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Effects of acetazolamide on aerobic exercise capacity and pulmonary hemodynamics at high altitudes

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Faoro V, Huez S, Giltaire S, Pavelescu A, van Osta A, Moraine J-J, Guenard H, Martinot J-B, Naeije R. Effects of acetazolamide on aerobic exercise capacity and pulmonary hemodynamics at high altitudes. *J Appl Physiol* 103: 1161–1165, 2007. First published July 5, 2007; doi:10.1152/japplphysiol.00180.2007.—Aerobic exercise capacity is decreased at altitude because of combined decreases in arterial oxygenation and in cardiac output. Hypoxic pulmonary vasoconstriction could limit cardiac output in hypoxia. We tested the hypothesis that acetazolamide could improve exercise capacity at altitude by an increased arterial oxygenation and an inhibition of hypoxic pulmonary vasoconstriction. Resting and exercise pulmonary artery pressure (Ppa) and flow (Q) (Doppler echocardiography) and exercise capacity (cardiopulmonary exercise test) were determined at sea level, 10 days after arrival on the Bolivian altiplano, at Huayna Potosi (4,700 m), and again after the intake of 250 mg acetazolamide vs. a placebo three times a day for 24 h. Acetazolamide and placebo were administered double-blind and in a random sequence. Altitude shifted Ppa/Q plots to higher pressures and decreased maximum O_2 consumption ($\dot{V}o_{2max}$). Acetazolamide had no effect on Ppa/Q plots but increased arterial O_2 saturation at rest from 84 ± 5 to 90 ± 3% ($P < 0.05$) and at exercise from 79 ± 6 to 83 ± 4% ($P < 0.05$), and O_2 consumption at the anaerobic threshold (V-slope method) from 21 ± 5 to 25 ± 5 ml·min^{-1}·kg^{-1} ($P < 0.01$). However, acetazolamide did not affect $\dot{V}o_{2max}$ (from 31 ± 6 to 29 ± 7 ml·kg^{-1}·min^{-1}), and the maximum respiratory exchange ratio decreased from 1.2 ± 0.06 to 1.05 ± 0.03 ($P < 0.001$). We conclude that acetazolamide does not affect maximum exercise capacity or pulmonary hemodynamics at high altitudes. Associated changes in the respiratory exchange ratio may be due to altered CO_2 production kinetics.

echocardiography; cardiopulmonary exercise test; hypoxic pulmonary vasoconstriction; pulmonary vascular resistance

HIGH-ALTITUDE EXPOSURE has long been known to decrease aerobic exercise capacity. This is explained by a decrease in O_2 delivery to the tissues due to decreases in both arterial oxygenation and in maximum cardiac output (6, 11). The mechanisms of altitude-related decrease in maximum cardiac output are unclear. Previously proposed explanations have been a decreased peripheral demand due to altered matching of diffusional and convectional O_2 delivery processes (37), a decrease in venous return together with a decreased chronotropic reserve (27), or a decreased central nervous system output to the heart (20).

Most recently, Ghofrani et al. (14) reported the increase in exercise capacity in healthy subjects at high altitude after the intake of sildenafil, a PDE-5 inhibitor used for erectile dysfunction (7) and shown to be efficatious in the treatment of pulmonary arterial hypertension (12). This observation raised the possibility that the limitation of cardiac output at altitude could be related to an increase in pulmonary vascular resistance (PVR) and associated with right ventricular flow output limitation (14). However, sildenafil intake was also associated with higher exercise oxygen saturations (So_2) so that no definitive conclusions could be drawn as to whether the observed improvements in exercise capacity could be accounted for by improved cardiac output, arterial O_2 content, or both (29).

