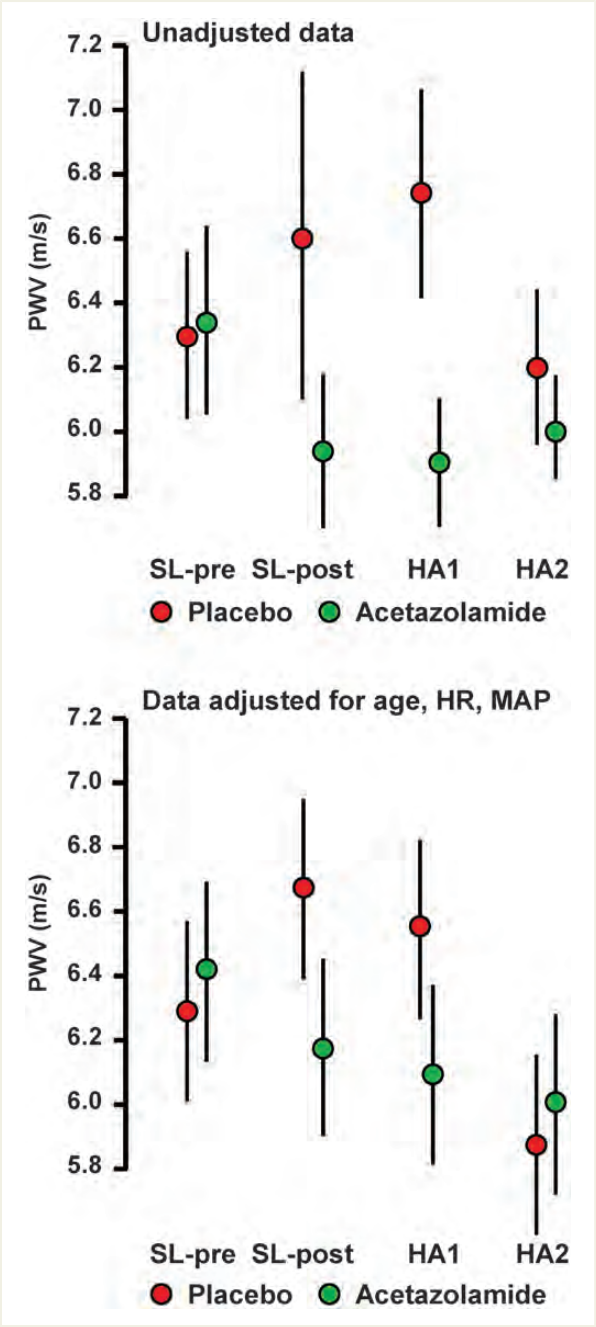

Figure 5 Changes in carotid-femoral pulse wave velocity in the placebo group and the acetazolamide group at the different steps of the study. Pulse wave velocity values are shown unadjusted (upper panel) and adjusted for age, heart rate, and mean arterial pressure (lower panel). Data are expressed as mean ± SE. SL-pre, sea level, off treatment; SL-post, sea level on treatment, HA1, high altitude, within 4–6 h after arrival to 4559 m a.s.l.; HA2, after two full days of permanence at high altitude.

whereas vasoconstriction increases it.[33] So a sympathetic activation increases HR and DBP values and, as a consequence, the AIx. The AIx increase shown in the PL group is most likely associated to the increase in peripheral vascular resistance at high altitude.

Our study shows that these phenomena are partially but effectively attenuated by AC. In fact in subjects on treatment with AC, the increase in BP, HR, and AIx was effectively blunted.

Actually, subjects under treatment with AC did not display any significant increase in BP values with altitude, their BP values remaining always significantly lower than those of the PL group. We can speculate that the protective effect of AC against high altitude-induced BP increases may depend on its action on the chemoreflex-mediated sympathetic activation.[7,15,16,34,35] While the inhibitory effects of AC on peripheral chemoreceptor activity do not seem to be able to completely abolish the effects of high altitude hypoxia on sympathetic activation, as shown by the persisting HR increase, its administration seems effective enough in reducing it and thus in buffering the BP elevation typical of this condition. Indeed, the reduced BP rise at altitude observed in AC-treated subjects seems to suggest that the interference of AC treatment with the sympathetically mediated vasoconstriction allowed the direct vasodilatory effect of hypoxia to prevail, even if AC-treated subjects were characterized by higher arterial oxygen saturation when compared with subjects randomized to PL. Acetazolamide can have vasodilating effects also through different mechanisms. The role of AC in the response to hypoxia of pulmonary vascular smooth muscle cells was investigated by Swenson *et al.*[18] in isolated pulmonary artery smooth muscle cells, isolated perfused lungs, and live animals. A potent reduction in hypoxic pulmonary vasoconstriction by AC was found, and this action did not appear to be related to carbonic anhydrase inhibition. It seems therefore that the response of pulmonary vasculature differs from that of systemic vasculature for which the evidence is more compelling in favour of a carbonic anhydrase-mediated role in vasomotor regulation.[36] In fact, it has been demonstrated that AC increases the carbonic anhydrase-catalyzed production of vasoactive NO from nitrite.[20] At high altitude, NO has a key role in counteracting pulmonary and systemic vasoconstriction, in fact in individuals susceptible to severe mountain sickness its synthesis is decreased[36] and NO inhalation has been successfully used in the treatment of high altitude pulmonary oedema.[37] Moreover, AC can act at the level of Ca^{2+} release from the sarcoplasmic reticulum[18] and caused a reduction in peripheral vascular resistance by opening Ca^{2+}-activated K^{+} channels.[19]

Perspectives

Acute exposure to high altitude induced both central BP and peripheral BP rise and changes in central pulse waveform, partly counteracted by treatment with AC. The impact of AC on the haemodynamic alterations induced by hypobaric hypoxia may be considered among the beneficial effects of this drug in subjects prone to acute mountain sickness. Based on these findings, also the possible clinical usefulness of AC in patients with diseases associated with hypoxaemia might deserve to be re-assessed.

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