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Original Article

Acetazolamide pre-treatment before ascending to high altitudes: sustained effect on systemic blood pressure during submaximal exercise

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Abstract: Acetazolamide (ACZ) is well known to prevent the development of acute mountain sickness and the increase of systemic blood pressure during resting conditions. Due to lacking data, this study aimed at investigating the effects of ACZ pretreatment on systemic blood pressure responses to submaximal exercise during the first 3 days at high altitude. Fifteen study participants were randomly assigned in a double blind fashion to receive placebo or acetazolamide (2 × 125 mg) before (10 hours and 1 hour) exposure to high altitude (Monte Rosa plateau, 3480 m). Beside AMS scoring, cardiorespiratory responses to submaximal exercise were measured at low altitude and on day 1, 2 and 3 at high altitude. Pre-treatment with acetazolamide on the day of ascent to high altitude resulted in a lower increase in arterial blood pressure (systolic, diastolic, mean) on day 2 (trend for systolic BP) and day 3 at high altitude when ACZ was already withdrawn. We speculate that ACZ may have prevented sensitization of peripheral chemoreceptors during acute high-altitude exposure with sustainable effects during the following 2 days. If confirmed in further studies, these findings may have beneficial clinical consequences for exercising high-altitude sojourners suffering from cardiovascular diseases.

Keywords: Acute mountain sickness, prevention, low-dose acetazolamide, pre-treatment

Introduction

Low-dose acetazolamide (ACZ; 250-500 mg/day) is the medication of choice for effective prevention of symptoms of acute mountain sickness (AMS) in subjects susceptible to AMS and/or those rapidly ascending to high altitude [1, 2]. ACZ has also been shown to counteract periodic breathing at altitude and to improve sleeping quality [3]. These beneficial effects of ACZ are primarily ascribed to its potent inhibition of carbonic anhydrase (CA) and the resulting diuresis and bicarbonate excretion causing metabolic acidosis [4]. The metabolic acidosis and the slight retention of carbon dioxide from vascular CA IV inhibition stimulate ventilation thereby improving arterial oxygenation and ventilatory control. The improved stability of ventilation by ACZ is attributed to increasing tonic output of the central chemoreceptors and lowering their apneic threshold [4]. Additionally, inhibition of CA in the peripheral chemoreceptors contributes to ventilatory stabilization by diminishing the hypoxic and hypercapnic sensitivity [4, 5]. Beside the hyperventilatory response ACZ related reduction in pulmonary vasoconstriction and changes in cerebral blood flow may help to optimize global systemic as well as cerebral oxygenation, thereby diminishing the development of AMS symptoms [6]. Another beneficial effect of ACZ that has been recently demonstrated represents its ability to attenuate the increase in systemic blood pressure during acute exposure to high altitude [7]. Such effects may be of particular importance for patients suffering from cardiovascular diseases in particular those with hypertension. ACZ effects on systemic blood pressure may be partly attributed to inhibition of sympathetic tone and to its favoring effects on the production of nitric oxide (NO) [8] representing a key role in counteracting pulmonary and systemic vasoconstriction [7, 8]. Data on the effects of ACZ on systemic blood pressure during acute exposure to high altitude are scarce and predominantly restricted to observations at rest.

Table 1. Baseline characteristics of the study participants

	Placebo group N=7	Acetazolamide group N=8
Age (yrs)	44.7±8.6	43.6±13.4
Height (cm)	170.7±5.4	173.4±4.2
Weight (kg)	64.5±12.5	68.3±8.4
Sex (male/female)	4/3	4/4
HR (b/min)	67.6±9.0	69.3±8.9
SpO_2 (%)	97.0±1.0	97.1±0.8

Heart rate, HR; arterial oxygen saturation by pulsoximetry, SpO_2.

However, subjects traveling to high altitude mostly perform some type of physical activity like hiking, climbing or skiing. It is well established that systemic blood pressure increases during exercise at low altitude [9] and at least in healthy subject these responses seem to be similar during acute high altitude exposure [10]. Parati and colleagues demonstrated increased systemic resting diastolic and mean arterial blood pressure after 6 h and 2 days of arrival at high altitude (4559 m) compared to sea level [7]. ACZ treatment (250 mg b.i.d) prevented this increase probably due to lower sympathetic stimulation and/or increased NO production causing reduced peripheral vasoconstriction [7]. Therefore, we expected a similar or even more pronounced effect of ACZ pre-treatment on systemic exercising blood pressure at least on the first day at altitude. This study aimed to investigate the effects of ACZ pre-treatment on systemic blood pressure responses to submaximal exercise during the first 3 days at high altitude.

Methods

The methods of this study have been described previously [11] and will be presented here only in brief.

