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Patients with chronic obstructive pulmonary disease (COPD) travelling to altitude: physiological and clinical changes and their prevention

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1 Summary

Due to the reduced barometric pressure at altitude, humans have to cope with a lower inspired partial pressure of oxygen ($P_{I_{O_2}}$), which induces several physiological responses to compensate the reduced $P_{I_{O_2}}$ and content of oxygen in the blood (hypoxemia). To improve arterial oxygenation, heart rate and minute ventilation increase within the first seconds to minutes at altitude. Dependent on the ascent rate and absolute altitude reached, hikers suffer not only from shortness of breath (dyspnea), but also from physical exercise intolerance, sleep-related breathing instabilities and acute mountain sickness (AMS), an altitude-related illness associated with headache, gastrointestinal symptoms, weakness and sleeping difficulties. To prevent AMS in healthy trekkers, acetazolamide, a carbonic anhydrase inhibitor that improves arterial oxygenation by increasing minute ventilation, is recommended in the first line. Alternatively, if acetazolamide is contraindicated, dexamethasone, a glucocorticoid, can be prescribed. Without treatment, worsening of AMS can lead to life-threatening situations, forcing trekkers to stop further ascents, take rescue medication such as acetazolamide, dexamethasone or supplemental oxygen, and force them to evacuate. As mountain tourism becomes more popular, millions of lowlanders travel to altitudes up to 4'000 meters above sea level (which will be abbreviated as "m" throughout this manuscript). Many patients with respiratory diseases such as chronic obstructive pulmonary disease (COPD) are also expected to be among them. COPD is characterized by chronic airflow obstruction related to airway inflammation and remodeling, as well as parenchymal destruction of the lung. This condition causes dyspnea, impaired exercise performance, hypoxemia, elevated pulmonary artery pressure and other manifestations already at low altitude. Although COPD is highly prevalent and the 4th leading cause of death worldwide, the degree and susceptibility to altitude-induced physiological and clinical changes and their prevention in COPD patients are currently unknown and are therefore the focus of this doctoral thesis encompassing three consecutive randomized controlled trials.

In a first, randomized cross-over trial in 32 patients with moderate to severe COPD, the purpose was to assess exercise endurance and elucidate contributing physiological limitation factors at 2'590 m compared to 490 m. Patients cycled at both altitudes in semi-recumbent position at 60 % of their maximum work capacity at 490 m until exhaustion. Altitude allocation sequence was randomized. At 2'590 m, patients had a 54 % reduction in exercise endurance associated with systemic and cerebral hypoxemia, exaggerated perception of dyspnea and worse pulmonary gas exchange compared to 490 m.

In a second study, a randomized, placebo-controlled, double-blind parallel trial in 118 patients with mild to moderate COPD, we assessed the efficacy of preventive dexamethasone intake on the incidence of altitude-related adverse health effects (ARAHE) during a 2-day stay at 3'100 m. Patients were randomized to either 2 x 4 mg dexamethasone daily or placebo starting 24 hours before ascending by minibus within 3 – 5 hours from 760 m to 3'100 m. ARAHE, a combined primary outcome, was defined as experiencing AMS or any other adverse health condition forcing the patient to receive medication, supplemental oxygen therapy or to relocate to lower altitude. In the placebo group, 24 % of all patients experienced an ARAHE, whereas in the dexamethasone group a similar incidence of 22 % was observed. Despite better arterial oxygenation, no effect in prevention of ARAHE with dexamethasone was observed. However, dexamethasone induced hyperglycemia, a common side effect of glucocorticoids, in 16 of 60 (28 %) patients assigned to dexamethasone.

The third study of this thesis was incorporated in the trial examining the effect of dexamethasone on the incidence of ARAHE. The same design and participants as in the second study were used with the purpose to assess the effect of preventive dexamethasone treatment on the nocturnal arterial oxygenation and breathing pattern at 3'100 m compared to placebo. During the two nights at 3'100 m, patients in the placebo group suffered from hypoxemia, breathing instability including periodic breathing pauses (apneas) and reported poor sleep quality. In the mornings, patients had higher heart rate and systemic blood pressure at 3'100 m compared to 760 m. Dexamethasone improved the nocturnal arterial oxygenation and breathing stability by reducing the number of apneas. Furthermore, dexamethasone reduced the heart rate and the systemic blood pressure in the morning and patients rated their sleep quality significantly higher compared to placebo.

In conclusion, this thesis quantified for the first time the degree of impairment in exercise endurance, the incidence of ARAHE, the nocturnal hypoxemia and the amount of periodic breathing that lowlanders with COPD experience during the first 2 nights at high altitude. The studies have further revealed that the altitude-induced nocturnal hypoxemia and breathing instability can be partly mitigated by preventive dexamethasone. Despite the exacerbation of hypoxemia at altitude, patients with COPD had an only moderate incidence of ARAHE and tolerated the altitude generally well. Dexamethasone, a medication used in healthy trekkers to prevent AMS, did not reduce the incidence of ARAHE in COPD patients but induced hyperglycemia, suggesting that this drug is not suitable to prevent ARAHE in patients with COPD.

2 Zusammenfassung

Der reduzierte Barometerdruck in den Bergen und der dadurch reduzierte inspiratorische Sauerstoffpartialdruck verringert den Sauerstoffgehalt im Blut (Hypoxämie) und dies führt zu verschiedenen physiologischen Adaptationsmechanismen: Um den Sauerstoffgehalt im Blut zu erhöhen werden die Herzfrequenz und die Ventilation innerhalb von Sekunden bis wenigen Minuten gesteigert. Abhängig von der Aufstiegsgeschwindigkeit, der erreichten Höhe und der individuellen Höhentoleranz können Berggänger unter Atemnot, körperlicher Leistungsintoleranz, nächtlichen Störungen der Atmung und an akuter Bergkrankheit (AMS) leiden. Zur Prävention von AMS wird in der Regel die Einnahme von Acetazolamid, einem Carboanhydrase Hemmer welcher die Ventilation stimuliert, empfohlen. Bei Unverträglichkeit gegenüber Acetazolamid kann Dexamethason, ein Glukokortikoid, eingesetzt werden. Die Verschlimmerung der AMS Symptome kann den weiteren Aufstieg verhindern und sogar zu lebensgefährlichen Situationen wie Hirn- oder Lungenödem führen, welche eine sofortige Behandlung, sowie eine Evakuierung erfordern. Der Bergtourismus erfährt einen starken Aufschwung. Millionen von Tiefländern reisen jährlich in Bergregionen bis oder gar über 4‘000 m Höhe. Darunter sind auch viele Personen mit chronischen Lungenkrankheiten, wie z.B. chronisch obstruktiver Lungenkrankheit (COPD), die bereits im Tiefland zur Hypoxämie führen kann und sich in der Höhe noch verschlimmert. Patienten mit COPD leiden an einer chronischen Entzündung mit Verengung der Atemwege sowie Umbau und Zerstörung des Lungenparenchyms. Dies führt zu Atemnot, Belastungsintoleranz, Hypoxämie, erhöhtem Lungenarteriendruck und weiteren Manifestationen. Obwohl die COPD sehr häufig ist und die World Health Organisation COPD als die 4. häufigste Todesursache weltweit eingestuft hat, sind die physiologischen und klinischen Auswirkungen der Höhe auf Patienten mit COPD noch nicht genau bekannt. Das Ausmass von Höhen-assoziierten physiologischen und klinischen Veränderungen und Massnahmen zur Vermeidung schädlicher Auswirkungen eines Höhenaufenthalts bei COPD Patienten wurden bisher nicht wissenschaftlich untersucht. Aus diesem Grund werden die damit verbundenen Fragen in dieser Doktorarbeit untersucht.

In einer ersten randomisierten cross-over Studie bei 32 Patienten mit mittelschwerer bis schwerer COPD, wurde die körperliche Leistungsfähigkeit zwischen 2'590 m und 490 m verglichen. Die Patienten fuhren, auf beiden Höhen, auf einem Halb-Liegefahrrad mit 60 % ihrer maximal körperlichen Leistung von 490 m, bis zur Erschöpfung. Die Reihenfolge der Höhenaufenthalte wurde randomisiert. Die Ergebnisse zeigten, dass die körperliche Ausdauer der Patienten auf

2‘590 m auf rund die Hälfte derjenigen auf 490 m reduziert war. Dies war auf eine systemische und zerebrale Hypoxämie aufgrund des schlechterem Gasaustausch in der Lunge und ausgeprägterer Atemnot zurückzuführen.

In einer zweiten randomisierten, Placebo-kontrollierten, doppelt-verblindeten parallel-Gruppen Studie bei 118 Patienten mit leichter bis mittelschwerer COPD wurde die Wirksamkeit von Dexamethason zur Prävention von Höhen-assoziierten schädlichen Gesundheitseffekten (altitude related adverse health effects, ARAHE) bei einem 2-tägigem Höhenaufenthalt auf 3‘100 m geprüft. Die Patienten wurden zu 2 x 4 mg Dexamethason täglich oder Placebo randomisiert. Die Einnahme begann 24 Stunden vor der 3 – 5 stündigen Fahrt auf 3’100 m. ARAHE war definiert als kombinierter Endpunkt, zusammengesetzt aus AMS und / oder anderen Zuständen, welche eine Sauerstoff- oder Medikamententherapie, oder sogar die Evakuierung des Patienten erforderte. Auf 3’100 m erfüllten 24 % der Patienten in der Placebo und 22 % in der Dexamethason Gruppe die Kriterien eines ARAHE. Die Einnahme von Dexamethason hatte keine Wirksamkeit zur Verhinderung von ARAHE, hingegen verursachte Dexamethason bei 16 der 60 (28 %) Patienten mit Dexamethason eine Hyperglykämie als Nebenwirkung.

Die dritte Untersuchung dieser Doktorarbeit wurde im Rahmen der zweiten randomisierten Studie durchgeführt und verwendete somit das gleiche Studiendesign und die gleichen Patienten, jedoch war die Fragestellung hier, ob Dexamethason die nächtliche Sauerstoffsättigung und die Störung des Atemmusters auf 3‘100 m verbessern kann. Während den 2 Nächten auf 3‘100 m, litten Patienten in der Placebo Gruppe an ausgeprägter nächtlicher Hypoxämie, periodischer Atmung und verringerter Schlafqualität. Die Herzfrequenz und der Blutdruck waren am folgenden Morgen gegenüber 760 m erhöht. Dexamethason, verglichen zu Placebo, erhöhte die arterielle Sauerstoffsättigung, stabilisierte die Atmung, reduzierte die Herzfrequenz und den Blutdruck, und die Patienten empfanden eine bessere Schlafqualität.

Die Resultate dieser Doktorarbeit zeigen erstmals die quantitative Einschränkung der körperlichen Leistungsfähigkeit, die ARAHE Inzidenz, das Ausmass der nächtlichen Hypoxämie und der dadurch bedingten periodischen Atmung von Patienten mit COPD bei einem 2-tätigem Höhenaufenthalt. Die Auswirkungen des Höhenaufenthaltes auf die nächtliche Oxygenierung und das Atemmuster können durch eine prophylaktische Einnahme von Dexamethason gemildert oder sogar verhindert werden. Hingegen wurde die insgesamt eher geringe Inzidenz von ARAHE von 24 % auf 3‘100 m durch eine prophylaktische Dexamethason Behandlung nicht weiter reduziert, zudem begünstigte Dexamethason das Auftreten von Hyperglykämie.