We therefore got interested in revisiting the cardiovascular and exercise effects of acetazolamide, a carbonic anhydrase inhibitor of established efficacy in the treatment of acute mountain sickness (1). Acetazolamide decreases the renal reabsorption of bicarbonate and thereby induces a metabolic acidosis with increased ventilation and improved oxygenation (34). Interestingly, acetazolamide has been reported to inhibit hypoxic pulmonary vasoconstriction (HPV) in experimental animal preparations (2, 8, 17, 18) and, most recently, in humans (36). In the present study, we investigated the respective contributions of pulmonary vascular and gas exchange changes induced by acetazolamide intake on exercise capacity in normal volunteers at high altitude.

METHODS

Subjects. Fifteen lowlanders, 8 women and 7 men, aged from 16 to 61 years, mean 35 years, with a height of 169 ± 7 cm (mean ± SD) and a weight of 63 ± 12 kg, gave a written informed consent to the study, which was approved by the Ethical Committee of the Erasme University Hospital. For the 16-yr-old volunteer, informed written consent was also obtained from his parents. All the subjects were healthy and active, with an unremarkable previous history, and normal clinical examination, chest X-ray, and electrocardiogram.

Experimental design. Each subject underwent an echocardiographic examination in a semirecumbent position, at rest, and at a moderated level of exercise (pedaling without load) to increase cardiac output (Q), and an incremental maximum cycle ergometer cardiopulmonary exercise test (CPET), at sea level in Brussels, and 10 days after arrival on the Bolivian altiplano (3,700–4,700 m), before and after 24 h treatment with acetazolamide or a placebo on Huayna Potosi, at 4,700 m. Acetazolamide and placebo were administered

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Table 1. *Effects of high altitude on hemodynamics and echocardiographics variables in normal subjects*

Variables	Normoxia	High Altitude
So_2, %	98±1	85±5†
HR, beats/min	59±8	71±11†
Psa, mmHg	91±9	96±10
Q, l/min	4.6±0.9	5.2±0.8*
AT, ms	145±5	115±10†
TR, m/s	2.1±0.2	2.7±0.3†

Values are means ± SD. So_2, O_2 saturation; HR, heart rate; Psa, mean systemic arterial pressure; Q, cardiac output; AT, pulmonary artery flow acceleration time; TR, maximum velocity of tricuspid regurgitation. *$P < 0.05$, †$P < 0.001$, high altitude compared with normoxia.

double-blind and in a random sequence. The dose of acetazolamide was 250 mg three times per day for 24 h. This dose had been decided on the basis of the upper range of doses recommended for the treatment of acute mountain sickness (AMS) (1). The subjects were requested to drink 1.5 liters of water within the hour preceding the echocardiographic examination to optimize the Doppler signals.

Clinical measurements. Systemic arterial pressure (Psa) was measured by sphygmomanometry, with mean pressure calculated as diastolic pressure + one-third pulse pressure. A three-lead ECG was used to measure heart rate (HR). So_2 was measured by pulse oximetry (Konica Minolta Pulsox-3i; Konica Minolta Sensing, Osaka, Japan), which was tested and calibrated following the manufacturer's recommendations. Particular attention was paid to quality of the signal, especially during exercise, as it is known that accuracy and precision of pulse oximetry at exercise may be decreased by local perfusion (40). The presence of AMS was assessed by use of the Lake Louise consensus scoring system (28), which was obtained just before echocardiographic examination.

Echocardiography. Echocardiography was performed using a portable ultrasound system equipped with a 2.5-MHz probe (Cypress, Acuson/Siemens, Erlangen, Germany). Recordings were stored on optical disks and analyzed by two independent cardiologists experienced in echocardiography and blinded to the study. Q was estimated from left ventricular outflow tract cross-sectional area and continuous Doppler velocity-time integral measurements. Mean pulmonary artery pressure (Ppa) was calculated from the pulsed Doppler pulmonary artery flow acceleration time (AT) (21). Systolic Ppa was estimated from the maximum velocity of continuous Doppler tricuspid regurgitation (TR) (41). The intraobserver and interobserver variabilities for these measurements remained below 6%, with repeatability coefficients (39) of 14.4 ms for AT, 0.14 m/s for TR, and 0.25 l/min for Q.

