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Dexamethasone Improves Maximal Exercise Capacity of Individuals Susceptible to High Altitude Pulmonary Edema at 4559 m

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Abstract

Siebenmann, Christoph, Bloch, Konrad E., Lundby, Carsten, Yvonne Nussbaumer-Ochsner, Michèle Schoeb, and Marco Maggiorini. Dexamethasone improves maximal exercise capacity of individuals susceptible to high altitude pulmonary edema at 4559 m. *High Alt. Med. Biol.* 12:169–177, 2011.—We have previously demonstrated that prophylactic intake of dexamethasone improves maximal oxygen uptake (VO_2max) in high altitude pulmonary edema (HAPE) susceptible subjects 4 to 6 h after a 2-day climb to 4559 m. However, since with this ascent protocol HAPE usually develops after the first night at 4559 m or later, we hypothesized that a continued dexamethasone prophylaxis would result in an even more pronounced improvement of VO_2max after an additional night at high altitude.

VO_2max of 24 HAPE susceptibles was evaluated on a bicycle ergometer at an altitude of 490 m and at 24 h after rapid ascent to 4559 m. Subjects were divided into two groups: The control group ($n = 14$) performed both tests without dexamethasone, whereas the dexamethasone group ($n = 10$) received dexamethasone 8 mg twice a day (b.i.d), starting 24 h prior to ascent.

At 4559 m, VO_2max was $61\% \pm 6\%$ of the baseline value in the control group and $70\% \pm 9\%$ in the dexamethasone group ($p = 0.025$). Similarly, O_2 pulse ($\text{VO}_2/\text{heart rate}$) was $68\% \pm 7\%$ and $77\% \pm 11\%$ of baseline, respectively ($p = 0.043$). Arterial O_2 saturation at maximal exercise did not differ between groups, whereas at rest it was $83\% \pm 10\%$ in the control group and $91\% \pm 4\%$ in the dexamethasone group ($p = 0.009$).

Dexamethasone prophylaxis increased VO_2max of HAPE-susceptible individuals after the first night at 4559 m without affecting arterial O_2 saturation at maximal exercise. This might be explained by a sustained effect of dexamethasone on maximal cardiac output and pulmonary O_2 diffusion, both resulting in enhanced convective O_2 transport to the locomotor muscles.

Key Words: hypoxia; VO_2max ; pulmonary circulation

Introduction

MAXIMAL O_2 UPTAKE (VO_2MAX) IS REDUCED in acute hypoxia (Wagner, 2000; Calbet and Lundby, 2009) owing to two main mechanisms (Calbet et al., 2003): First, the arterial Po_2 (PaO_2) is decreased due to both a lower alveolar Po_2 and a resulting pulmonary diffusion limitation for O_2 (Wagner, 2000; Calbet et al., 2003; Lundby et al., 2006). Second, maximal cardiac output is reduced in severe hypoxia

owing to a decrease in stroke volume and maximal heart rate (HR) (Calbet et al., 2003). Each mechanism contributes to a lower O_2 delivery to the locomotor muscles and therefore a decline in VO_2max .

The decline in VO_2max might be even more prominent in persons who develop a subclinical (Cremona et al., 2002) or overt high altitude pulmonary edema (HAPE) (Bartsch et al., 2003). HAPE is a noncardiogenic edema, typically occurring after rapid ascent to altitudes higher than 2500 m (Bartsch

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et al., 2003). In individuals susceptible to HAPE (HAPE-s), the mechanism of HAPE pathogenesis is an excessive and inhomogeneous increase in pulmonary artery resistance because of vasoconstriction in response to acute hypoxia (Bartsch et al., 2005). This leads to overperfusion of remaining patent vessels and subsequent injury of pulmonary capillary walls, with leakage of red blood cells and proteins into the airways and alveoli (Hultgren, 1996). Although HAPE is a life-threatening and rare disease, subclinical pulmonary extravascular fluid accumulation is more prevalent and may be present in about 75% of non-HAPE-s mountaineers examined shortly after arrival at an altitude of 4559 m (Cremona et al., 2002).

The pathogenesis of HAPE may potentiate the VO_2max -reducing factors in acute hypoxia. Interstitial pulmonary edema elongates the diffusion distance of O_2 from the alveoli into the pulmonary capillaries (Steinacker et al., 1998) and negatively influences ventilation-perfusion matching, thereby deteriorating respiratory efficiency during heavy exercise (Podolsky et al., 1996). All these factors result in a more prominent decrease in PaO_2 . In addition, excessive elevations in pulmonary arterial resistance could increase the afterload of the right ventricle and reduce its stroke volume, thereby decreasing left ventricular preload and maximal cardiac output (Ghofrani et al., 2004).