3 General introduction

3.1 Altitude and hypobaric hypoxia

With increasing altitude, the atmospheric pressure falls and the inspired partial pressure of oxygen (PI_{O_2}) also decreases proportionally, since the atmospheric oxygen concentration remains virtually constant at 0.209 over the range of terrestrial altitudes (Figure 3-1). As a reference, at an altitude of 5'000 m, the atmospheric pressure is about half of that at sea level and the cabin pressures of long-distance airplanes are pressurized to a maximum altitude equivalent of 8000 ft (2'438 m).[1,2] With lower atmospheric pressure, the diffusion gradient for oxygen from the alveoli through their membrane into the blood and to the hemoglobin in the red cells is reduced, resulting in lower blood oxygenation, a condition termed hypoxemia. As a consequence, hypoxia, an insufficient availability of oxygen in tissues may develop that may lead to altitude-induced physiological and clinical adaptations, and when insufficiently compensated, to organ dysfunctions.

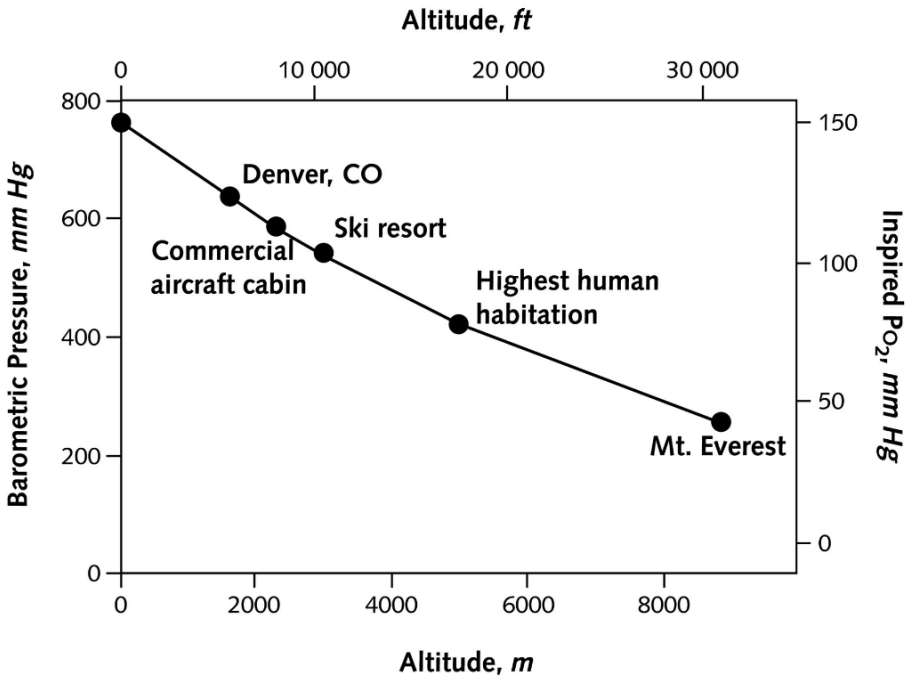

Figure 3-1. Relationship between barometric pressure, altitude and PI_{O_2}. *Figure from West JB.[1]*

3.2 Normal physiological adaptations and maladaptations to altitude

Almost all organ systems undergo physiologic adaptations when exposed to a reduced oxygen partial pressure at high altitude. Of particular interest in the context of the current thesis are the control of breathing, the lung and the pulmonary and systemic circulation, in particular also the cerebral circulation, the autonomic nervous system and the muscles. These changes will be discussed in detail below along with the impairments in exercise performance and disturbances of sleep and control of breathing that I have further investigated in my thesis. Other adaptations such as those occurring in the blood, the kidneys, the endocrine system, the gastro-intestinal system and the immune system are beyond the scope of this general introduction.

It is recommended to not exceed the ascent rate of 300 to 500 meters per day at altitudes above 3'000 m.[3] Exceeding this ascent rate or an ascent within one day from an altitude below 1'000 m to an altitude >2'800 m is classified of moderate risk to develop AMS.[4] However, even when ascending within the recommended rate, many physiological adaptations and maladaptations take place.

3.2.1 Control of breathing

Among the immediate and most important physiological responses to hypobaric hypoxia is an increase in ventilation mediated by stimulation of peripheral chemoreceptors (carotid and aortic bodies). The ventilatory response to hypoxia, termed hypoxic ventilatory response (HVR) reduces the partial pressure of CO_2 in arterial blood (Pa_{CO_2}) and mitigates hypoxemia. It remains still elusive whether a high or a low HVR is beneficial at altitude, since the relationship to acute mountain sickness (AMS) or other adverse effects are poor.[5] Minute ventilation progressively increases over the time course of several days and normalizes after several weeks, whereas it remains higher than sea level values. Even highlanders permanently living at high altitude have elevated minute ventilation.[6] The sustained hyperventilation over several weeks, despite hypocapnia, is assumed to be due to metabolic acidosis due to bicarbonate loss in the urine (as a compensation for the respiratory alkalosis). Another mechanism resulting in persistent hyperventilation is the altered chemoreceptor sensitivity to oxygen and carbon dioxide.[7]

3.2.2 Lung function and pulmonary gas exchange

Above 2'500 m, lung vital capacity is reduced[8] most likely due to reduced respiratory muscle strength[9] and subclinical interstitial fluid accumulation in the lungs (pulmonary edema).[10] Changes in forced expiratory volume in the first second (FEV_1) with altitude has been shown

to increase[11], decrease[10,12] or remain unchanged.[13] Cremona et al. reported improved FEV_1 compared to no changes in mountaineers without and with subclinical high altitude pulmonary edema (HAPE), suggesting that interstitial fluid accumulations in the lung might be an explanation for the different findings in altitude-induced changes of FEV_1.[14] Improvements in FEV_1 have been accounted for the lower gas density and less turbulent flow in the airways.[15] Additionally, due to subclinical pulmonary edema, diffusion capacity assessed by single breath diffusing capacity measurements, has been shown to be reduced at altitude.[16]

3.2.3 Cardiovascular system

Another immediate response to hypobaric hypoxia is an increase in heart rate to protect the body from hypoxemia and hypoxia. Resting and submaximal heart rate remains increased for several weeks, although it normalizes nearly completely to sea level values with prolonged acclimatization.[17] However, maximal heart rate achieved by maximal exercise challenges is reduced with acute and remains reduced with chronic exposure to hypobaric hypoxia. This effect correlates with the absolute altitude exposure. The underlying mechanisms are unclear, one suggestion is to protect the heart from cardiac ischemia, assuring enough time for the diastolic filling of the ventricle and re-oxygenation of the heart. Overall, the cardiac output increases with acute exposure, due to increased heart rate, with acclimatization, heart rate remain slightly elevated whereas stroke volume of the ventricle remains lower, this might be due to loss of blood plasma volume at altitude.[18]

3.2.4 Cerebral circulation

Altitude-induced hypoxemia acts as vasodilator in the cerebral arterial vessels, therefore, cerebral blood flow, a surrogate for blood volume measured by transcranial Doppler ultrasound of the middle cerebral artery, towards the brain is suggested to increase to maintain an adequate oxygen supply. An excessive increase might be an underlying mechanism for the development of cerebral edema, increased intracranial pressures, headache and high altitude cerebral edema (HACE). It has been shown in several studies that, dependent of the ascent rate and absolute altitude stay, cerebral blood flow is increased during the first hours at high altitude. After 3 – 5 days of acclimatization the cerebral blood flow normalizes, but remains elevated compared to sea level.[19] Cerebral tissue oxygenation (CTO) non-invasively measured by near-infrared spectroscopy (NIRS) is a surrogate for an adequate oxygen supply to cover the oxygen demand of the brain. However, despite an increase in cerebral blood flow, CTO is reduced at altitude and further decreases with exercise in healthy trekkers at altitude higher than 3’500 m.[20]

3.2.5 Autonomic nervous system

Sympathetic activity is elevated at altitude due to pronounced hypoxemia. In humans, indirect measurements of sympathetic activity are more prevalent, therefore, measurements of muscle sympathetic nerve activity, heart rate variability, arterial baroreflex or catecholamine (noradrenaline and adrenaline) concentration in the blood or urine are often reported in high altitude studies. During the acute (several hours) exposure to hypobaric hypoxia, mainly adrenaline is elevated, whereas later, noradrenaline seems to be the driving force. The controversy of elevated sympathetic activity but lower maximal heart rates might be due to a reduction of cardiac β – adrenergic receptors, however this has been shown in rats and not in humans.[21]

The parasympathetic system is reduced with acute,[22] but was suggested to be increased following 9 weeks of altitude exposure to 5'260 m, explaining in part the normalization of heart rate with chronic altitude exposure. This was indirectly measured from the response to muscarinic blockage.[23]

3.2.6 Muscles

Whether acute hypobaric hypoxia effects muscle structure is unknown, however sustained exposure to hypobaric hypoxia leads to several maladaptations, i.e. reductions in mitochondrial volume and muscle fiber density. These alterations reduce the aerobic muscle capacity. Furthermore, hypoxemia induces blood re-distribution towards breathing muscles due to higher breathing work at high altitude, therefore locomotor muscles are undersupplied during whole body exercises at altitude.[7]

3.2.7 Exercise intolerance

Due to decrement in $P_{I_{O_2}}$ with higher altitude, maximum oxygen uptake ($\dot{V}_{O_2}max$) and, therefore, exercise performance negatively correlates with altitude. In particular aerobic exercise capacity is altered, whereas anaerobic exercise capacity (high-intensity exercises lasting less than 2 minutes) are largely unaffected.[24] Thus, it has been estimated that $\dot{V}_{O_2}max$ decreases by about 8 % for each 1'000 m of ascent starting at 700 m up to an altitude of 6'300 m and a recent meta-analysis has concluded that subjects with higher sea level $\dot{V}_{O_2}max$ are more prone to hypoxia compared to less trained individuals, therefore have stronger decrements in $\dot{V}_{O_2}max$.[2526] Contributing factors for a reduced exercise performance at high altitude in healthy individuals include a reduced oxygen delivery to vital organs and working muscles because of the lower oxygen saturation of the hemoglobin, a reduced maximum cardiac output due to a reduced

maximum heart rate related to a hypoxia-induced sympathetic/parasympathetic imbalance and pulmonary diffusion limitation with exercise-induced further hypoxemia.[20,27,28] Additional mechanisms limiting exercise performance at high altitude related to impairments in central command have been proposed but have remained controversial. Thus, it has been suggested that under moderate hypoxia (FiO_2 0.15, approximately 2'500 m) peripheral locomotor muscle fatigue and not 'central' fatigue might be an important limiting factor shown in a study in 8 elite cyclists who were not able to continue exercise with hyperoxygenation given at their point of failure. The degree of quadriceps fatigue, as represented by a decrease of 35 % of quadriceps twitch force was similar between normoxia and hypoxia, despite different arterial and cerebral oxygenations.[29]

3.2.8 Sleep and breathing disturbances at high altitude

Acute exposure to high altitude is associated with alterations in sleep structure that include a reduced sleep efficiency, more superficial (non-rapid eye movement stages N1 and N2) and less deep sleep (N3) and a reduced amount of rapid eye movement (REM sleep). These changes may impair not only the subjective sleep quality but cognitive and psychomotor performance during daytime as well. A shift to more superficial sleep stages, prolonged wakefulness, and frequent transients from wakefulness to sleep during arousals are associated with an increased and frequently changing ventilatory drive. Together with the increased ventilator response to hypoxia and carbon dioxide these changes contribute to the destabilizing effect of altitude exposure on ventilation.[30] When the HVR is strong, due to a low partial pressure of O_2 in the arterial blood (Pa_{O_2}) at high altitude or a high individual sensitivity to hypoxemia, the Pa_{CO_2} falls below the lower limit of the range which ensures spontaneous breathing (apneic threshold), and ventilation transiently ceases until the metabolic production of CO_2 causes Pa_{CO_2} to rise again.[31] The rise of Pa_{CO_2} above the apneic threshold re-activates spontaneous breathing and triggers an overshooting burst of hyperventilation which again, can reduce Pa_{CO_2} below the apneic threshold. Consequently, especially during sleep, ventilation waxes and wanes, which is called high altitude periodic breathing (defined as three consecutive cycles of central apneas/hypopneas). At altitudes above 2'500 m, periodic breathing may become severe,[32] impair sleep[30,33,34] and even persist during wakefulness. It is unclear, to which extent alterations in sleep structure at high altitude promote high altitude periodic breathing and vice versa. Analysis of arousals in relation to apnea / hypopnea suggest that only a minor fraction of altitude-asso-

ciated sleep fragmentation is related to periodic breathing.[33]It has been suggested that acclimatization associated progression and regression of sleep-disordered breathing is altitude dependent, although this has not been extensively studied. Studies above 4'000 m report progression of periodic breathing with acclimatization over several days to weeks[34,35], whereas studies below 4'000 m report a regression.[8,33]