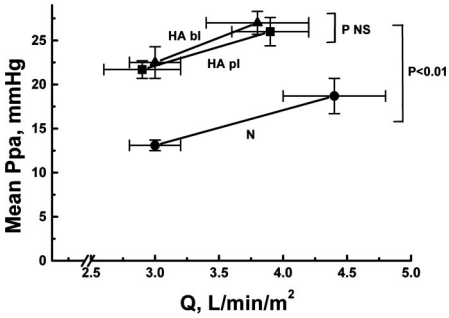

Fig. 1. Mean pulmonary artery pressure (Ppa) vs. cardiac index (Q) plots in normoxia (N), at high altitude at baseline without medication (HA bl) and after intake of a placebo (HA pl). Vertical and horizontal bars represent SE. Values of *P* are related to changes in mean Ppa (NS indicates no differences). High altitude shifted Ppa/Q plots to higher pressures, and the intake of a placebo had no effect.

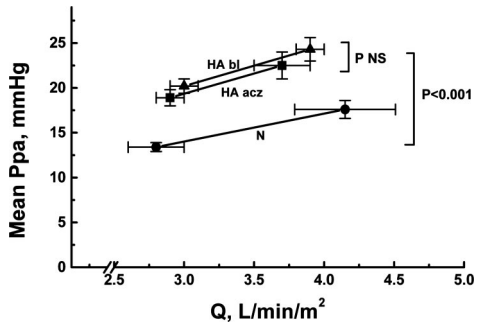

Fig. 2. Mean Ppa vs. Q plots in normoxia, in high altitude baseline without medication (HA bl) and after intake of acetazolamide (HA acz). Vertical and horizontal bars represent SE. Values of *P* are related to changes in mean Ppa. High altitude shifted Ppa/Q plots to higher pressures, and the intake of acetazolamide had no effect.

CPET. The CPET was performed in an erect position on an electronically braked cycle ergometer (Monark, Ergomedic 818 E, Vansbro, Sweden) with breath-by-breath measurements, through a tightly fitted facial mask, of ventilation ($\dot{V}_E$), O_2 uptake ($\dot{V}o_2$), and CO_2 output ($\dot{V}co_2$) using a Cardiopulmonary Exercise System (Oxycon Mobile, Jaeger, Hoechberg, Germany). After 3-min warmup at 0 W, the work rate was increased by 15–30 W according to previous CPET and predicted decrease by ~35% at high altitude so that the test would last for 10–12 min (38). Maximum $\dot{V}o_2$ ($\dot{V}o_{2max}$) was defined as the $\dot{V}o_2$ measured during the last 20 s of peak exercise. The respiratory exchange ratio (RER) was calculated as $\dot{V}co_2/\dot{V}o_2$, and O_2 pulse as $\dot{V}o_2$/HR. The ventilatory equivalents for CO_2 ($\dot{V}_E/\dot{V}co_2$) were calculated by dividing $\dot{V}_E$ by $\dot{V}co_2$. The anaerobic threshold was estimated by the V-slope method (38).

Statistics. Results are presented as means ± SE. The statistical analysis consisted in a two-way ANOVA. When the *F*-ratio of the ANOVA reached a $P < 0.05$ critical value, paired or unpaired modified Student's *t*-tests were applied as indicated to compare specific situations (39). Correlations were calculated by linear regression analysis.

RESULTS

Altitude exposure was well tolerated by the participants of the study, with minimal and transient increases in Lake Louise scores in La Paz. The day after arrival at the Potosi (4,700 m), the Lake Louise scores were increased to 4.5 ± 3, to decrease again 24 h later to 2.1 ± 2 in the placebo-treated subjects and to 3.0 ± 3 in the acetazolamide-treated group.