An efficient intervention to avoid health threat in climbers and travelers that do not have the opportunity to acclimatize before an ascent to altitudes higher than 2500 m is the prophylactic administration of dexamethasone, a synthetic glucocorticoid. Dexamethasone is known to be effective as a prophylaxis against acute mountain sickness (AMS) (Johnson et al., 1984) and even superior to the broadly used carbonic anhydrase inhibitor acetazolamide (Ellsworth et al., 1991). If treatment is started prior to exposure to hypoxia, dexamethasone prophylaxis decreases pulmonary arterial resistance (Maggiorini et al., 2006) and enhances alveolar fluid clearance (Folkesson et al., 2000; Noda et al., 2003; Guney et al., 2007). Both mechanisms contribute to a lower incidence of HAPE. Dexamethasone was also found to increase resting PaO_2 in acute hypoxia (Maggiorini et al., 2006).

The effect of dexamethasone on HAPE-s has been broadly examined in resting conditions; however, the influences on exercise performance are poorly explored. Fischler and colleagues (Fischler et al., 2009) reported that dexamethasone taken before a 2-day ascent to the Capanna Regina Margherita research facility (Italy, 4559 m) increased the VO_2max of HAPE-s subjects measured 4 to 6 h after arrival. However, since HAPE normally develops after 2 to 5 days of hypoxic exposure (Bartsch et al., 2005) and, in our experience with this ascent profile, usually after the first night at the Margherita hut or later, the adverse impact of HAPE pathogenesis on VO_2max may be more pronounced after a longer period of hypoxic exposure, which may enhance the beneficial effect of dexamethasone. We therefore tested the hypothesis that the benefit of a dexamethasone prophylaxis on VO_2max would be maintained and more pronounced in HAPE-s subjects after staying an additional night at the Margherita hut.

Methods

The current study includes 16 of 25 HAPE-s mountaineers who initially participated in a randomized, double-blind, placebo-controlled study in 2007. Because of 9 dropouts due

to bad weather conditions and incapacitating acute mountain sickness (AMS) before arriving at 4559 m, 8 additional HAPE-s mountaineers were recruited according to the same inclusion criteria in a complementary open-label study in 2009. Both studies followed similar protocols and were approved by the Ethical Committee of the University of Zurich and conformed to the Declaration of Helsinki. Subjects gave written informed consent to participation.

Subjects

In total, 24 subjects were finally included into the present analysis. Criteria of inclusion was susceptibility to HAPE, which was defined by a history of radiologically or clinically diagnosed HAPE and confirmed in an interview by a physician with long-time experience in high altitude medicine. Criteria of exclusion included age below 18 and above 65 yr, chronic intake of medication, or previous diagnosis of cardiopulmonary and other chronic diseases. Further, we excluded mountaineers who had spent more than 5 nights at an altitude higher than 2500 m within the last 30 days of the beginning of the investigation. Anthropometric data of the subjects included in the study are summarized in Table 1.

Protocol

Baseline examinations were conducted at the University Hospital of Zurich (490 m). Subjects spent 2 days in the hospital performing a baseline cardiopulmonary exercise test (CPET) in the late afternoon (2007) or during the course of the morning (2009). In both settings, CPET was performed at least 2 h after the last meal.

Two to three weeks after baseline measurements, all study participants traveled to Alagna (Italy, 1205 m) in groups of 2 to 4. From there they were carried by cable car to an altitude of 2900 m. They continued by foot to the Gnifetti hut (3647 m), where they arrived in the late afternoon and spent the night. The following morning they reached the Margherita hut (4559 m) after 4 to 6 h of ascent. Throughout the entire trip, all subjects were accompanied by a professional mountain guide. CPET was performed the morning following night 1 spent at the Margherita hut. Subjects then stayed at the hut 3 additional consecutive nights for further research and climbed back down in the morning of day 5.

Medication

The 16 subjects from the 2007 study were randomized to receive either 8 mg dexamethasone b.i.d (Fortecortin, Merck,

TABLE 1. ANTHROPOMETRIC DATA OF THE SUBJECTS

| | Control group | Dexamethasone group | p-values |
|--------------------------|---------------|---------------------|----------|
| Number of subjects | 14 | 10 | |
| Male | 9 | 8 | |
| Female | 5 | 2 | |
| Age (years) | 45 ± 8.6 | 47 ± 9.6 | 0.51 |
| Height (m) | 1.74 ± 0.08 | 1.72 ± 0.05 | 0.34 |
| Weight (kg) | 70.2 ± 7.2 | 75.7 ± 12.9 | 0.31 |
| BMI (kg/m ²) | 23.1 ± 1.5 | 25.5 ± 3.7 | 0.15 |

Control group = untreated group; Dexamethasone group = Dexamethasone-treated group; BMI = Body mass index.

Whitehouse, NJ, USA) (dexamethasone group, $n=10$) or placebo (control group, $n=6$) during their stay at high altitude, with treatment beginning 24h prior to ascent. They started intake autonomously, but the remaining number of pills and further intake were controlled at the Margherita hut. Dexamethasone and placebo were packed into identical white capsules so that neither subjects nor investigators could distinguish between them. However, open-labeled emergency treatment with dexamethasone was always available for subjects of the control group presenting with severe AMS.