3.3 Altitude-related illnesses

AMS, the most common of the acute and chronic forms of altitude-related illnesses, affects 20 – 50 % of unacclimatized lowlanders ascending to altitudes of 3'500 m.[36] The incidence of AMS depends on the diagnostic instrument, prior acclimatization and altitude travel or altitude residence, ascent rate, sleeping altitude, and individual susceptibility.[3] Importantly, different scores and diagnostic criteria for AMS have been used, therefore comparisons of the prevalence and incidence of AMS in different studies have to account for such discrepancies. AMS generally starts within 6 – 12 hours of arrival at altitude manifesting itself with headache, loss of appetite, weakness, fatigue and insomnia.[37] The pathophysiology of AMS remains elusive,[38] it has been suggested that AMS develops due to inadequate physiological responses to hypobaric hypoxia, such as impaired pulmonary gas exchange,[39-41] decreased HVR,[42] insufficient early hypoxic diuresis,[43] and increased sympathoadrenal activity.[44]

All of the scientific research about AMS susceptibility, risk factors, prevention and treatment of AMS has been done in healthy trekkers or mountaineers ascending to high altitude. To date, very little is known on the physiological and clinical response of patients with chronic respiratory diseases (i.e. COPD) to hypobaric hypoxia. The presence of headache when suffering from AMS might be related to increases in intracranial pressures,[45,46] therefore it has been suggested that severe, untreated AMS may progress to HACE characterized by severe headache, ataxia, loss of consciousness and, finally, death.[4] Another form of acute altitude-related illnesses is HAPE, but HACE and HAPE are much less common than AMS. Subacute and chronic altitude illnesses affect long-term high altitude residents living at >2'500 m. The prevalence is estimated to be 5 to 10 %.[47] Main manifestations and diagnostic criteria are summarized in Table 3-1.

Table 3-1. Summary of altitude-related illnesses.

	Condition	Time of exposure	Main manifestations and diagnostic criteria
Acute	AMS	Hours to days	Headache, loss of appetite, insomnia and / or fatigue
	HACE	Hours to days	Severe headache, ataxia, confusion and / or loss of consciousness
	HAPE	Days	Dyspnea, cough, cyanosis, exercise intolerance and / or pulmonary hypertension
Subacute / chronic	High altitude pulmonary hypertension (HAPH), or cardiac chronic mountain sickness	Years	Dyspnea, exercise intolerance, right heart failure. Mean pulmonary artery pressure >30 mmHg or systolic PAP >50 mmHg; absence of excessive erythrocytosis (hemoglobin concentration <19 g/dL in women, <21 g/dL in men)
	Chronic mountain sickness, Monge's disease (CMS)	Years	Headache, dizziness, dyspnea, sleep disturbances, fatigue. Excessive erythrocytosis (Hemoglobin >19 g/dL in women, >21 g/dL in men). In some patients, pulmonary hypertension, right heart failure and / or hypoventilation
	Subacute mountain sickness, or adult and infantile forms of cardiac subacute mountain sickness	Weeks to months	Dyspnea, exercise intolerance, pulmonary hypertension and / or right heart failure

3.4 COPD

COPD is a major health problem worldwide being one of the leading causes of morbidity, mortality and health care costs. In 2010, 384 million cases of COPD were registered, and 3 million deaths were estimated to be caused by the disease annually.[48] COPD is characterized by chronic airflow obstruction related to airway inflammation, remodeling and parenchymal destruction of the lung. According to the Global Initiative for Obstructive Lung Disease (GOLD) guidelines, the diagnosis of COPD requires a lung function test (spirometry) with a post bronchodilator ratio of FEV_1 and the forced vital capacity (FVC) of FEV_1 / FVC <0.7 in the appropriate clinical setting.[48] COPD is incurable, therefore, the care of patients with COPD includes reduction of risk factors, in particular smoking cessation, patient education, pharmacological therapy, and supplemental oxygen and many patients survive for decades with this condition in a relatively good performance status. Depending on disease severity, inhaled $beta_2$-agonists, anticholinergics and glucocorticosteroids are prescribed and in some cases combined with oral methylxanthins and short-term systemic glucocorticosteroids.[48] Rehabilitation, nutrition counseling and vaccinations are important adjuncts. COPD exacerbations require intensified bronchodilator

therapy, systemic glucocorticosteroids, antibiotics and, in certain patients, mechanical ventilation. In some cases with very severe COPD, lung volume reduction surgery or transplantation are performed.

COPD is a multifactorial systemic disease affecting the whole body with many physiological maladaptions. The impact of hypoxemia has been studied in regard of certain physiological and clinical consequences, but it is still unclear which clinical consequences occur at which degree and for what duration of hypoxemia. Current guidelines recommend long-term oxygen therapy (LTOT) for stable COPD patients when Pa_{O_2} at or below 7.3 kPa (55 mmHg) or Sa_{O_2} at or below 88 %.[48] However, these recommendations are based on only 2 studies conducted in the 1970s.[49,50] A recent randomized trial in 738 patients with COPD has provided additional evidence on the indication of oxygen therapy. Patients were divided into stable non-hypoxemic COPD and moderate hypoxemic COPD patients (resting SpO_2 of 89 – 93 %). Primary outcome was the time until death or first hospitalization. Patients in both groups were randomized to LTOT or non-LTOT therapy. After following these patients for 1 to 6 years, this large multicenter trial concluded that LTOT did not result in a longer time to death or hospitalization (hazard ratio [95% confidence interval] of 0.94 [0.79 to 1.12], P = 0.52) in these only mildly hypoxemic or non-hypoxemic patients corroborating and expanding the conclusions from the earlier trials.[51]

COPD patients suffer from exercise intolerance due to various pathophysiological mechanisms. Compared to healthy elderly who can increase their minute ventilation 10 to 15-fold, depending on the degree of lung function impairment, COPD patients have airflow obstruction and dynamic hyperinflation preventing an adequate increase in their minute ventilation during exercise. Thus, COPD patient's exercise limitation is mainly due to reaching their maximum ventilatory capacity (MVC), whereas healthy elderly have cardiac limitations while maintaining reserves in their MVC. Underlying mechanisms for reaching the MVC in COPD patients are, increased ventilatory demand (i.e. due to higher dead space ventilation, ventilation / perfusion mismatching), which lead to hypoxemia and hypercapnia and higher ventilatory stimulation. In addition to these maladaptions, gas exchange impairments due to destruction of lung parenchyma and remodeling of the pulmonary vasculature are common, resulting in worse ventilatory equivalents for carbonic dioxide clearance and impaired oxygen uptake.[52] As mentioned above, airflow obstruction can lead to dynamic hyperinflation during exercise, which is one of the main causes for excessive dyspnea sensation. Dyspnea is an unpleasant perception of breathing due to a mismatch of respiratory neural drive and the respiratory mechanical response (due

to dynamic hyperinflation, expressed as reduced inspiratory capacity or elevated end-expiratory lung volumes during exercise).[53] In addition to ventilator constraints, many COPD patients are also limited in exercise performance due to deconditioning and comorbid conditions including systemic hypertension, coronary heart disease and peripheral muscle dysfunction. In combination, all these factors are major limitations to exercise performance in particular during altitude exposure.

With worsening of the disease, patients become more hypoxemic. It has been shown that COPD patients are exposed to even further hypoxemia during sleep. Especially during non-rapid eye movement sleep, even non-hypoxemic COPD patients during wakefulness may become hypoxemic, have impaired cerebral autoregulation, which has been shown to result in brain damage with white matter degradation. Clinical consequences of the sleep related breathing disturbances and hypoxemia on mortality, quality of life, COPD exacerbation or hospitalization have not been conclusively assessed.[54,55]

3.5 Altitude and air travel for COPD patients

Worldwide, a large number of lowlanders travel to higher elevations for work and leisure activities. Many Swiss villages and tourist resorts are located at moderate altitudes of 1’000 – 2’000 m. In the Americas and Asia, large settlements are located at even higher elevations, up to 4’300 m. Considering the high prevalence of COPD, the number of patients with the disease is also expected to be high among high altitude travelers and residents. In Switzerland and in other countries, high altitude clinics originally built for patients with tuberculosis, such as the clinics in Davos or Montana, have been converted to rehabilitation clinics where lowlanders are treated for various cardiac and pulmonary diseases including COPD.[56,57]

A very large number of patients with COPD are expected to be exposed to hypobaric hypoxia as airline passengers although no reliable statistics are available. In 2016, 3.8 billion airline passengers have been reported by the International Air Transport Association (IATA). In 2017, the number has increased to 4.1 billion passengers.[58] It seems reasonable to assume that a considerable proportion of COPD patients are among them. Although the global incidence of inflight emergencies is not known, analysis of events occurring in 5 airlines over 3 years revealed that 12.1 % of 11’920 inflight emergencies reported by crew members were due to respiratory symptoms, presumably also due to COPD.[59] These findings and other reviews suggest that flights remain relatively safe for patients with COPD.[60] However, during air flights patients are

physically inactive and are only shortly exposed to hypobaric hypoxia. Therefore, these findings are not representative for an altitude sojourn associated with physical activity and much longer exposure to hypobaric hypoxia.

Especially the degree and consequences of altitude-induced hypoxemia during longer exposure to hypobaric hypoxia are of great interest. Patients with COPD have a reduced Pa_{O_2} already at sea level. Therefore, they are at an increased risk of experiencing profound hypoxemia according to the shape of the oxygen-hemoglobin dissociation curve that results in major oxygen desaturations with further reductions in Pa_{O_2} in its steeper part. Consequences of altitude-induced hypoxemia are not only limited to increased dyspnea, altitude-related illness, exercise and sleep impairment but they also included potentially serious complications including cardiovascular events (heart attack, cardiac arrhythmias, stroke). Unfortunately, the effects of exposure to various altitudes and degrees of hypoxemia have not conclusively been studied neither in terms of physiological consequences nor in terms of clinical complications as will be discussed in the following.

3.6 Are there health risks for COPD patients at altitude?

Mountain areas cover about 24 % of the earth's land surface and about 12 % of the world population live in mountain areas, with another 14 % living close to mountains.[61] As described in 3.2 and 3.5, acute altitude exposure can have adverse effects in healthy persons, and conceivably even more so in persons with pre-existing respiratory diseases.[62] However, very little scientific data is available on the effects of altitude in patients with COPD and there is no guidance on how to counsel these patients regarding prevention and treatment of altitude-related adverse health effects. COPD patients may experience limitations at altitude through ventilatory and gas exchange impairment, altered control of breathing, excessively increased pulmonary artery pressure, reduced skeletal and respiratory muscle strength, and metabolic and inflammatory responses. Whether and to which extent these hypothetical mechanisms impact on wellbeing and physical performance of COPD patients and predispose to adverse events at altitude has not been conclusively studied. Nevertheless, an analysis of 12.1 million death records has raised concerns that the mortality rate by COPD was increased in COPD patients permanently living at elevated altitudes compared to lower altitudes, suggesting that chronic exposure to hypobaric hypoxia may represent a mortality risk for these patients.[63]

In a systematic PubMed / MedLine literature search (last performed on June 20, 2018) using terms "COPD and altitude" (228 retrievals), "COPD and hypobaric hypoxia" (20 retrievals)

and "COPD and air travel" (72 retrievals), we identified only 13 studies with evidence level 1 – 2;[64] only 3 of these[65-67] were randomized controlled trials in lowlanders with COPD exposed to simulated altitude. No randomized trial performed at real altitude has been identified, excluding the two randomized studies performed during this doctoral thesis.[68,69] Only three reports,[56,57,70] all observational case studies, described clinical manifestations of a stay at real altitude in lowlanders with COPD. The three randomized trials are summarized in Table 3-2.