Table 2. *Effects of high altitude on cardiopulmonary exercise variables in normal subjects*

Variables	Normoxia	High Altitude
*W*max, W	244±81	177±29‡
$\dot{V}o_{2max}$, ml·kg^{-1}·min^{-1}	41±10	31±5†
$\dot{V}_E$ max, l/min	108±33	120±38
RER max	1.26±0.07	1.17±0.06*
HR max, beats/min	179±9	162±18*
O_2 pulse, ml/beat	16±7	12±4*
$\dot{V}o_2$ at VT, ml·kg^{-1}·min^{-1}	29±10	21±4*
Exercise So_2, %	97±2	80±5‡

Values are means ± SD. *W*max, maximum workload; $\dot{V}o_2$, O_2 uptake; $\dot{V}o_{2max}$, maximum O_2 uptake; $\dot{V}_E$ max, maximum ventilation; RER max, maximum respiratory exchange ratio; HR max, maximum HR; VT, anaerobic threshold. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, high altitude compared with normoxia.

Table 3. *Effects of acetazolamide or placebo on hemodynamics and echocardiographics variables in normal subjects at the altitude of 4,700 m*

	Placebo		Acetazolamide	
Variables	Baseline	Placebo	Baseline	Acetazolamide
LL score	5±4	2±2*	4±2	3±3
S_{O_2}, %	88±3	85±4	84±5	90±3†
$\dot{V}_E$, l/min	12±2	12±2	13±3	16±2†
HR, beats/min	70±13	63±11	72±11	67±11
Q, l/min	5.1±1	4.9±1	5.4±1	5±1
AT, ms	111±13	113±7	119±7	122±8
TR, m/s	2.7±0.2	2.8±0.3	2.7±0.2	2.6±0.2

Values are means ± SD. LL score, Lake Louise score. *$P < 0.05$, placebo compared with baseline. †$P < 0.05$, acetazolamide compared with baseline.

Effects of altitude. Altitude exposure was associated with increases in HR, Q, and TR, while AT and S_{O_2} decreased, and Psa remained unchanged (Table 1). The mean Ppa/Q plots were shifted to higher pressures (Figs. 1 and 2). Altitude decreased $\dot{V}_{O_{2max}}$, maximum workload, HR, O_2 pulse, and RER. At the anaerobic threshold, $\dot{V}_{O_2}$ was decreased (Table 2) and $\dot{V}_E/\dot{V}_{CO_2}$ increased.

Effects of acetazolamide. In the placebo group, an additional day at 4,700 m was associated with unchanged resting S_{O_2}, $\dot{V}_E$, HR, Q, AT, and TR (Table 3) and maximum workload, $\dot{V}_{O_2}$, $\dot{V}_E$, RER, HR, O_2 pulse, S_{O_2}, $\dot{V}_E/\dot{V}_{CO_2}$, or anaerobic threshold workload, $\dot{V}_{O_2}$, and HR (Table 4). Placebo had no effect on mean Ppa/Q relationships with mean Ppa calculated from AT (Fig. 2). There was no effect either on systolic Ppa/Q relationships with systolic Ppa calculated from TR (not shown).

In the acetazolamide group, an additional day at 4,700 m was associated with an increase in resting S_{O_2} and $\dot{V}_E$ but otherwise unchanged HR, Q, AT, and TR (Table 3). Acetazolamide increased workload, $\dot{V}_{O_2}$, HR, and $\dot{V}_E$ at the anaerobic threshold but had no effect on $\dot{V}_{O_{2max}}$ or maximum workload, HR, and O_2 pulse, and increased maximum exercise S_{O_2} and $\dot{V}_E/\dot{V}_{CO_2}$ (Table 4). Acetazolamide had no effect on Ppa/Q plots with mean Ppa calculated from AT (Fig. 2). There was no effect either on systolic Ppa/Q relationships with systolic Ppa calculated from TR (not shown).