Study participants

A total of 15 volunteers with a history of AMS were recruited. Exclusion criteria were any type of acute or chronic illness, regular smoking (> 5 cigarettes per day), regular medications, sojourns at an altitude > 2500 meters during the previous 4 weeks, age < 20 or > 60 years, pregnancy or lactation, and hemoglobin concentration < 12.0 g/dL. The study was approved by the ethics committee of the Medical University of Innsbruck and written informed consent was obtained from each subject.

Study protocol

Study participants were randomly assigned in a double blind fashion to receive placebo (placebo group) or ACZ (ACZ group) before exposure to high altitude. Baseline characteristics are shown in **Table 1**. After routine examination and submaximal exercise testing at low altitude (600 m), subjects were transported by car and cable car to high altitude for 3 days (Monte Rosa plateau, Italy, 3480 m). Each subject took only two tablets (2 × 125 ACZ or placebo); 10 hours and 1 hour before arrival at high altitude.

Measurements

Resting measurements were conducted in the evening hours at low altitude (without ACZ pre-treatment) and in the evening of the first, the second and the third day at high altitude (after ACZ pre-treatment). They were performed after a 10-minute rest in a sitting position and included the determination of heart rate and oxygen saturation by pulse oximetry (Onyx 9500 finger pulse oximeter, Nonin Medical Inc, USA), and systolic and diastolic blood pressure using the Omron R3 (Germany; validated by Eckert et al. [12]) around the left wrist held at the subjects' heart level. AMS symptoms were recorded according to the Lake-Louise-Score. Subjects were considered to suffer from AMS when the score was ≥ 3 [13]. After completing resting measurements, subjects exercised for 3 minutes by stepping 90 times up and down a 24 cm step. Values of heart rate, oxygen saturation and blood pressure (holding the arm still at the subjects' heart level) were taken close to the end of the step test. As reported recently, participants had no physical activity during the first day at altitude and climbed up to about 3800 meters within 2.5 to 3 hours on the second and third days. Nutrition has been standardized.

Statistics

Statistical analyses were conducted by PASW Statistics 18 (IBM, Austria). Normality in the distribution of data was tested by the Kolmogorov-Smirnov test. A mixed-design ANOVA was performed to analyze interaction effects

Table 2. Resting cardiorespiratory data at low (LA) and high altitude (HA day1-3) for the placebo and the acetazolamide group

	Placebo group				Acetazolamide group				ANOVA
	LA	HA1	HA2	HA3	LA	HA1	HA2	HA3	P
HR (bpm)	67.6±9.0	81.9±9.0	79.1±7.1	76.1±8.4	69.3±8.9	79.4±13.0	84.4±8.0	84.8±10.9	0.08
BPsys (mmHg)	114.9±9.6	115.9±13.6	124.4±13.3	128.7±17.5	122.6±17.0	120.5±14.2	120.5±14.3	121.1±12.1	0.13
BPdia (mmHg)	70.3±7.1	80.7±9.1	73.3±12.1	83.4±8.8	76.8±15.5	83.4±9.7	78.4±10.7	80.0±6.3	0.37
BPmean (mmHg)	85.1±7.0	87.5±12.4	95.3±8.8	98.5±9.9	92.0±15.6	92.4±11.3	95.8±10.0	93.7±7.1	0.19
Rate-Pressure Product	7766±1259	9533±1800	9893±1701	9833±1902	8576±2070	9567±1938	10414±1790	10939±1113	0.49

HR: heart rate; BPsys, dia, mean: systolic, diastolic and mean systemic arterial blood pressure.

(pre-treatment x time). T-tests with Bonferroni correction were used to evaluate different changes between groups from low altitude to the first, second and third day at high altitude. Spearman correlation analysis was used to test the relationship between AMS scores and physiological variables. A *P* value < 0.05 was considered to indicate statistical significance. Data are presented as mean ± SD.

Results

As reported previously, on day 1 at high altitude a trend towards a reduced AMS incidence was seen in the ACZ group compared to the placebo group (P = 0.07) and the AMS score on day 1 was negatively related to resting PaO_2 (r = -0.720, P = 0.002) [11]. Subjects suffering from AMS were treated with ibuprofen (600 mg) only during the first night or in the morning of the second day at high altitude. In the afternoon of the second day at high altitude participants were free of AMS [11]. Baseline characteristics are shown in **Table 1** [11].

Resting values

Resting values of heart rate and blood pressure at low altitude and during the 3-day stay at high altitude are shown in **Table 2**. ANOVA revealed no significant interaction effects between pre-treatment and time on resting values of heart rate and blood pressure.

Exercising values

Significant interaction effects were found between pre-treatment and time on blood pressure values (**Table 3**). Changes in systolic, diastolic and mean arterial blood pressure values from low altitude to day 2 (trend for systolic blood pressure) and day 3 at high altitude were all less pronounced in the ACZ group compared to the placebo group. Interestingly, the blood pressure lowering effects of ACZ did not occur on the day of pretreatment with ACZ (first day at high altitude) but on the second and third day when ACZ was already withdrawn.