Table 3-2. Randomized trials in COPD patients at simulated altitude.

	Design and setting	Participants	Main findings	Comments
Christensen CC et al. 2000[65]	Hypobaric chamber study simulating short-term exposure to 0, 2'438 and 3'048 m, according to a randomized cross-over design.	16 COPD patients, FEV_1 30 % predicted.	Resting Pa_{O_2} dropped below 7.3 kPa in 33 % and 66 % of patients at 2'438 m and 3'048 m, respectively. During light exercise in hypoxia, Pa_{O_2} dropped further.	Pa_{O_2} at altitude could not be predicted at sea level. Clinical relevance of hypoxemia remains uncertain.
Akero A et al. 2011[66]	Hypobaric chamber study simulating short-term exposure to 2'438 m. Nasal O_2 by pulsed / continuous flow, and portable concentrator according to a randomized cross-over design.	16 COPD patients, FEV_1 % predicted not reported.	Titration of O_2 therapy during a high altitude simulation test was not accurate; pulse- or continuous-flow O_2 provided similar Pa_{O_2} and the output of a portable O_2 concentrator was satisfactory.	Results applicable to air travel.
Sabit R et al. 2010[67]	Short-term exposure to normobaric hypoxia with 15 % fraction of inspired O_2 (FI_{O_2}) or ambient air according to a randomized cross-over design.	20 COPD patients, FEV_1 >50 % predicted.	Markers of coagulation and systemic inflammation was increased in the group exposed to hypoxia.	Clinical relevance of the findings uncertain.

Some insights into the response to hypoxia in COPD patients have been gained from observational studies evaluating fitness for flight in hypobaric chambers at an altitude equivalent to 2'438 m (8'000 ft, corresponding to the maximum allowed altitude equivalent during commercial air travel),[71] or by letting patients breathe a low inspiratory oxygen fraction near sea level (for example, FI_{O_2} 15 – 16 %, corresponding to about 8'000 ft) during a hypoxia-altitude simulation test.[72-74] During brief (<1 hour) simulations, COPD patients generally felt well although the Pa_{O_2} dropped significantly.[65,73] The clinical relevance of these findings is uncertain.

As mentioned above, observations in COPD patients travelling to real altitude are scant. Karrer and coworkers[56] described blood gases and pulmonary function in newcomers to the Luzerner Höhenklinik Montana, among them 48 with COPD (mean FEV_1 56 % predicted). Their Pa_{O_2} dropped from 9.36 kPa at Siders (535 m) to 7.94 kPa at Montana (1'472 m) which was well tolerated. In a study performed in New Zealand,[75] 18 COPD patients (mean FEV_1 42 % predicted) were transported by car from sea level to Mt. Hutt (2'086 m). The patient's walk distance was reduced to less than half (from 467 to 245 m). In 8 COPD patients (FEV_1 25 – 78 % predicted) travelling from sea level to Mount Washington (1'920 m), Vermont, Pa_{O_2} initially dropped from 8.8 to 6.8 kPa but values increased to 7.3 kPa with acclimatization over 4 days.[70] In the Dutch Asthma Center Davos (1'560 m) 37 lowlanders with COPD (FEV_1 63 % predicted) completed a 5 weeks rehabilitation training. It was associated with an increase in exercise capacity in this uncontrolled observational study.[57]

Exercise intolerance is a particular hallmark in COPD patients near sea level and exercise limiting factors might be modified during hypobaric hypoxia. Conceivably, the low barometric pressure and PI_{O_2} and the resulting hypoxemia will reduce the already impaired exercise performance in COPD patients when travelling to higher altitude. Alternatively, due to a lower air density at higher altitude, airway resistance and MVC might be higher, potentially reducing dyspnea sensation. At the same time, the PI_{O_2} is reduced, potentially inducing more profound stimulation of ventilation due to excessive hypoxemia. As mentioned before, it has been suggested that healthy subjects with higher sea level $\dot{V}_{O_2}max$ are more prone to hypoxia and since most COPD patients have a low $\dot{V}_{O_2}max$, they might experience a less pronounce altitude-induced exercise limitation. Another major factor relevant for exercise performance might be the altered cerebral function, which has been found to be compromised at altitudes higher than 4'000 m in healthy trekkers.[20] Whether COPD patients exposed to high altitude are even more susceptible or protected from cerebral hypoxia and whether cerebral hypoxia additionally limits exercise performance in these patients require further investigations.

In patients with COPD, other potential effects of altitude exposure that are very relevant for well-being such as sleep-related breathing disturbances and sleep quality are also unknown. It remains elusive to which degree patients with COPD respond to excessive hypoxemia during wakefulness and sleep at altitude. Some patients might have strong HVR due to hyperinflation and airflow obstruction, therefore making them more sensitive to hypoxemia in terms of unstable control of ventilation.

Altitude exposure may also have opposing influences on COPD patients in terms of their susceptibility to AMS. The greater degree of hypoxemia at altitude compared to healthy individuals without lung disease may expose COPD patients to greater risks of AMS. On the other hand, it has been shown that preconditioning to hypobaric hypoxia is protective against AMS to some degree. Whether chronic hypoxemia seen in patients with COPD acts as preconditioning has not been studied.

Thus, there are many open questions regarding the potentially adverse altitude-related health effects in COPD patients and studies quantifying the physiological and clinical response of the patients to altitude exposure and helping to assess the related risks are urgently needed.

3.7 Treatment of COPD patients at altitude

Guidelines of the British Thoracic Society suggest that pre-flight assessment of patients with stable respiratory disease should take previous flight experience and time since the last exacerbation into consideration.[76] In patients at greatest risk such as those with severe COPD (FEV_1 <30 % predicted), evaluation by a hypoxic challenge test should be considered. If Pa_{O_2} or arterial oxygen saturation measured by pulse oximetry (SpO_2) fall below 6.6 kPa or 85 %, respectively, during a hypoxic challenge consisting of breathing a nitrogen-air mixture with 15 % oxygen for 20 min, the use of 2 L / min inflight oxygen is recommended, despite the lack of evidence. No studies have conclusively evaluated the risks and their prevention in COPD patients during a stay of more than a few hours at altitude. In the absence of robust scientific data, it seems reasonable to encourage patients to refrain from smoking in general and in particular during altitude or air travel, and to continue their usual treatment. Travelers should take along sufficient supply of medication, prednisone and antibiotics to treat exacerbations.[77] It has been suggested that supplemental oxygen should be used to maintain an arterial oxygen saturation (Sa_{O_2}) of >90 % during flight.[66] However, it is not known which patients would benefit from this. Drawbacks of oxygen therapy are the associated fire hazard and logistic requirements that prevent its use in remote mountain areas.

Oxygen: To evaluate whether nocturnal supplemental oxygen therapy would prevent altitude-induced impairments in exercise performance, severe nocturnal hypoxemia and emergence of central sleep apnea, we performed a randomized sham-controlled, single-blind cross-over trial in 32 patients with moderate to severe COPD staying for two days at 490 m and two times 2 days at 2’050 m, with a 2-week washout at 490 m in-between the stays at high altitude. During

the altitude stays, patients received either nocturnal supplemental oxygen or sham therapy (ambient air) via a nasal cannula in a randomized order. The results revealed that in the nights at 2'050 m, patients suffered from hypoxemia, superficial sleep stages, reduced sleep efficiency and periodic breathing. These effects were prevented by oxygen therapy although exercise performance assessed by the 6-minute walk test remained unchanged (data in preparation for publication). Maximal and submaximal bicycle exercise performance were reduced (data in preparation for publication) and did not improve with nocturnal oxygen therapy at 2'050 compared to 490 m.

Acetazolamide: This carbonic anhydrase inhibitor is a respiratory stimulant that promotes renal bicarbonate excretion, thus correcting the respiratory alkalosis induced by hypoxia. Acetazolamide improves the arterial oxygenation and periodic breathing and prevents AMS in healthy mountaineers.[78,79] In patients with obstructive sleep apnea syndrome (OSAS), acetazolamide improved oxygen saturation and sleep apnea when given alone or combined with continuous positive airway pressure during altitude travel.[80,81] However, there are concerns that treating COPD patients travelling to altitude with acetazolamide might exacerbate dyspnea, and even trigger respiratory muscle failure due to rigorous ventilatory stimulation by metabolic acidosis and hypoxia.[82]

Drugs that lower pulmonary artery pressure: In some COPD patients, pulmonary artery pressure is moderately elevated and may rise further due to hypoxic pulmonary vasoconstriction leading to increased pulmonary vascular resistance at altitude, which may limit exercise performance. Therefore, drugs that reduce the pulmonary artery pressure might be of potential use in this setting. In healthy subjects exposed to hypoxia, the phosphodiesterase-5 inhibitor sildenafil reduced the elevated pulmonary artery pressures and improved exercise capacity.[83] In HAPE-susceptible subjects at 4'559 m, tadalafil improved arterial oxygen saturation, prevented an excessive rise in pulmonary artery pressure and reduced the incidence of HAPE.[84] In patients with COPD associated pulmonary hypertension, sildenafil improved pulmonary hemodynamics at rest and during exercise but induced a fall in Pa_{O_2} at rest.[85] Thus, whether COPD patients might benefit from sildenafil or other pulmonary vasodilators during an altitude sojourn is uncertain and there are concerns about aggravation of hypoxemia, headache and other side effects of these drugs.

Dexamethasone: Another approach to improve altitude tolerance in COPD patients may be the administration of glucocorticosteroids. Dexamethasone is a potent drug for prevention and

treatment of AMS.[3] Underlying mechanism are still under debate. Main mechanism is suggested to be that dexamethasone intake improves blood-brain barrier (BBB) integrity by upregulating proteins that build the tight junctions between cells, reducing the permeability and improving therefore the integrity of the BBB. With hypoxia, hypoxia-inducible factor 1 activity is upregulated, which promotes vascular endothelial growth factor (VEGF) transcription.[86] Dexamethasone has been shown to inhibit VEGF expression in brain microvascular endothelial cells and their accompanying increase in permeability, which might promote the manifestations of cerebral edemas.[87] Dexamethasone also mitigates altitude-induced hypoxemia, which is the promoter of all underlying pathophysiologic mechanisms behind AMS. Improvement in arterial oxygenation might be due to stimulations of ventilation, improvement in ventilation / perfusion matching by a sympatholytic effect, by increased surfactant secretion or by inhibition of hypoxic pulmonary vasoconstriction.[88] Indeed, it prevented the excessive rise in pulmonary artery pressure and HAPE in susceptible subjects ascending rapidly to 4'559 m.[84,89] This might be related in part to the beneficial effect of dexamethasone on hypoxia-induced impairment of nitric oxide mediated arterial relaxation and by modulation of sympathetic activity.[90] Glucocorticosteroids also improve airway inflammation and airflow obstruction in COPD patients, especially during exacerbations. Current guidelines suggest a dose of 40 mg prednisone per day for 5 days.[48] Therapy with glucocorticoids during COPD exacerbation can reduce length of hospitalization, improve lung function and arterial oxygenation.[91] In comparison, a dose of 2 x 4 mg/day dexamethasone as recommended for prevention of AMS by the Wilderness Medical Society corresponds to 53 mg/day prednisone and seems to be a reasonable dosage for COPD patients travelling to altitude.[92] Downsides of glucocorticosteroids are the risk of side effects, i.e. hyperglycemia. Osteoporosis, muscle weakness, impairment of immune response and mood changes are side effects associated with prolonged treatment.