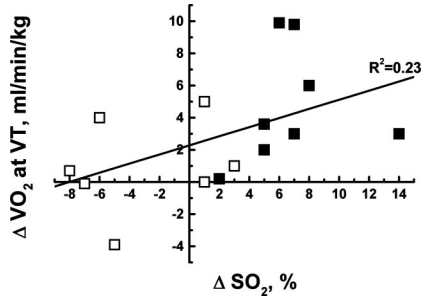

Fig. 3. Changes in oxygen consumption at the anaerobic threshold induced by the intake of acetazolamide or a placebo ($\Delta\dot{V}_{O_2}$ at VT) vs. changes in arterial oxygen saturation at rest induced by the intake of acetazolamide or a placebo (ΔS_{O_2}) plots in high altitude. Individual values are presented. White squares represent the subjects with a placebo. Black squares represent subjects with acetazolamide. Changes in $\dot{V}_{O_2}$ at the anaerobic threshold were correlated to the changes in resting S_{O_2}. Subjects under acetazolamide increased their S_{O_2} at rest and $\dot{V}_{O_2}$ at anaerobic threshold compared with placebo.

Changes in workload and $\dot{V}_{O_2}$ at the anaerobic threshold were correlated to the changes in resting S_{O_2} induced by a placebo or acetazolamide (Fig. 3).

DISCUSSION

The present results suggest that the intake of acetazolamide at the upper limit of doses used for the treatment of AMS does not affect maximum aerobic exercise capacity or pulmonary hemodynamics at high altitudes.

Acetazolamide has been shown to be efficient in the prevention and the treatment of AMS (1). The drug inhibits carbonic anhydrase, an enzyme widely distributed in the body and concentrated in the proximal renal tube and erythrocytes. This causes metabolic acidosis and increases ventilation and arterial P_{O_2} (34). The doses of acetazolamide effective in the treatment of AMS are thought to be below 5 $mg \cdot kg^{-1} \cdot day^{-1}$, but doses up to 10 $mg \cdot kg^{-1} \cdot day^{-1}$ are often used with satisfactory clinical results (1). Higher doses have more pronounced inhibition of red blood cell and tissue carbonic anhydrase, which leads to respiratory acidosis at the tissue level and further increases ventilation (34). The dose of acetazolamide used in the present study corresponded to an average of 11.5 mg/kg,

Table 4. *Effects of acetazolamide and placebo on cardiopulmonary exercise variables in normal subjects at the altitude of 4,700 m*

	Placebo		Acetazolamide	
Variables	Baseline	Placebo	Baseline	Acetazolamide
*W*max, W	177±20	166±19	176±37	167±39
$\dot{V}_{O_{2max}}$, $ml \cdot kg^{-1} \cdot min^{-1}$	31±4	29±3	31±6	29±7
$\dot{V}_E$ max, l/min	104±22	100±15	134±45	132±44
RER max	1.14±0.06	1.10±0.07	1.20±0.06	1.05±0.03‡
HR max, beats/min	157±22	162±18	159±10	164±12
O_2 pulse, ml/beat	12±4	11±3	13±4	12±4
Exercise S_{O_2}, %	80±3	81±4	79±6	83±4*
$\dot{V}_E/\dot{V}_{CO_2}$ at end exercise	50±8	54±10	53±6	63±7†
*W*max at VT, W	105±23	113±36	101±38	131±42†
$\dot{V}_{O_2}$ at VT, $ml \cdot kg^{-1} \cdot min^{-1}$	22±3	23±5	21±5	25±5†
HR at VT, ml/beat	137±24	148±20	134±13	154±11‡

Values are means ± SD. VT, anaerobic threshold measure by V-slope method; $\dot{V}_{CO_2}$, CO_2 output. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, acetazolamide compared with baseline.

most likely optimal to increase arterial oxygenation through enhanced metabolic acidosis-increased chemosensitivity (1).

In the present study, acetazolamide intake was associated with no changes in the Lake Louise AMS score. However, this effect was observed on average below the threshold score of 7 considered to be diagnostic of severe AMS (28). The absence of improvement of the AMS score after acetazolamide intake may be related to nonspecific side effects of the drug, which include dizziness, somnolence, asthenia, dyspnea, headache, nausea, vomiting, loss of appetite, and gastrointestinal discomfort (1).