The 8 additional subjects included in the 2009 open-label study to increase the number of participants within the control group (final $n=14$) did not receive placebo or dexamethasone before CPET. As in the 2007 study, dexamethasone was provided as emergency treatment. However, in both years, no participant randomized to the control group required emergency treatment with dexamethasone before CPET.

Assessment of AMS and HAPE

In the morning before CPET, AMS was assessed by the Lake Louise protocol, which consists of an interview and a clinical examination (for details, see Maggiorini et al., 1998). A score >4 was used as an indicator for AMS. Further, subjects were regularly examined for symptoms and signs of HAPE. These examinations included daily auscultation of the lungs and chest radiography on the second day at the Margherita hut.

Conduction of CPET

CPET was performed on an electronically braked bicycle ergometer in an upright position (Cyclus 2, RBM Elektronik, Leipzig, Germany). Subjects wore a face mask that covered the mouth and nose for complete breath collection. Amperometric solid-state electrolyte sensors continuously measured O_2 and CO_2 concentration in the expired gas. Results were monitored and saved as breath-by-breath values on a portable computer. The utilized system (ZAN 600 USB, nSpire Health, Louisville, KY, USA) was calibrated immediately before each test. HR was detected by electrocardiogram (CardioCollect 12, Spacelabs Healthcare, Feucht, Germany), and peripheral arterial O_2 saturation (SpO_2) was measured by pulse oximetry (Masimo SET Radical, Inspiration Medical, Bochum, Germany) on the subject's earlobe. Estimated maximal voluntary ventilation (MVV) was calculated as forced expiratory volume in 1 sec (FEV_1) $\times 40$ (ACCP, 2003).

Resting values were obtained with the subjects sitting still on the bicycle for 2 min. They then started exercising at a workload (W) of 50 W that was increased by 10 to 40 W/min according to a progressive ramp protocol individually tailored to lead to exhaustion within 8 to 12 min (ACCP, 2003). To maintain test duration, increases in work rate were approximately 30% lower at 4559 m than at baseline (490 m). During the last minutes, subjects were vigorously motivated to continue until maximal exhaustion. All subjects reached maximal exhaustion according to standard criteria (ACCP, 2003).

Respiratory parameters of 2 subjects of the control group could not be properly measured because of technical difficulties while at 4559 m; therefore, these parameters,

along with the corresponding low-altitude values, were discarded.

Statistical analysis

Data were analyzed using Statistica 6.0 (Statsoft, USA) To evaluate differences between the two groups, the values at high altitude were compared in percents of the values at low altitude using a Mann-Whitney U test for nonparametric and independent samples. The effect of the exposure to high altitude within each group was evaluated by the Wilcoxon matched pairs test. Results are given as mean \pm SD; a p value of <0.05 was considered statistically significant.

Results

Baseline testing

Baseline examinations at 490 m revealed that subjects were healthy, with normal pulmonary functions and free of signs of pulmonary hypertension. None were on any medications or supplements that might interfere with our experiments. All were able and motivated to perform CPET to complete exhaustion (Table 2).

Altitude exposure

Exposure to hypoxia was well tolerated by all subjects, and they were able to perform the exercise trials (Table 2). Nevertheless, Lake Louise scores evaluated in the morning before CPET were 5.71 ± 2.55 in the control group and 3.70 ± 1.95 in the dexamethasone-group ($p=0.036$); a Lake Louise score >4 , indicating the presence of AMS, was found in 9 controls, but in only 3 subjects of the dexamethasone group. No signs of HAPE were observed in either group on the first 2 days at the Margherita hut.

Resting HR was increased by 26% in the control group and reduced by 2% in the dexamethasone group ($p=0.007$) from baseline values, while resting SpO_2 was $83\% \pm 10\%$ in the control group and $91 \pm 4\%$ in the dexamethasone group, respectively ($p=0.009$). Table 2 summarizes the CPET results for both conditions and illustrates the influence of the rapid ascent to 4559 m on exercise capacity. In both groups, hypoxia induced a substantial decrease in VO_{2max} . Nevertheless, the respiratory exchange ratio ($RER = V_{CO_2}/V_{O_2}$) was similar to baseline in both groups, indicating maximal effort at high altitude despite the presence of AMS, especially in the control group, and no significant difference in RER between groups was observed. Further, no correlation was found between Lake Louise scores and RER ($R^2=0.06$).