3.8 Methodological considerations related to high altitude field studies involving patients with lung disease

Conducting high altitude field studies demand a well deliberated balance between the gold standard of a measurement and study design, the feasibility and potential risks. In all studies, safety concerns were major considerations that influenced the design and practical execution of the trials. Since we performed the first clinical trials in patients with COPD at high altitude we could not base on experience from previous studies by other investigators. A detailed plan for prevention and handling of any medical emergencies and of logistical difficulties was prepared.

Standard operating procedures for all activities of the research team consisting of up to 30 persons at one time were elaborated and trained and work schedules and other logistical arrangements were prepared well in advance.

In this chapter, some particular methodological considerations behind each trial of this thesis will be discussed.

All three trials included in this thesis focused on patient-centered outcomes. Thus, the primary aim of this thesis was to assess clinical changes relevant to patients. The secondary aims were to investigate the associated physiological mechanisms in order to better understand the clinical changes and to identify potential targets for prevention and treatment of altitude-related adverse health effects. Power calculations were performed for each primary outcome, however, negative results in any secondary outcome might be due to the lack of power due to insufficient sample sizes.

In the first trial, exercise testing was the main examination. Exercise testing in patients with COPD should not be done without caution, especially at altitude. These patients have multiple comorbidities, some diagnosed, some undiagnosed, and therefore a trained physician should be present during every exercise session equipped with the necessary medications and a defibrillator. Additionally, oxygen desaturation thresholds related to altitude or exercise should be prespecified. In healthy individuals, one can argue that even very severe hypoxemia can be tolerated without persistent harm, but this might not be the case in patients with COPD, a systemic disease affecting all organs, including the heart and the cerebral circulation. We conducted several trials in COPD patients and, apart of short syncopes after exercise or requested oxygen therapy after exercise due to dyspnea, no emergencies and no persistent adverse effects occurred. To avoid any severe adverse events in this trial, we decided to let patients exercise on a semi-supine bicycle so that patients could not fall down in case of any sudden weakness or syncopy. Additional advantages are the relatively small movement artefacts that reduce artifacts in physiological measurements compared to upright bicycle exercise. However, maximal oxygen uptake and exercise performance is reduced with semi-recumbent compared to upright sitting bicycle exercise.[93]

We decided to assess endurance of submaximal exercise instead of assessing maximal performance also in part for safety reasons. In addition, in comparison to 6-minute walk test or maximal bicycle exercise test, it has been shown that submaximal exercise performance is the most sensible to changes in COPD therapy.[94] Thus, in a double-blind, placebo-controlled, crossover

trial in 38 stable COPD patients inhaling an anticholinergic agent (oxitropium bromide), it was observed that 6-minute walk distance increased by only 1 % ($P<0.05$), $\dot{V}_{O_2}max$ remained unchanged but the endurance performance increased by 19 %. Apart of being more sensitive to changes, submaximal endurance is more meaningful for daily activities than maximal exercise capacity. This is supported by the broad application of endurance exercises during pulmonary rehabilitation.

Physiological outcomes were mainly assessed by simple and non-invasive techniques. In high altitude field studies such as those performed within my thesis it was not feasible to study brain metabolism, perfusion or oxygenation by magnetic resonance imaging, jugular venous saturation or brain tissue oxygen tension measurements, the latter both invasive techniques. Instead of applying invasive measurement techniques, I decided to use noninvasive, simple, validated measurements which correlate well with the gold standards, such as NIRS or transcranial Doppler ultrasound measurements of the middle cerebral artery.[95,96] There has been a debate whether the signal of NIRS sensors placed on the forehead might be contaminated by extracranial microcirculation. However after separating the emitting and detecting sensor to a minimal distance of 4 cm and applying the correct differential path length factor as in our studies, this contamination has been reduced to a minimum and validation studies showed no changes in the NIRS signals when manipulating extracranial microcirculation.[95,97] Additionally, cerebral tissue oxygenation measured at the frontal lobe correlates well with other brain areas, such as premotor and motor cortices.[98] Furthermore, instead of performing inspiratory capacity maneuvers during exercise to assess the degree of dynamic hyperinflation, operational lung volumes were recorded unobtrusively without requirement for specialized maneuvers by calibrated inductive plethysmography. Inspiratory capacity maneuvers in COPD bear the risk of additionally hyperinflate the patient and artificially terminate exercise.

Altitude related adverse health effects (ARAHE) was the primary outcome of the second trial of this thesis. This outcome, described in detail in section 5, is a composite endpoint including various clinically relevant conditions which might expose patients with COPD at increased health risk when staying at high altitude without therapy. Standard treatment when experiencing an ARAHE was administering supplemental oxygen. This intervention prohibited further assessment of altitude effects since hypoxemia was eliminated. As a result, results of secondary physiological outcomes in several COPD patients experiencing ARAHE were not available.

However, the main purpose of the trial was to evaluate the incidence of ARAHE and the efficacy of dexamethasone in preventing them. The secondary and exploratory outcomes were not primarily in the focus.

Nocturnal hypoxemia was the primary outcome of the third trial of this thesis. An important secondary outcome was sleep-disordered breathing characterized as the number of apneas / hypopneas per hour (the apnea/hypopnea index, AHI). This was assessed by standard respiratory polygraphy including finger pulse oximetry. To guarantee a good signal quality and to protect our patients from severe nocturnal hypoxemia, all patients were monitored throughout the entire night by an investigator. In case of severe hypoxemia or discomfort, supplemental oxygen therapy was administered. Patients receiving supplemental oxygen were excluded from the per protocol analysis of the secondary outcomes, however, data were imputed by using the multiple chained equations approach for the primary outcome (more details are available in chapter 6). Finger pulse oximetry is a reliable measurement technique at altitude.[35] Accuracy is within 2 – 3 % for a Sa_{O_2} of 70 – 100 % and maximum operation altitude is up to 12'000 m. These measurement limitations were not exceeded during our studies. Sources of error are among others, excess ambient light, hypothermia, motion artefact, nail polish, dark skin pigmentation and digital clubbing.[99] These sources of error were avoided and eliminated whenever possible.

The third trial was incorporated into the second trial. The reason for conducting two parallel, instead of two sequential studies are of ethical, financial and logistical nature to avoid unnecessary exposures of patients and excessive expenses of resources. For these two studies, over 1'000 kilogram of equipment had to be transported by airplane to Kyrgyzstan. Due to the limited examination period at high altitude (temperature, location accessible by road), the time schedule forced the study to examine up to 10 patients per day. To handle such a large volume of challenging clinical and physiological examinations, 10 – 15 investigators were constantly present during the complete study. Due to these conditions, it is obvious that we nested the second and third trial. However, both trials were prepared individually, i.e. two separate study protocols, data analysis plans, sample size estimations and two independent registrations on the ClinicalTrials website.

3.9 Purpose and objectives of this thesis

Often, due to fast passive transportation, a limited window to reach a mountain peak due to good weather conditions or other reasons, the recommended ascent rate of 300 – 500 m per day is ignored. Dependent on the individual susceptibility to hypobaric hypoxia and ascent rate, several maladaptations can occur, some life-threatening. As mentioned above, namely three major conditions are central and should be prevented as good as possible to prevent any adverse events at high altitude. First, development of *altitude-related illnesses* can significantly alter or terminate the stay at altitude. Second, *exercise intolerance* is pronounced due to lower PI_{O_2}, temperature, dehydration or altitude-related illnesses and can also result in dramatic situations. Third, *sleep disordered breathing* can alter sleep structure, sleep quality and might influence daytime performance and risk of accidents.

Little is known about physiological and clinical changes in patients with COPD travelling to high altitude, in particular with regards to these three major conditions including exercise performance, acute mountain sickness and other altitude-related adverse health effects (ARAHE) and sleep disordered breathing and their prevention with medication. It is expected that patients with COPD excessively suffer from these maladaptations since these maladaptations are strongly correlated with hypoxemia, which is assumed to be out of proportion in COPD patients travelling to high altitude due to their disease-related hypoxemia. Guidelines recommending acetazolamide or dexamethasone for prevention of AMS are applied for all subjects travelling to high altitude, independent on the underlying diseases, which might bear the risks of giving patients a false sense of security since the efficacy of these medications have not been shown in patients, i.e. COPD. The purpose of the current thesis was, therefore, to investigate physiological and clinical consequences of acute altitude exposure in patients with COPD and to investigate whether preventive dexamethasone intake mitigates these altitude-induced effects.

The main objectives of this thesis were:

1) To assess exercise performance, arterial oxygenation, nocturnal breathing stability and the incidence of ARAHE in COPD patients travelling to 2’590 m or 3’100 m compared to the same parameters at low altitude.
2) To assess efficacy of preventive dexamethasone therapy on altitude-induced physiological and clinical changes in COPD patients travelling to 3’100 m, compared to placebo.

4 Exercise performance in lowlanders with COPD at 2’590 m

The author’s contribution

MF wrote the study protocol and the ethics application including case report forms, tested physiological assessments in preliminary experiments, was involved in the recruitment of COPD patients, performed 38 out of 52 (73 %) consecutive study days, processed all raw data, performed all statistics, created all figures, and drafted the manuscript.

Citation

Furian M, Hartmann SE, Latshang TD, Flueck D, Murer C, Scheiwiller PM, Osmonov B, Ulrich S, Kohler M, Poulin MJ, Bloch KE. Exercise performance of lowlanders with COPD at 2,590 m: Data from a randomized trial. Respiration 2018;95(6):422-432.[68]

4.1 Introduction

Worldwide, millions of people travel to high altitude for professional or recreational activities, which is generally well tolerated by healthy individuals. In turn, patients with pre-existing lung disease such as COPD may experience pronounced exercise limitation at altitude that restrict their daily activities. Near sea level, exercise performance in COPD patients is impaired by dyspnea,[100] gas exchange and ventilatory limitations with dynamic hyperinflation,[101,102] muscle dysfunction[103] and several other factors.[52] The reduced $P_{I_{O_2}}$ at higher altitude may aggravate the impairment of exercise performance by inducing hypoxemia and pulmonary vasoconstriction. Further, mechanical ventilatory constraints that impair the response to hypoxemia may unmask additional factors limiting exercise performance such as cerebral hypoxia as suggested by studies in healthy subjects.[20,104] In COPD patients the physiological effects of altitude exposure have not been studied in detail. Therefore, the purpose of the current study was to quantify the changes in exercise performance in lowlanders with COPD ascending from 490 to 2’590 m and to test the hypothesis that altitude-induced changes in exercise performance are associated with changes in systemic and cerebral availability of oxygen.

4.2 Materials and Methods

4.2.1 Design

The current data were collected in participants of a randomized trial evaluating adverse effects of altitude exposure in COPD patients travelling from 490 to 2’590 m (ClinicalTrial.gov NCT01875133). The data on cardiopulmonary exercise and cerebral blood flow presented here have not been published as part of another publication.

4.2.2 Participants

Patients with COPD, GOLD grade 2 – 3 (FEV_1 / FVC <0.7 and FEV_1 30 – 80 % predicted) according to GOLD criteria, aged 18 to 75 years, both genders, residing below 800 m, were invited to participate. Exclusion criteria were a resting SpO_2 <92 % at 490 m or <80 % at 2’590 m right before exercise, any acute intercurrent disease, or inadequately controlled cardiovascular disease, previous stroke, and obstructive sleep apnea. Informed written consent was obtained and the study was approved by the institutional ethics committee of the Canton Zurich, Switzerland (EK-2013-0088).