Within the placebo group but not the ACZ group correlation analyses revealed a relationship between the changes in mean arterial blood pressure values and changes in minute ventilation from low to high altitude (day 2 and day 3) during submaximal exercise (**Figure 1**).

Discussion

The presented findings demonstrate that pre-treatment with acetazolamide (2 × 125 mg) on the day of ascent to high altitude (3,480 m) resulted in a lower increase in arterial blood pressure (systolic, diastolic, mean) during submaximal exercise on day 2 (trend for systolic blood pressure) and day 3 at high altitude when ACZ was already withdrawn. Furthermore, changes in exercising mean arterial blood pressure from low altitude to high altitude were related to changes in minute ventilation during exercise only within the placebo group.

Although we did not detect any between-group changes in resting systemic blood pressure or heart rate from low altitude to the 3-day sojourn at high altitude blood pressure values increased within the placebo group but not in the ACZ group when exercising. This observation is well in line with other studies demonstrating no or only minor blood pressure changes from low to high altitude when based on daytime spot measurements during resting conditions [7, 14]. Probably more sophisticated measurements as performed by Parati and colleagues or Rhodes et al. [7, 15] would have been necessary to show more pronounced between-group differences. However, this study was predominantly designed to investigate ACZ effects on systemic blood pressure during short submaximal exercise bouts on the first 3 days at high altitude.

Table 3. Submaximal exercise responses at low (LA) and high altitude (HA) within the placebo and the acetazolamide group

	Placebo group				Acetazolamide group				ANOVA
	LA	HA1	HA2	HA3	LA	HA1	HA2	HA3	P
HR (bpm)	125±12	144±14	140±12	140±12	126±14	141±19	142±14	139±15	0.89
VE (L/min)	42.7±7.8	64.2±19.3	70.5±19.2	73.6±21.2	45.6±6.7	64.7±12.0	70.9±8.8	68.8±9.9	0.87
BPsys (mmHg)	127.6±14.9	133.4±22.5	141.1±22.8	142.1±25.7	136.6±14.6	137.4±13.5	134.8±17.9^{t}	128.9±14.9*	0.04
BPdia (mmHg)	72.9±6.8	74.0±7.5	83.4±6.9	83.7±4.7	80.4±9.0	79.9±7.5	79.4±7.8*	78.6±4.8*	0.02
BPmean (mmHg)	91.1±7.9	93.8±12.0	102.7±11.5	103.2±11.2	99.1±9.9	99.0±8.5	97.8±10.5*	95.4±7.7*	0.004
Rate-Pressure Product	15988±2829	19177±3589	19749±2531	19782±3121	17249±2724	19244±1758	18964±2299	17869±2246^{t}	0.07

HR: heart rate; VE: minute ventilation; BPsys, dia, mean: systolic, diastolic and mean systemic arterial blood pressure; *significantly different changes from low altitude (LA) compared to the placebo group; ^{t}different changes from low altitude (LA) by trend when compared to the placebo group.

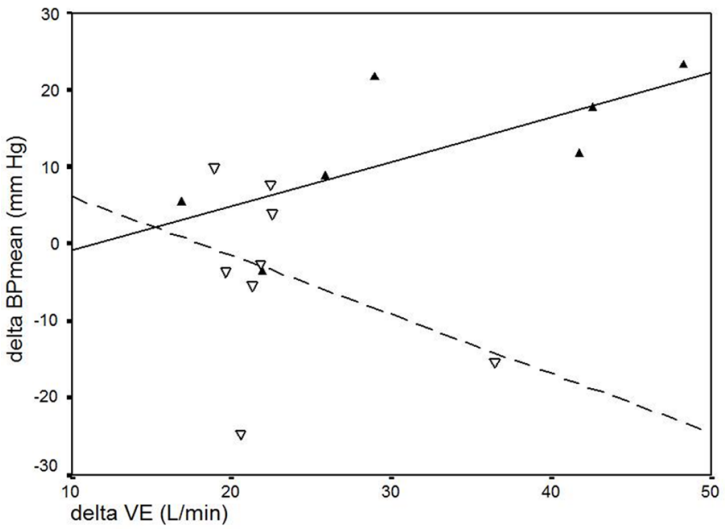

Figure 1. Relationship between delta (low altitude vs. 3rd day at high altitude) of minute ventilation (delta VE) and delta arterial mean blood pressure (BPmean) for the placebo (R^2 = 0.51) and the acetazolamide group (R^2 = 0.14) during submaximal exercise Placebo group is represented by filled triangles and the acetazolamide group by open triangles. Placebo group is represented by filled triangles and the acetazolamide group by open triangles.