Effects of dexamethasone prophylaxis on maximal exercise capacity

To evaluate the influence of the dexamethasone prophylaxis on maximal exercise capacity, we compared the results achieved at 4559 m in percents of the baseline values (Table 3). Compared with the control group, the decrease in maximal workload (W_{max}) was 7% smaller in the dexamethasone group ($p=0.004$). This was accompanied by an almost 10% smaller decrease in VO_{2max} in the dexamethasone group ($p=0.025$). Despite these differences, minute ventilation (V_E) was similar between groups and to values obtained at low altitude, as was V_E/V_{O_2} . However, V_E/V_{CO_2} at high altitude was increased in both groups, whereas the increase was

TABLE 2. CARDIORESPIRATORY PARAMETERS DURING MAXIMAL EXERCISE AT 490 M AND 4559 M

| Group | Zurich, 490m | | Margherita, Day 2, 4,559 m | | p-value for altitude effect | |
|----------------------------------|---------------|---------------------|----------------------------|---------------------|-----------------------------|---------------------|
| | Control group | Dexamethasone group | Control group | Dexamethasone group | Control group | Dexamethasone group |
| VO ₂ max [L/min] | 3.58 ± 0.69 | 3.59 ± 0.78 | 2.17 ± 0.43 | 2.47 ± 0.44 | 0.002 | 0.005 |
| VCO ₂ [L/min] | 4.15 ± 0.82 | 4.18 ± 0.89 | 2.44 ± 0.55 | 2.93 ± 0.57 | 0.002 | 0.005 |
| Wmax [W] | 279 ± 68 | 300 ± 58 | 178 ± 51 | 213 ± 50 | 0.001 | 0.005 |
| HR [1/min] | 179 ± 8 | 179 ± 14 | 164 ± 12 | 163 ± 13 | 0.002 | 0.008 |
| V _E [L/min] | 131 ± 22.7 | 131 ± 22.8 | 129 ± 28.9 | 137 ± 26 | 0.754 | 0.241 |
| (% max) | (85) | (91) | (93) | (102) | | |
| MVV [L/min] | 154 ± 21.4 | 145 ± 21.1 | 138 ± 22.2 | 136 ± 23.1 | 0.002 | 0.007 |
| V _E /VO ₂ | 37.1 ± 5.2 | 37.0 ± 5.3 | 59.3 ± 8.0 | 56.0 ± 7.7 | 0.002 | 0.005 |
| V _E /VCO ₂ | 32.0 ± 4.2 | 31.8 ± 4.6 | 53.1 ± 7.0 | 47.3 ± 6.9 | 0.002 | 0.005 |
| F [1/min] | 45.8 ± 5.4 | 47.1 ± 7.5 | 50.4 ± 9.8 | 50.8 ± 9.2 | 0.060 | 0.074 |
| V _T [L] | 2.87 ± 0.43 | 2.83 ± 0.60 | 2.58 ± 0.49 | 2.74 ± 0.51 | 0.002 | 0.445 |
| F/V _T [1/[L*min]] | 16.3 ± 3.6 | 17.9 ± 6.6 | 20.4 ± 6.4 | 19.5 ± 6.7 | 0.005 | 0.093 |
| RER | 1.16 ± 0.04 | 1.16 ± 0.05 | 1.12 ± 0.07 | 1.19 ± 0.07 | 0.084 | 0.333 |
| Spo ₂ [%] | 96.1 ± 2.7 | 97.6 ± 2.2 | 72.6 ± 14.2 | 74.0 ± 8.98 | 0.001 | 0.005 |

Control-group = untreated group; Dexamethasone-group = Dexamethasone-treated group; VO₂max = maximal O₂ uptake; VCO₂ = CO₂ output; Wmax = maximal workload; HR = heart rate; V_E = minute ventilation; MVV = calculated maximal voluntary ventilation; F = respiratory frequency; V_T = tidal volume; RER = respiratory exchange ratio (VCO₂/VO₂); Spo₂ = arterial O₂ Saturation.

almost 18% higher in the control group than in the dexamethasone group ($p = 0.0001$). Tidal volume (V_T) tended to be larger in the dexamethasone group ($p = 0.050$) in group comparison, whereas it was reduced at high altitude in the control group only.

At maximal exercise, neither HR nor Spo₂ differed between the groups. O₂ pulse (VO₂/HR), an indirect measurement of stroke volume (ACCP, 2003), was 67.7% ± 6.5% of the baseline value in the control group and 76.6% ± 11.2% in the dexamethasone group ($p = 0.043$). Individual responses in Wmax, VO₂max and Spo₂ to the hypoxic exposure are illustrated in Fig. 1.

Figure 2 depicts the correlation between VO₂max and Spo₂ at 4559 m, both expressed as percentages of the values

at low altitudes. A strong and significant correlation was present in the dexamethasone group, but not in the control group.

Effects of the placebo treatment

To establish the effect of the placebo treatment that was applied in 2007, but not in 2009, to subjects of the control group, the hypoxic VO₂max of these two subgroups was compared. In the placebo-treated control-group subjects of 2007, VO₂max was 60% ± 7% of the baseline value, whereas control-group subjects of 2009 that did not receive placebo obtained 62% ± 4% ($p = 0.7$). Further, VO₂max in both subgroups was significantly lower than in the dexamethasone group.