4.2.3 Interventions

Participants spent 2 days each at 490, 1'650, and 2'590 m (mean barometric pressures (P_B) of 720, 626 and 562 mmHg, respectively). According to the rationale of the main trial, patients were randomized to one of the following 4 different altitude exposure sequences: A) 490 – 1'650 – 2'590 m; B) 490 – 2'590 – 1'650 m; C) 1'650 – 2'590 – 490 m; D) 2'590 – 1'650 – 490 m. Due to logistic reasons, assessments for the current study could only be performed at 490 and 2'590 m. Transfers between locations were made by train (Zurich to Davos) and cable car (1'650 to 2'590 m) within 2 – 5 hours.

On the second day, after the first night at 490 and 2'590 m, between 14:00 – 17:00, patients performed cycling exercise to exhaustion in a semi recumbent position (60° head-up, Ergoline GmbH, Bitz, Germany). At 490 and 2'590 m individually, identical constant load protocols were applied with a mean ± SD load of 65 ± 29 watts corresponding to 60 % of maximum work rate assessed by ramp protocol at 490 m. Baseline measurements were obtained during 3 minutes at rest on the bicycle. Patients then started cycling at 60 rpm and were encouraged to continue as long as possible. End-exercise was defined as a reduction of cycling frequency to <40 rpm.

4.2.4 Assessments

Work rate and breath-by-breath pulmonary gas exchange were recorded by a metabolic unit (Ergostick, Geratherm Medical AG, Gschwenda, Germany) according to standard techniques.[105] According to convention, minute ventilation ($\dot{V}_E$) and tidal volume (V_T) were expressed in body temperature, pressure and humidity conditions (BTPS), oxygen uptake ($\dot{V}_{O_2}$) and carbon dioxide output ($\dot{V}_{CO_2}$) in standard temperature, pressure, dry (STPD) conditions. To adjust for the increase in $\dot{V}_E$ (measured in BTPS) related to the lower barometric pressure (PB) at 2,590 m, values of ventilatory equivalents adjusted to barometric pressure at 490 m were computed so that the molecular gas flow corresponded to that at 490 m, i.e., $\dot{V}_E / \dot{V}_{CO_2}$ adj = $[\dot{V}_{E\,2'590\,m} * (P_{B\,2'590\,m} - P_{H_2O}) / (P_{B\,490\,m} - P_{H_2O})] / \dot{V}_{CO_2}$. Breathing reserve was computed as 40* FEV_1-$\dot{V}_E$ at end-exercise and the dead space to V_T ratio as $V_D / V_T = [(Pa_{CO_2} - PET_{CO_2}) / Pa_{CO_2}]$.[105] Breath by breath changes in end-expiratory lung volume (EELV) were monitored unobtrusively by calibrated respiratory inductive plethysmography operated in the direct current (DC) mode (Respitrace, NIMS, Miami Beach, USA).[106,107] The intention was to avoid potential alterations in the natural breathing pattern by repeated inspiratory capacity

maneuvers. Operating lung volumes were calculated as follows: functional residual capacity (FRC) at rest was measured by body plethysmography (see below); EELV over the course of exercise was calculated as FRC + change in EELV over the course of exercise; end-inspiratory lung volume (EILV) was calculated as EELV + tidal volume; inspiratory reserve volume (IRV) was calculated as TLC - EILV. SpO_2, the electrocardiography (ECG), blood pressure, near-infrared spectroscopy (NIRS) of the frontal brain and quadriceps muscles, and blood flow velocity in the middle cerebral artery (MCA) by transcranial Doppler ultrasound were continuously recorded.

NIRS optodes (NIRO 200NX, Hamamatsu, Japan) were placed bilaterally at the Fp1 and Fp2 landmarks of the 10-10 electrode placement system[108] and bilaterally over the vastus lateralis muscles.[109] Mean values of bilateral cerebral (CTO) and bilateral quadriceps muscle (MTO) tissue oxygenation, calculated as ratio of oxygenated / (oxygenated + deoxygenated hemoglobin concentration), are reported. A 2 MHz ultrasound Doppler probe (TOC2M, Multigon Industries, New York, USA) was placed over the temporal window to record the right MCA peak blood flow velocity (MCAv).[110] The cerebral blood flow response to the exercise-induced change in CTO was quantified by calculating the ratio of change in MCAv per change in SpO_2. Continuous blood pressure recordings were obtained by the finger-cuff technique (Finometer Midi, Finapress Measurement Systems, Amsterdam, The Netherlands). At both altitudes arterial blood samples were drawn during a resting period before exercise and during the final 30 seconds of end-exercise. Spirometry, body plethysmography and measurement of single breath diffusing capacity were performed according to standard techniques with reference values of the Global Lung Function Initiative (GLI) and Quanjer et al.[111-115] Dyspnea and leg fatigue were rated on the Borg CR10 scale.

4.2.5 Outcomes

The main outcome of this study was the change in cycling endurance between measurements at 490 and 2’590 m. Additional outcomes were changes in physiological variables.

4.2.6 Data analysis

Data are summarized as medians and quartiles. Analyses were performed according to the per protocol approach including data from patients with complete data. Median values of physiological variables measured during 3 minutes of quiet rest, during the final 30 sec of end-exercise and during the time (isotime) corresponding to end-exercise time in tests with shorter endurance

were computed. Paired comparisons were performed by Wilcoxon signed rank tests and by computing median differences with 95 % confidence intervals (CI). Multivariate regression analysis was performed to elucidate whether the order of altitude exposure, baseline endurance or other baseline variables were independent predictors of exercise endurance at 2’590 m. Outcome assessors were blinded to altitude allocation. A probability <0.05 was considered statistically significant.

4.3 Results

The patient flow chart is shown in Figure ***4-1***. Of 40 randomized patients, 9 datasets had to be excluded, leaving 31 for the per protocol analysis. Patient characteristics are summarized in Table 4-1.

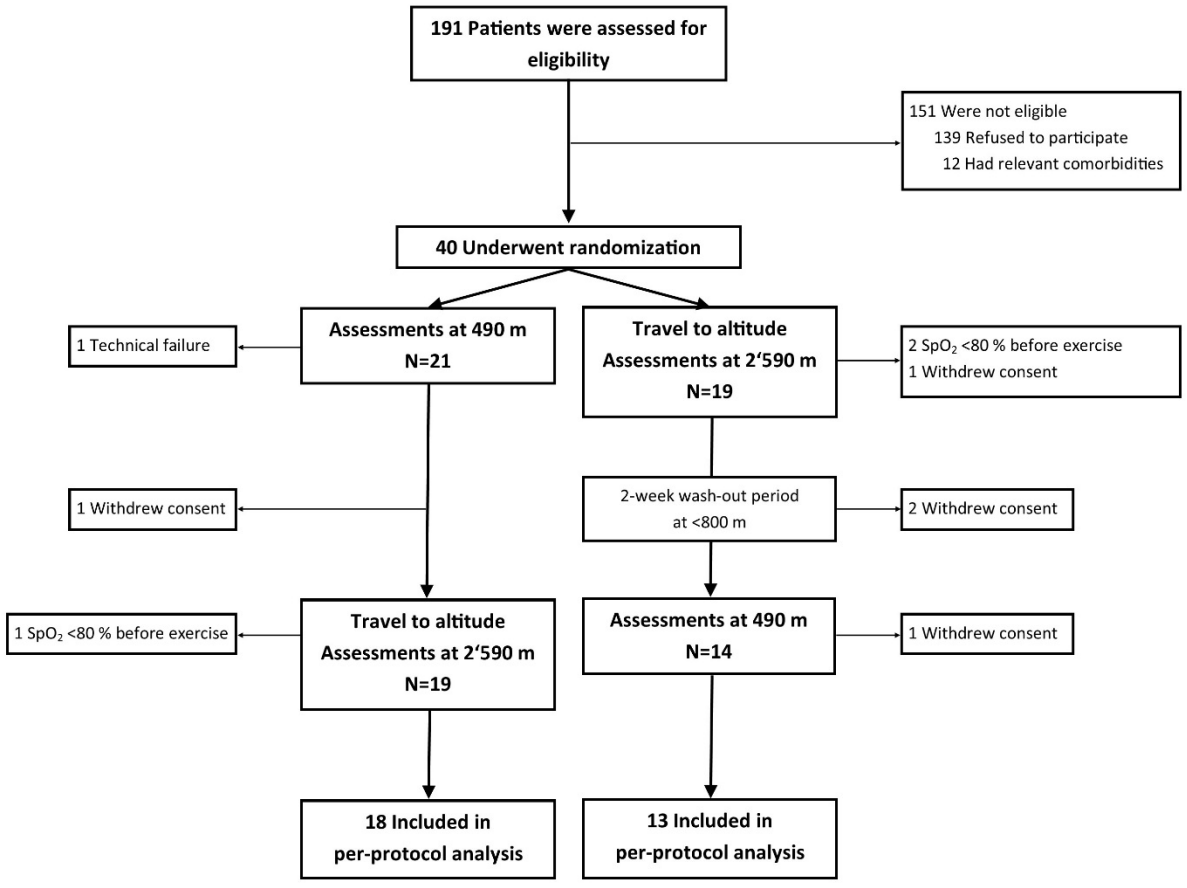

Figure 4-1. Patient flow in the study.

Table 4-1. Patient characteristics.

N, (males / females)	31 (19 / 12)	
Age, years	66 (59;69), range 51 to 74	
Body mass index, kg/m^2	27.3 (22.0;29.4)	
Smoking habits, current / former / never	7 / 22 / 2	
Smoking, pack years	40 (20;60)	
Pulmonary function and oxygen uptake	**At 490 m**	**At 2’590 m**
FVC, L	3.36 (2.63;4.01)	3.30 (2.87;4.07)
FVC, % predicted	88 (77;100)	92 (77;101)
FEV_1, L	1.69 (1.28;2.14)	1.76 (1.33;2.17)
FEV_1, % predicted	56 (49;69)	53 (48;66)
FEV_1 / FVC, %	52 (46;63)	55 (46;64)
FEV_1 / FVC, % predicted	66 (58;80)	70 (57;81)
TLC, L	6.79 (5.77;7.79)	
TLC, % predicted	110 (96;117)	
RV, L	2.94 (2.55;3.39)	
RV, % predicted	127 (118;140)	
RV / TLC, %	45 (40;50)	
FRC, L	4.36 (3.62;5.14)	
FRC, % predicted	135 (125;153)	
DLCO, mmol/min/kPa	4.58 (3.78;6.92)	
DLCO, % predicted	58 (47;77)	
$\dot{V}_{O_2 max}$, L/min	1.24 (1.04;1.46)	
$\dot{V}_{O_2 max}$, % predicted	67 (54;78)	
$\dot{V}_{O_2 max}$, mL/min/kg	16.95 (14.55;19.95)	
Comorbidities		
Arterial hypertension, n (%)	13 (42)	
Coronary heart disease, n (%)	4 (13)	
Diabetes, n (%)	2 (6)	
Medications		
Inhaled beta-adrenergics, n (%)	23 (74)	
Inhaled anti-cholinergics, n (%)	25 (81)	
Inhaled corticosteroids, n (%)	17 (55)	
ACE inhibitor, n (%)	5 (16)	
Beta blocker, n (%)	7 (23)	

Values are numbers of patients (% of group) and medians (quartiles). FVC = Forced vital capacity; FEV_1 = Forced expiratory volume in the first second; TLC = Total lung capacity; RV = Residual volume; FRC = Functional residual volume; DLCO = Diffusion capacity of the lung for carbon monoxide; $\dot{V}_{O_2 max}$ = Maximum oxygen uptake; ACE = Angiotensin converting enzyme.

With ascent from 490 to 2’590 m, there was a major reduction in exercise endurance time from a median (quartiles) 500 (256 ; 795) sec at 490 m to 205 (139 ; 297) sec at 2’590 m, i.e., by a median difference (95 % CI) of −303 (−420 to −150) sec corresponding to a mean relative change of −54 (−67 to −40) % (Figure 4-2). Numerical results are listed in Table 4-2 and a synopsis of the physiological response is provided in Figure 4-3.