In contrast to resting conditions, blood pressure responses to submaximal exercise were significantly lower on the second and the third day at high altitude when pre-treated with ACZ compared to placebo. These effects are similar to those reported by Parati and colleagues on resting peripheral and central blood pressure [7]. In their study however, ACZ was administered during the entire stay at high altitude (4559 m, 4 days). The authors suggested that the altitude-dependent blood pressure elevation seen in the placebo group has been primarily prevented by the inhibitory effect of ACZ on peripheral chemoreceptors. Which physiological mechanisms may explain our observation on the sustained effects of ACZ pre-treatment on exercising blood pressure?

Systemic blood pressure responses to high-altitude (hypoxia) exposure predominantly depend on complex interactions between chemoreceptor and baroreceptor activities and become even more complicated by metaboreceptor activation during exercise.

Primary effects of hypoxia-mediated stimulation of peripheral chemoreceptors are hyperventilation, sympathetic outflow to systemic blood vessels (vasoconstriction) and vagal activity to the heart (bradycardia) [16, 17]. However, secondary effects of hyperventilation (via lung stretch receptors) provoke vasodilation and tachycardia [16, 17]. With acclimatization hyperventilation and sympathetically mediated vasoconstriction gradually increase [17]. During acute high-altitude exposure the direct vasodilating effect of hypoxia is at least partly offset by the systemic vasoconstriction due to chemoreceptor activation but with acclimatization the increasing systemic vasoconstriction results in systemic blood pressure elevation [17]. However, baroreceptor reflex activation inhibits peripheral chemoreceptor activity and prevents, at least in healthy people, excessive blood pressure increases [16]. During exercise however, stimulation of the metaboreflex activates peripheral chemoreceptor activity [18]. Thus, progressive ventilatory and blood pressure increases might be suspected with progressive sensitization of peripheral chemoreceptors during acclimatization [17]. This was in fact what we observed in the placebo group but not after pre-treatment with ACZ (**Table 2**; **Figure 1**). ACZ acts directly inhibitory on peripheral chemoreceptor activity and thus likely contributes to the diminished blood pressure response to submaximal exercise at high altitude. The dissociation between blood pressure response and ventilation may be associated with the inhibitory effect of ACZ on peripheral chemoreceptors and its effect of central chemoreceptors by the ACZ-mediated metabolic azidosis [4]. However, exceptionally surprising is the observation that pre-treatment with ACZ did not result in different cardiorespiratory responses to submaximal exercise on the first day at altitude when ACZ has been administered but only on the second and/or the third day at high altitude when ACZ has already been withdrawn. The only reasonable explanation left is that ACZ may have prevented sensitization of peripheral chemoreceptors during acute high-altitude exposure with sustainable effects during the following 2 days. Although it has to be proved, it is conceivable that the initial inhibition of sensitization may prevent the gradually increasing sympathetic activation and blood pressure values during the succeeding days at high altitude. The proposed mechanism of ACZ action on systemic blood pressure

by inhibition of peripheral chemoreceptors seems to be reasonable, but at least two other mechanisms may be involved. First, ACZ favors the increase of nitric oxide (NO) which has been shown to play a key role in counteracting pulmonary and systemic vasoconstriction [19]. Second, systemic vasodilation may also be promoted by ACZ effects on Ca^{++} release and the opening of Ca^{++}-activated K^{+} channels [20]. However, these mechanisms might be effective only on the first day at altitude when ACZ was taken. Nevertheless, the presented findings are convincing and may have beneficial clinical consequences for exercising high-altitude sojourners suffering from cardiovascular diseases.

There are at least three limitations to be mentioned. First, although the wrist self-measuring device (OMRON R3) has been shown to measures the blood pressure reliably and accurately [12], its use during or immediately after exercise is challenging and requires careful operation and practice. Thus, all these measurements have been performed by the same very well trained investigator. Second, the sample size is relatively low but the study power seems to be high enough for comparison between ACZ and placebo effects but do not allow analyzing sex-specific effects. Third, AMS symptoms were treated with ibuprofen within the ACZ and placebo groups and have disappeared on the second day at high altitude. Although there is no evidence that blood pressure values have been influenced by ibuprofen treatment, interactions between ACZ and ibuprofen cannot be entirely excluded.

In conclusion, the presented findings demonstrate that pre-treatment with low-dose ACZ on the day of ascent to high altitude resulted in a lower systemic blood pressure response to submaximal exercise on the subsequent two days at altitude. We speculate that ACZ may have prevented sensitization of peripheral chemoreceptors during acute high-altitude exposure with sustainable effects during the following 2 days. If confirmed in further studies, these findings may have beneficial clinical consequences for exercising high-altitude sojourners suffering from cardiovascular diseases.

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Disclosure of conflict of interest

None.

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