Discussion

The purpose of the present study was to test the hypothesis that a prophylactic oral administration of dexamethasone 8 mg b.i.d, starting 24 h prior to ascent and maintained throughout an overnight stay at 4559 m, provides persistent increases in hypoxic VO₂max in HAPE-s subjects. Our major finding is that dexamethasone significantly reduced the hypoxia-related decline in VO₂max and resting Spo₂. Further, symptoms of AMS were significantly abated in the dexamethasone group.

Our results confirm and extend a previous study that reported an improvement of VO₂max after rapid ascent to 4559 m by prophylactic dexamethasone administration (Fischler et al., 2009). However, in the earlier investigation, CPET was conducted only 4 to 6 h after arrival at 4559 m and thus several hours or days before development of HAPE generally occurs (Bartsch et al., 2005). To evaluate whether continued administration of dexamethasone would provide persistent and more distinct improvements of VO₂max, the present results were collected following an additional 24 h of hypoxic exposure. Indeed, in the earlier study, VO₂max of untreated subjects decreased by 52% from values at low altitude, and dexamethasone prophylaxis reduced this decrease

TABLE 3. CARDIORESPIRATORY PARAMETERS DURING MAXIMAL EXERCISE AT 4559 M IN PERCENTS OF BASELINE VALUES

| | Control group | Dexamethasone group | p-value |
|--------------------------------------|---------------|---------------------|---------|
| VO ₂ max [%] | 60.9 ± 5.7 | 69.7 ± 8.6 | 0.025 |
| VCO ₂ [%] | 58.9 ± 7.1 | 71.0 ± 8.4 | 0.003 |
| Wmax [%] | 63.4 ± 6.2 | 70.5 ± 4.3 | 0.004 |
| HR [%] | 91.7 ± 5.9 | 91.4 ± 6.3 | 0.98 |
| V _E [%] | 97.6 ± 10.0 | 105.9 ± 16.0 | 0.16 |
| V _E /VO ₂ [%] | 160.5 ± 11.0 | 151.8 ± 11.2 | 0.16 |
| V _E /VCO ₂ [%] | 166.4 ± 11.6 | 148.8 ± 7.9 | 0.0001 |
| F [%] | 109.7 ± 14.0 | 108.0 ± 12.9 | 0.77 |
| V _T [%] | 89.6 ± 8.2 | 98.1 ± 9.7 | 0.05 |
| F/V _T [%] | 124.3 ± 25.8 | 111.1 ± 18.4 | 0.14 |
| RER [%] | 96.6 ± 6.6 | 102.0 ± 5.3 | 0.06 |
| Spo ₂ [%] | 75.5 ± 13.6 | 75.7 ± 7.9 | 0.58 |

Control group = untreated group; Dexamethasone group = Dexamethasone-treated group; VO₂max = maximal O₂ uptake; VCO₂ = CO₂ output; Wmax = maximal workload; HR = heart rate; V_E = minute ventilation; MVV = calculated maximal voluntary ventilation; F = respiratory frequency; V_T = tidal volume; RER = respiratory exchange ratio (VCO₂/VO₂); Spo₂ = arterial O₂ Saturation.