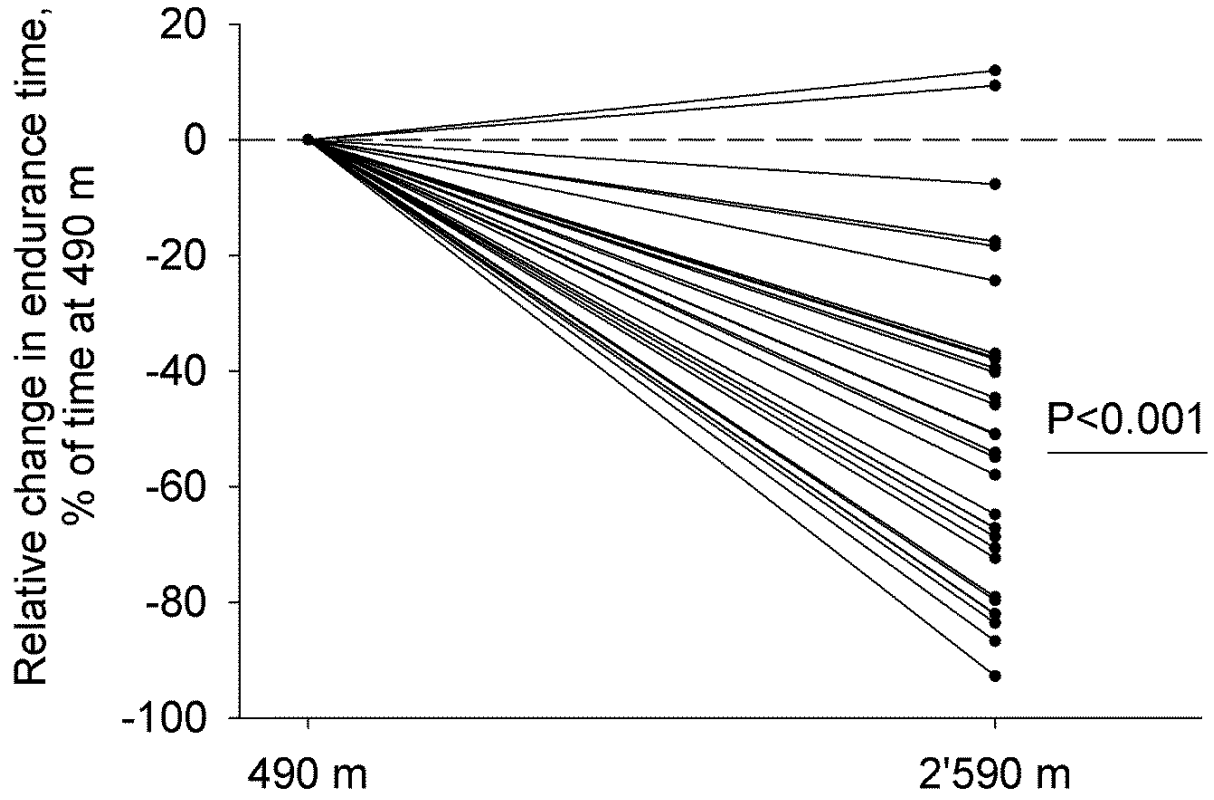

Figure 4-2. Relative changes in endurance assessed by constant load bicycle exercise in patients with COPD at 2’590 m compared to the baseline value at 490 m. *Individual values and the median change (horizontal line, reduction by 54%) are shown.*

Compared to 490 m, resting Pa_{O_2}, Sa_{O_2} and Pa_{CO_2}, were reduced at 2’590 m in association with an increased $\dot{V}_E$, breath rate and ventilatory equivalents for oxygen uptake ($\dot{V}_E$ / $\dot{V}_{O_2}$) and carbon dioxide output ($\dot{V}_E$ / $\dot{V}_{CO_2}$) (Table 4-2, Figure 4-3, Panels A-I). Resting and end-exercise CTO were also reduced at 2’590 m compared to 490 m but the differences in MCAv and in MTO between values at 490 and 2’590 m, respectively, were not statistically significant (Figure 4-3, Panels B-C).

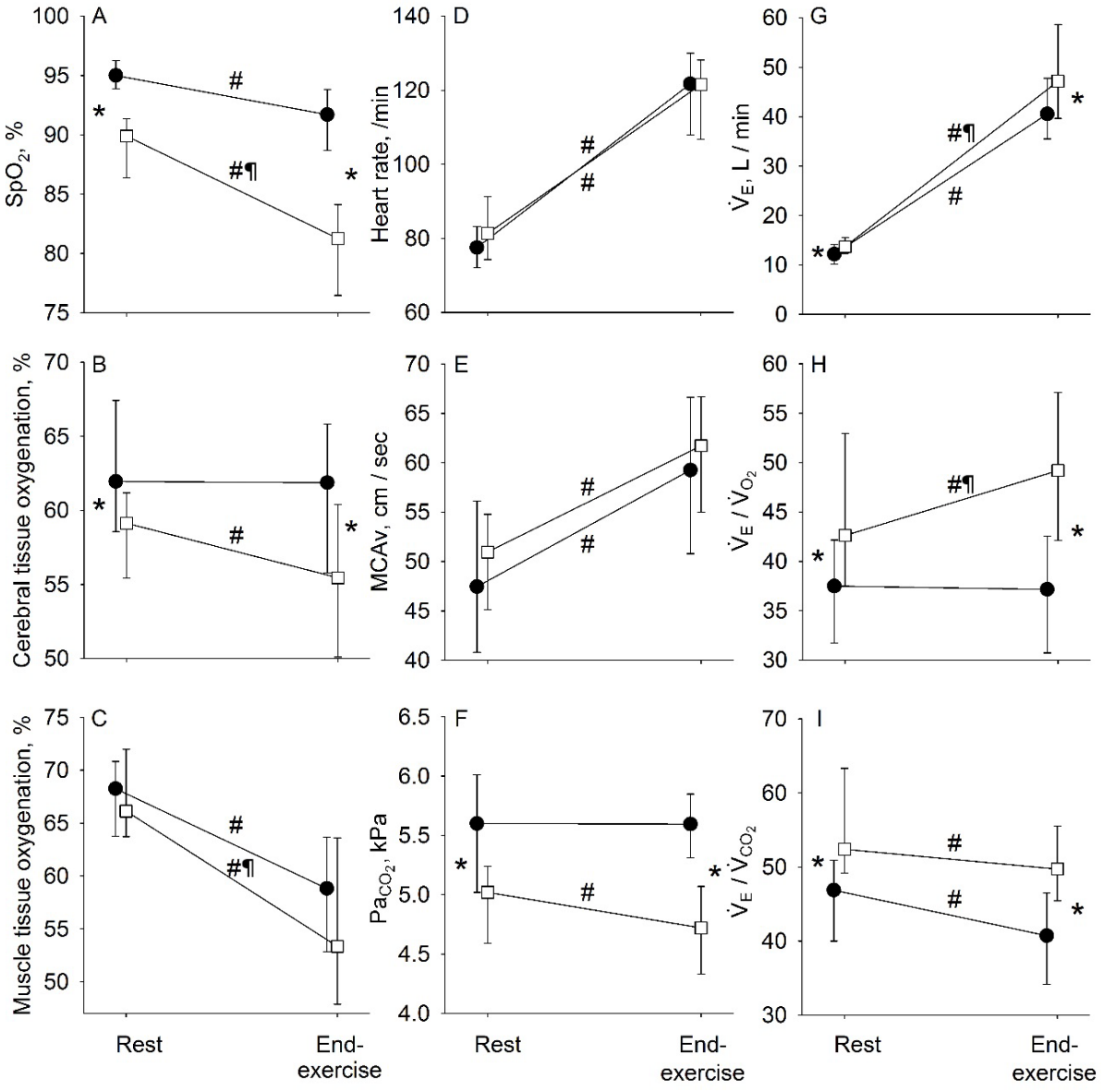

Figure 4-3. Changes in physiological variables from rest to end-exercise at 490 m (filled circles) and 2’590 m (open squares) shown as median and quartile ranges. *Panel A: Pulse oximetry (SpO_2); Panel B: Cerebral tissue oxygenation; Panel C: Muscle tissue oxygenation; Panel D: Heart rate; Panel E: Middle cerebral artery peak blood flow velocity (MCAv); Panel F: Partial pressure of CO_2 in arterial blood (Pa_{CO_2}); Panel G: Minute ventilation ($\dot{V}_E$); Panel H: Ventilatory equivalent for O_2 ($\dot{V}_E / \dot{V}_{O_2}$); Panel I: Ventilatory equivalent for CO_2 ($\dot{V}_E / \dot{V}_{CO_2}$). *p <0.05 for comparison of corresponding variables at 490 m and 2’590 m; #p <0.05 for exercise-induced changes at corresponding altitude; ¶p <0.05 for comparison of corresponding exercise-induced changes from rest to end-exercise at 2’590 m vs. 490 m.*

During the final 30 secs of end-exercise at 2’590 m, $\dot{V}_{CO_2}$ and, to a greater extent $\dot{V}_{O_2}$, were lower than corresponding values at 490 m so that the respiratory exchange ratio (RER) was

increased at 2'590 m. At end-exercise, $\dot{V}_E$, breath rate and ventilatory equivalents were all elevated at 2'590 m vs. 490 m (Table 4-2, Figure 4-3). Adjusted ventilatory equivalents at 2'590 m were still slightly elevated over values at 490 m with exception of $\dot{V}_E / \dot{V}_{CO_2}$ at end-exercise (Table 4-2).

Breathing reserve, computed as ($40 * FEV_1 - \dot{V}_E$), was reduced more at 2'590 m than at 490 m. End-expiratory lung volumes increased significantly from rest to end-exercise to a similar degree at both altitudes. Operational lung volumes (IRV and EILV) at end-exercise were also similar at both altitudes (Table 4-2 and Table 4-3).

Table 4-2. Performance and physiological response to exercise at 490 and 2'590 m.