Acetazolamide has been reported to inhibit HPV in experimental animal models (2, 8, 17, 18) and, more recently, in humans (36). The inhibition of HPV by acetazolamide has been shown to be independent of the inhibition of carbonic anhydrase or changes in intracellular pH or membrane potential but entirely explained by a specific inhibition of hypoxia-induced calcium responses (32). The inhibition of human HPV by acetazolamide was reported after the intake of 250 mg of the drug three times per day during 3 days and estimated by changes in TR in normal subjects exposed to 4 h of hypoxic breathing (36). In the present study, the same dose of acetazolamide taken during 24 h did not reverse hypoxic pulmonary hypertension in subjects who had been acclimatized for 10 days at altitudes ~4,000 m before climbing to 4,700 m. A false-negative result appears unlikely, as pulmonary artery pressure was estimated using two independent Doppler measurements, respectively: the acceleration time of pulsed Doppler pulmonary flow waves (21) and the maximum velocity of continuous Doppler tricuspid regurgitation (41). Both methods have been shown to allow for satisfactory estimates of pulmonary artery pressures (26), with the advantage of a higher recovery rate of good quality signals for pulmonary flow waves in case of no or only mild pulmonary hypertension, as seen at high altitudes (22, 26). In addition, the measurements were repeated at exercise to refine the measurement of pulmonary vascular resistance by measurements of pressures at two different flows (25).

A possible explanation for the discrepancy between the present results and those reported by Teppema et al. (36) may be in the time course of hypoxia-induced pulmonary hypertension. Previous studies in normal subjects indicate that the reversibility of hypoxia-induced pulmonary hypertension with oxygen administration decreases rapidly over time, with no return to baseline already after a few hours, and marked loss of reversibility after only a few days at high altitudes (9, 15, 23). These observations are suggestive of early progression from hypoxic constriction to remodeling and explain the loss or decreased efficacy of acute vasodilating interventions. However, it would be interesting to see if higher doses of acetazolamide would be able to reverse established hypoxic pulmonary hypertension.

Acetazolamide in normoxic conditions has been reported either to decrease (10, 31) or to leave unchanged (33, 35) aerobic exercise capacity. Acetazolamide-induced decrease in exercise capacity has been explained by relative dehydration (3, 5) and muscle acidosis due to impaired buffer capacity (19). The effects of acetazolamide on hypoxic exercise capacity has been reported variably, with decreased (4, 13, 16), increased (24, 31), or unchanged $\dot{V}O_{2max}$ and maximal workload (10, 33). These discrepant results are related to variable experimental conditions, dose regimens, altitude acclimatization, exercise mode, and degree of AMS during exercise testing. In better standardized exhaustive constant-work rate, one-leg knee-extension exercise compared with placebo, acetazolamide impaired endurance performance at sea level but not at altitude, which the authors explained by offsetting secondary effects of acidosis and increased arterial oxygenation (10).

In the present study, we tried to limit acetazolamide-induced dehydration by liberal and unlimited intake of fluid and food. HR and Q were unchanged compared with placebo-treated controls. However, we cannot exclude that isosmotic hypovolemia previously reported after intake of acetazolamide (4) could have affected our results. On the other hand, the finding of absence of effect of acetazolamide on maximum workload and $\dot{V}O_{2max}$ is in keeping with previous work (10, 33). The maximum RER was decreased, which has also been previously reported (31). This could be explained by altered $\dot{V}CO_2$ kinetics, which could also have delayed the anaerobic threshold as measured by the V-slope method, even though there are data suggesting that the intake of the drug does not delay the appearance of lactic acid in the blood (30). We found a significant correlation between increased S_{O_2} and anaerobic threshold $\dot{V}O_2$, but this is of uncertain causality.

In summary, acetazolamide at the upper doses recommended for the treatment of AMS does not affect pulmonary vascular resistance or maximum aerobic exercise capacity in subjects acclimatized to high altitude. Associated decrease in the RER may be due to altered $\dot{V}CO_2$ kinetics.

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