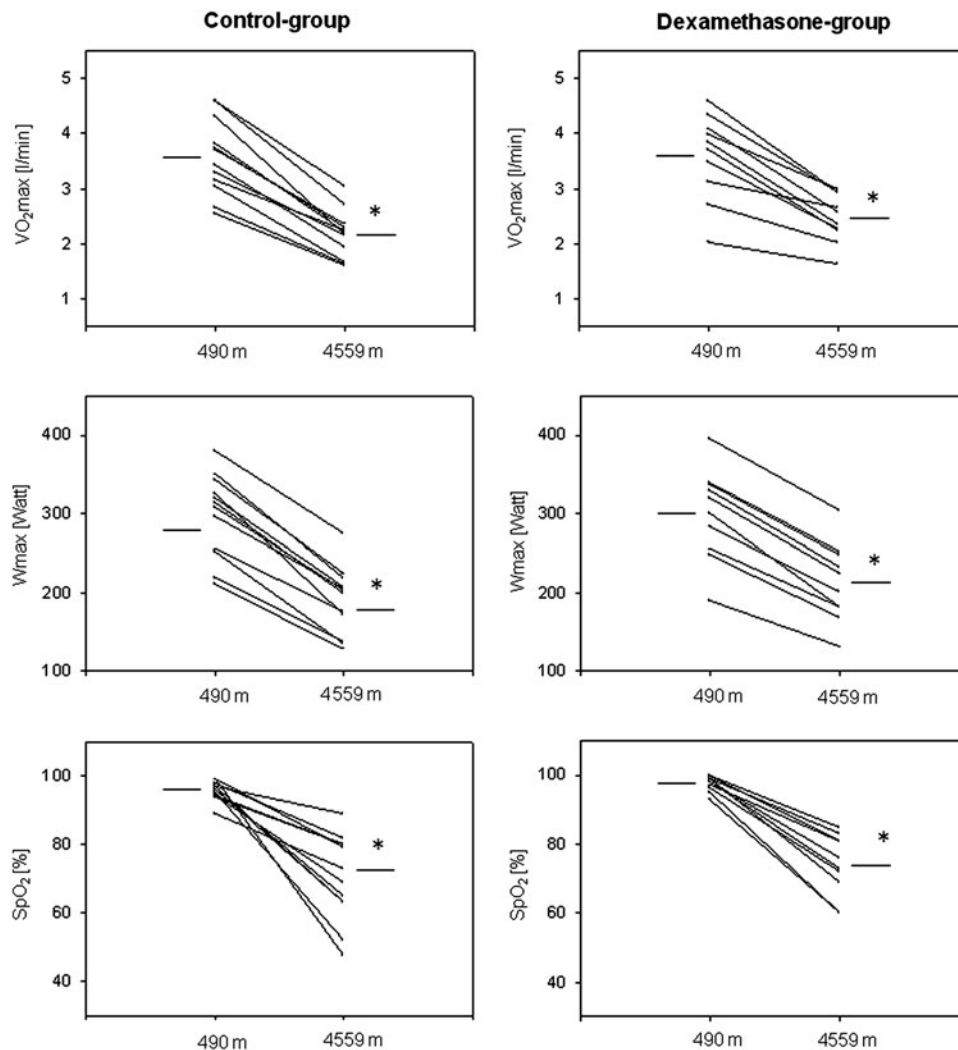


FIG. 1. Effect of acute hypoxia on treated and untreated subjects. Control group, untreated group; dexamethasone group, dexamethasone-treated group; $VO_2\text{max}$, maximal O_2 uptake; $W\text{max}$, maximal workload; SpO_2 , arterial O_2 saturation during maximal exercise; horizontal lines represent mean values at both altitudes; * $p < 0.05$ vs. mean value at 490 m.

by 7% (Fischler et al., 2009). The present study shows that dexamethasone reduced the 39% decrease in the control group subjects by 9%. Furthermore, in the earlier study (Fischler et al., 2009), dexamethasone treatment improved only $VO_2\text{max}$, but not $W\text{max}$, which is surprising, because acute hypoxia has been shown not to alter external work efficiency (Lundby et al., 2007). In contrast, we observed dexamethasone to improve $W\text{max}$ and $VO_2\text{max}$ similarly, which is in accordance with an unchanged work efficiency (VO_2/W relationship) in hypoxia. Our observations further extend the data by Fischler and colleagues (2009); they tested their subjects in a very unusual semirecumbent exercise position, whereas we demonstrate beneficial effects of dexamethasone on $VO_2\text{max}$ in a more familiar upright body position.

Generally, rapid ascent to high altitude is associated with an impairment of $VO_2\text{max}$ that becomes more severe with increasing altitude. According to Fulco and colleagues (1998), the expected decrease at 4559 m compared with 490 m is about 30%. In accordance with this, previous observations on $VO_2\text{max}$ at the Margherita hut in non-HAPE-s subjects report an average decrease of 31% (Lundby, 2008) or 21% (Lundby

et al., 2001). In the current study, rapid ascent led to a reduction of 39% in the control group. Although comparisons between studies should be interpreted cautiously since different protocols and measurement techniques may influence the outcomes, our results indicate a rather marked deterioration in exercise capacity in untreated HAPE-s subjects compared with normal individuals. This is in line with previous findings (Fischler et al., 2009) that reported an even larger impairment, with untreated HAPE-s persons decreasing by 52%. The additional impairment in that study may be explained by the semirecumbent exercise position, which reduces $VO_2\text{max}$ in healthy subjects at sea level (Pedersen et al., 1996) and might additionally impair exercise in HAPE-s subjects at high altitude by spreading extravascular fluid, originally trapped by gravity in the basal region of the lung, over a larger pulmonary area. Further, CPET in the earlier study was performed only a few hours after the subjects' arrival at the Margherita hut. The strenuous ascent on the testing day may have further contributed to the larger decrease in maximal exercise capacity by fatiguing the subjects (Fischler et al., 2009).

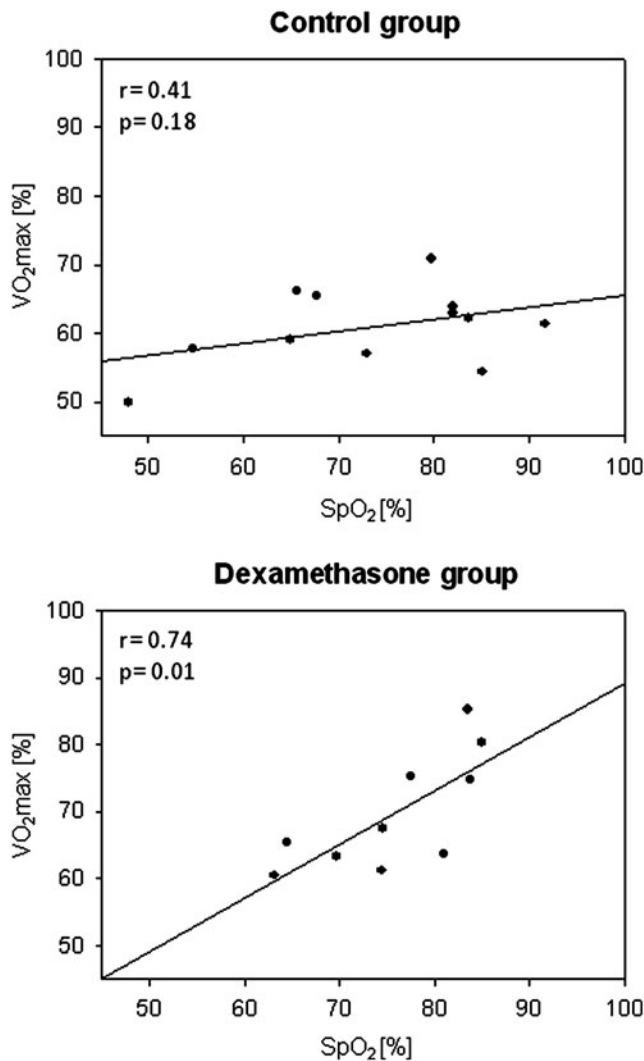


FIG. 2. Correlation between arterial O_2 saturation and maximal O_2 uptake at 4559 m. Control group, untreated group; dexamethasone group, dexamethasone-treated group; VO_{2max} , maximal O_2 uptake expressed in percent of value at low altitude; SpO_2 , arterial O_2 saturation during maximal exercise expressed in percent of value at low altitude.

What are the mechanisms by which dexamethasone induces improvements in VO_{2max} in HAPE-s individuals? During acute exposure to altitudes higher than 4000 m, VO_{2max} is mainly decreased by reductions in arterial O_2 content and in maximal cardiac output, both contributing to an attenuation in convective O_2 transport to the locomotor muscles (Calbet et al., 2003). The dexamethasone prophylaxis may beneficially influence both of these factors: in acute hypoxia, dexamethasone acts as a vasodilator that abates the exaggerated rise in pulmonary artery pressure that is characteristic for the development of HAPE (Maggiolini et al., 2006). Increases in hypoxic VO_{2max} with pulmonary vasodilatation have been reported previously in studies that induced vasodilatation with the phosphodiesterase-5 inhibitor sildenafil (Ghofrani et al., 2004; Richalet et al., 2005; Faoro et al., 2007). In these studies, the performance-enhancing effect was explained by either a reduction in right ventricular afterload, resulting in higher cardiac output (Ghofrani et al., 2004), an improved

arterial oxygenation (Faoro et al., 2007), or both (Richalet et al., 2005).

In the present data, O_2 pulse is higher in the dexamethasone group than in the control group despite similar maximal HR and SpO_2 . This suggests that the dexamethasone prophylaxis led to an increase in maximal cardiac output, which may enhance peripheral O_2 delivery and therefore VO_{2max} . Although there is some concern about using O_2 pulse as an approximation for stroke volume during exercise in hypoxic environments owing to arterial O_2 desaturation (ACCP, 2003), we argue that the estimation remains applicable in our data, because exercise SpO_2 is very similar in both groups, indicating a fairly equal amount of transported O_2 in a given volume of blood. Of interest, a similar exercise SpO_2 was also reported previously (Fischler et al., 2009) and is observed despite the higher levels VO_{2max} and likely cardiac output that may shorten pulmonary transit time and promote pulmonary diffusion limitation in the dexamethasone group (Hopkins et al., 1996). Therefore, the lack of a difference in exercise SpO_2 between subject groups in the present study indicates an enhanced pulmonary O_2 diffusion in the dexamethasone group, allowing for SpO_2 to obtain similar levels as in the controls despite higher exercise intensities, an explanation that is supported by the finding of higher resting SpO_2 in the dexamethasone group. An improved pulmonary O_2 diffusion in subjects receiving dexamethasone may have emerged from either an optimized blood distribution over the pulmonary vessels, because subclinical HAPE has been reported to promote ventilation-perfusion inequalities (Podolsky et al., 1996), or from an elevated transpulmonary O_2 diffusion, resulting from a reduction in pulmonary extravascular fluid accumulation (Steinacker et al., 1998). These explanations are supported by the lower VE/VCO_2 in the dexamethasone group, which indicates a better ventilatory efficiency with dexamethasone. Thus, the improvement in VO_{2max} in the dexamethasone group may be explained by a combination of both, an increase in maximal cardiac output, and an improvement in pulmonary O_2 diffusion. In favor of this explanation, we observed that VO_{2max} and SpO_2 were significantly correlated only in the dexamethasone group. A hampered right ventricular performance with excessive afterload may have caused exhaustion in the control group before SpO_2 became a limiting factor.

However, the question about the mechanism by which dexamethasone may increase maximal cardiac output remains debatable. As suggested in several similar studies applying different pulmonary vasodilators (Ghofrani et al., 2004; Richalet et al., 2005; Faoro et al., 2009), a decrease in right ventricular afterload may explain higher levels of cardiac output. In turn, it has been proposed that the reduction in maximal cardiac output in hypoxia may result from a cardiac downregulation aiming to prevent an excessive widening of the alveolar-arterial PO_2 difference with decreasing pulmonary transit times (Calbet et al., 2003). Therefore, an improved pulmonary O_2 diffusion may allow for cardiac output to obtain higher levels before reaching the point where further increases would result in no or even negative changes in peripheral O_2 delivery. This explanation is supported by the finding that SpO_2 was higher in the dexamethasone group at rest, but did not differ between groups at maximal exercise where a potential downregulation of cardiac output may have prevented further desaturation. Nevertheless, in a recent study the effect of the dual endothelin receptor antagonist

bosentan on hypoxic VO_2max was investigated (Faoro et al., 2009). It was demonstrated that bosentan significantly lowers pulmonary artery pressures and concomitantly improves hypoxic VO_2max without affecting SpO_2 . Therefore, the conclusion was drawn that right ventricular afterload reduction is a key to improve exercise capacity at high altitude. Taken together, these findings indicate that the cause or effect question concerning increased cardiac output with improved pulmonary O_2 diffusion remains controversial and requires further investigation with a reliable assessment of cardiac output.

We also observed an increase in resting HR at 4559 m only in the control group, whereas in those participants receiving dexamethasone, resting HR was similar to baseline values. This is surprising, because acute exposure to hypoxia is normally accompanied by higher resting HR (Vogel and Harris, 1967). Nevertheless, a blunted HR after intake of dexamethasone in acute hypoxia has been reported previously and may be related to a modulation of increased sympathetic drive (Maggiorini et al., 2006), which is a potential contributor to increased pulmonary vascular resistance and pulmonary capillary permeability (Duplain et al., 1999). However, in agreement with earlier observations (Fischler et al., 2009), acute hypoxia decreased maximal HR to a very similar degree in both groups. Consequently, there is a larger difference between resting and maximal HR; thus, an increased HR reserve in the dexamethasone group may have contributed to the gain in maximal exercise capacity and supports the explanation of right ventricular unloading in dexamethasone-treated subjects.

It is important to note that dexamethasone might improve exercise capacity even in normoxic conditions: high dosages have been used in endurance sports on various occasions to enhance performance (Arlettaz et al., 2006). Therefore, the World Anti-Doping Agency (WADA) prohibits administration of glucocorticosteroids during competitions. This raises the question of whether our finding is at all hypoxia related or just a consequence of a general performance-enhancing effect of dexamethasone that is also present in normoxic conditions. However, several studies that have investigated the effect of dexamethasone on normoxic exercise capacity found no improvement in submaximal (Virus and Smirnova, 1982; Arlettaz et al., 2006; Cordova Martinez, 2006; Arlettaz et al., 2008a) or maximal (Marquet et al., 1999; Cordova Martinez, 2006; Arlettaz et al., 2008b) exercise capacity, suggesting that the amelioration that dexamethasone brought to our subjects was indeed owing to a reduction of hypoxia-related impairment of exercise tolerance.

Limitations

We tested our hypothesis by comparing a treatment group to untreated subjects. The optimal design would have been a crossover protocol in which each subject is its own control. However, the obvious inconvenience for the subjects of traveling to the Margherita hut twice argued against this design. Further, the scheduling of the second ascent would have been problematic. A short interim would have allowed for an altitude acclimatization carry-over. On the other hand, with a long break, other factors, such as altered physical conditioning of the subjects, might have influenced the outcome of the study.

Further, we included subjects of two separate studies with differences in the treatment of our control subjects, and so it may be argued that subjects receiving placebo cannot be matched to untreated subjects. Since no differences were observed in hypoxic VO_2max between the 2007 and 2009 control groups and since both groups presented with lower values than the dexamethasone group, we assume that the fact that only a part of the control group received placebo did not significantly alter the outcome of the study.

It is also true that the two experimental groups were not equal with regard to gender distribution. We do not expect this circumstance to bias our findings. Women can acclimatize and perform at altitude as well as men (West et al., 2007), and the menstrual cycle does not affect performance at high altitude (Beidleman et al., 1999).

Since in our study we included only HAPE-s individuals, we cannot transfer our findings to a general population. However, assuming that subclinical HAPE is a common phenomenon after climbing to Margherita hut within <24 h (Cremona et al., 2002), it is possible that dexamethasone might have the same effect on individuals not susceptible to HAPE, but this will have to be tested separately.

Conclusion

In conclusion, we found that a prophylactic administration of 8 mg dexamethasone b.i.d reduces the hypoxia-related decline in VO_2max of HAPE-s subjects at 4559-m-high altitude. This is most likely related to an increase in maximal cardiac output and an improved pulmonary O_2 diffusion, both resulting in a higher convective O_2 transport to the exercising muscles.

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Disclosures

The author's have no conflicts of interest or financial ties to disclose.

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