	490 m		2'590 m	
	Rest	**End-exercise**	**Rest**	**End-exercise**
Endurance, time in sec	NA	500 (256;795)	NA	205 (139;297)*
$\dot{V}_{O_2}$, L/min	0.25 (0.20;0.30)	1.01 (0.82;1.23)*	0.26 (0.19;0.33)	0.89 (0.64;1.08)*¶
$\dot{V}_{O_2}$, % pred. $\dot{V}_{O_2 max}$	15 (12;16)	62 (50;72)*	14 (12;16)	50 (40;61)*¶
$\dot{V}_{CO_2}$, L/min	0.22 (0.16;0.24)	0.91 (0.69;1.13)*	0.21 (0.15;0.26)	0.88 (0.64;1.07)*¶
Respiratory exchange ratio	0.80 (0.75;0.84)	0.90 (0.84;0.94)*	0.80 (0.75;0.84	0.99 (0.90;1.06)*¶
Minute ventilation, L/min	12.2 (10.2;14.1)	40.6 (35.5;47.8)*	13.7 (12.4;15.6)¶	47.2 (39.6;58.7)*¶
Tidal volume, L	0.7 (0.5;0.9)	1.2 (1.1;1.7)*	0.7 (0.6;0.9)	1.3 (1.1;1.6)*
Breathing rate, 1/min	20 (18;23)	35 (31;37)*	21 (18;28)¶	36 (31;42)*¶
Breathing reserve, L/min	55.4 (38.1;76.1)	23.2 (11.9;37.8)*	54.4 (37.7;73.7)	17.6 (8.2;26.5)*¶
Change in EELV, L	0	0.28 (0.06;0.50)*	0	0.26 (0.05;0.47)*
IRV, L	1.66 (1.10;1.89)	0.95 (0.45;1.24)*	1.52 (1.10;1.83)	0.84 (0.63;1.17)*
IRV / predicted TLC	0.15 (0.05;0.26)	0.05 (-0.08;0.16)*	0.12 (-0.01;0.28)	0.02 (-0.11;0.15)*
EILV / TLC	0.78 (0.72;0.81)	0.86 (0.82;0.92)*	0.78 (0.70;0.82)	0.86 (0.82;0.91)*
EILV / predicted TLC	0.85 (0.74;0.95)	0.95 (0.84;1.08)*	0.88 (0.72;1.01)	0.98 (0.85;1.11)*
$\dot{V}_E / \dot{V}_{O_2}$	37.5 (31.7;42.2)	37.2 (30.7;42.6)	42.6 (37.5;53.0)¶	49.2 (42.1;57.1)*¶
$\dot{V}_E / \dot{V}_{O_2}$ adj.to $P_{B490\,m}$	NA	NA	40.1 (35.9;53.3)¶	41.2 (35.6;49.3)¶
$\dot{V}_E / \dot{V}_{CO_2}$	46.9 (40.0;50.9)	40.7 (34.2;46.5)*	52.4 (49.2;63.3)¶	49.7 (45.5;55.5)*¶
$\dot{V}_E / \dot{V}_{CO_2}$ adj.to $P_{B490\,m}$	NA	NA	50.3 (44.7;65.4)¶	42.4 (38.1;47.4)
$P_{ET_{CO_2}}$, kPa	3.8 (3.5;4.0)	4.6 (4.0;4.9)*	2.9 (2.2;3.4)¶	3.3 (2.9;3.5)*¶
V_D / V_T	0.33 (0.25;0.36)	0.22 (0.11;0.32)*	0.44 (0.30;0.51)¶	0.27 (0.22;0.37)*¶
SpO_2, %	95 (94;96)	92 (89;94)*	90 (86;91)¶	81 (77;84)*¶
pH	7.42 (7.40;7.44)	7.38 (7.35;7.41)*	7.45 (7.43;7.46)¶	7.42 (7.39;7.45)*¶
Pa_{CO_2}, kPa	5.6 (5.0;6.0)	5.6 (5.5;5.8)	5.0 (4.6;5.2)¶	4.7 (4.3;5.1)*¶
Pa_{O_2}, kPa	9.0 (8.4;9.4)	8.3 (6.8;8.7)	6.7 (6.3;7.4)¶	5.8 (5.5;6.5)*¶
Sa_{O_2}, %	94 (92;95)	93 (92;94)	85 (82;89)¶	80 (75;83)*¶
$DAaP_{O_2}$, kPa	5.6 (5.0;6.8)	6.8 (5.7;7.5)	3.0 (2.4;3.4)¶	3.7 (2.8;4.2)*¶

Table 4-2. Performance and physiological response to exercise at 490 and 2'590 m.

	490 m		2'590 m	
	Rest	**End-exercise**	**Rest**	**End-exercise**
Heart rate, 1/min	78 (72;83)	122 (108;130)*	81 (74;91)	122 (107;128)*
Heart rate reserve, 1/min	78 (70;85)	33 (24;46)*	75 (62;82)	34 (25;47)*
Mean arterial BP, mmHg	108 (99;116)	138 (119;157)*	113 (99;120)	147 (126;155)*
CTO, %	62 (59;67)	62 (56;66)	59 (55;61)¶	55 (50;60)*¶
MTO, %	68 (64;71)	59 (53;64)*	66 (64;72)	53 (49;64)*
MCAv, cm/sec	47 (41;56)	59 (51;67)*	51 (45;55)	62 (55;67)*
MCAv response to hypoxia, %/%	NA	6 (3;12)	NA	3 (2;5)¶
Borg Dyspnea	0.5 (0;1)	5 (4;7)*	0 (0;1)	7 (5;8)*¶
Borg Leg fatigue	0 (0;0.5)	4 (3;6)*	0 (0;1)	4 (2;5)*

N = 31, medians (quartiles). Arterial blood gases were available at rest and during exercise in 31 and 10 patients at 490 m, respectively, and in all patients at 2'590 m. *p <0.05 vs. rest at corresponding altitude; ¶p <0.05 vs. corresponding value at 490 m at rest or end-exercise, respectively. $\dot{V}_{O_2}$ = Oxygen uptake; $\dot{V}_{CO_2}$ = Carbon dioxide production; EELV = End-expiratory lung volume; IRV = Inspiratory reserve volume; TLC = Total lung capacity; EILV = End-inspiratory lung volume; $\dot{V}_E$= Minute ventilation; $\dot{V}_E / \dot{V}_{CO_2}$ and $\dot{V}_E / \dot{V}_{O_2}$ adj.to $P_{B490\,m}$ = Adjusted values that account for changes in barometric pressure in values expressed in BTPS, see methods for explanation; PET_{CO_2}= End-tidal CO_2 partial pressure; V_D / V_T = Dead space to tidal volume ratio; SpO_2 / Sa_{O_2} = Arterial oxygen saturation by pulse oximetry and by co-oximetry, respectively; Pa_{CO_2}= Partial pressure of CO_2 in arterial blood; Pa_{O_2} = Partial pressure of O_2 in arterial blood; $DAaP_{O_2}$ = Alveolar-arterial P_{O_2} difference[116]; BP = Blood pressure; CTO = Cerebral tissue oxygenation; MTO = Muscle tissue oxygenation; MCAv = Middle cerebral artery peak blood flow velocity; MCAv response to hypoxia = % increase MCAv / % SpO_2 desaturation. Breathing reserve was computed as 40 * $FEV_1 - \dot{V}_E$ at end-exercise.

Pulse oximetry revealed a significant fall in SpO_2 at rest and during exercise at 2'590 m vs. 490 m and the exercise-induced drop in SpO_2 was more pronounced at 2'590 m (Table 4-2, Figure 4-3, Panel A). Arterial blood gas analysis at 2'590 m revealed a considerable exercise-induced fall in Pa_{O_2} and Sa_{O_2} from resting values and the Pa_{CO_2} at end-exercise at 2'590 m was also reduced compared to resting values. Calculation of the death space fraction (physiological dead space (V_D) / V_T = Pa_{CO_2}− partial pressure of end-tidal CO_2 (PET_{CO_2}) / Pa_{CO_2}) revealed a reduction with exercise at both altitudes.

The heart rate and mean blood pressure at end-exercise were similar at both altitudes. Despite a more pronounced exercise-induced arterial hypoxemia, a similar increase in MCAv was observed at both altitudes (Figure 4-3, Panel E). The cerebral blood flow response to exercise-induced arterial hypoxemia, expressed as change in MCAv per change in SpO_2, was therefore lower at 2'590 m compared to 490 m (Table 4-2, Figure 4-3). CTO remained stable over the

course of exercise at 490 m but decreased at 2’590 m to lower end-exercise values than those at 490 m (Figure 4-3, Panel B). MTO decreased with exercise at both altitudes (Figure 4-3, Panel C).

Comparison of values recorded at end-exercise at 2’590 m and at isotime at 490 m revealed that patients had lower $\dot{V}_{O_2}$ and higher $\dot{V}_E$, RER and heart rate, were more hypoxemic, had a lower CTO and MTO at 2’590 m compared to 490 m (Table 4-3). Borg dyspnea but not leg fatigue ratings at end-exercise were increased at 2’590 m vs. 490 m.

Multivariable regression analysis with endurance at 2’590 m as (log transformed) dependent variable revealed that altitude (coefficient [95% confidence interval] −0.452 [−0.558 to −0.347], P <0.001), baseline endurance (coefficient 0.0007 [0.0005 to 0.0008], P <0.001) and baseline FEV_1 % predicted (coefficient 0.014 [0.006 to 0.022], P = 0.001) were significant independent predictors, whereas the order of altitude exposure (coefficient 0.083 [−0.019 to 0.184], P = 0.112), baseline SpO_2 (coefficient −0.014 [−0.074 to 0.045], P = 0.633) and lung diffusing capacity (coefficient −0.409 [−1.062 to 0.245], P = 0.220) were not (R^2 = 0.7603, P <0.001).

Table 4-3. Physiological response to exercise at 490 and 2’590 m at isotime.

	490 m	**2’590 m**
Endurance, time in sec	205 (139;297)	205 (139;297)
$\dot{V}_{O_2}$, L/min	0.93 (0.78;1.14)*	0.90 (0.64;1.08)*¶
$\dot{V}_{O_2}$, % pred. $\dot{V}_{O_2 max}$	56 (48;68)*	50 (41;61)*¶
$\dot{V}_{CO_2}$, L/min	0.83 (0.65;1.06)*	0.88 (0.64;1.07)*
Respiratory exchange ratio	0.91 (0.84;0.93)*	0.99 (0.90;1.06)*¶
Minute ventilation, L/min	34 (31;43)*	47.5 (39.6;58.7)*¶
Tidal volume, L	1.3 (1.1;1.8)	1.4 (1.1;1.8)*
Breathing rate, 1/min	28 (23;32)*	36 (31;42)*¶
Breathing reserve, L/min	28.0 (17.2;49.0)*	18.7 (8.3;35.2)*¶
Change in EELV, L	0.27 (0.13;0.49)	0.12 (0.00;0.63)
IRV, L	0.81 (0.34;1.18)*	0.84 (0.62;1.17)*
IRV / predicted TLC	0.05 (-0.09;0.16)*	-0.01 (-0.13;0.15)*
EILV / TLC	0.87 (0.83;0.94)*	0.86 (0.82;0.91)*
EILV / predicted TLC	0.95 (0.84;1.09)*	1.01 (0.85;1.13)*
$\dot{V}_E / \dot{V}_{O_2}$	36 (29;40)	49 (42;57)*¶
$\dot{V}_E / \dot{V}_{O_2}$ adj.to $P_{B490\,m}$	NA	41 (36;49)
$\dot{V}_E / \dot{V}_{CO_2}$	40 (34;43)*	50 (45;55)*¶

$\dot{V}_E$ / $\dot{V}_{CO_2}$ adj.to $P_{B490\,m}$	NA	42 (38;47)*
SpO_2, %	93 (89;95)*	81 (77;84)*¶
Heart rate, 1/min	109 (103;119)*	122 (107;128)*¶
Heart rate reserve, 1/min	47 (32;54)*	35 (25;47)*¶
Mean arterial BP, mmHg	136 (126;148)*	149 (126;158)*¶
CTO, %	62 (57;65)	55 (50;60)*¶
MTO, %	58 (53;65)*	53 (48;64)*¶
MCAv, cm/sec	59 (52;70)*	62 (52;67)*
MCAv response to hypoxia, %/%	3 (1;7)	2 (1;2)

Isotime refers to the time of end-exercise in the test with the shorter endurance. In 29 of 31 instances, this was the test at 2’590 m (see *Figure 4-2*). Values are medians (quartiles). *p <0.05 vs. rest at corresponding altitude; ¶p <0.05 vs. isotime at 490 m; $\dot{V}_{O_2}$ = Oxygen uptake; $\dot{V}_{CO_2}$ = Carbon dioxide production; EELV = End-expiratory lung volume; IRV = Inspiratory reserve volume; TLC = Total lung capacity; EILV = End-inspiratory lung volume; $\dot{V}_E$= Minute ventilation; $\dot{V}_E$ / $\dot{V}_{CO_2}$ and $\dot{V}_E$ / $\dot{V}_{O_2}$ adj.to $P_{B490\,m}$ = Adjusted values that account for changes in barometric pressure in values expressed in BTPS, see methods for explanation; SpO_2 = Arterial oxygen saturation by pulse oximetry; BP = Blood pressure; CTO = Cerebral tissue oxygenation; MTO = Muscle tissue oxygenation; MCAv = Middle cerebral artery peak blood flow velocity; MCAv response to hypoxia = % increase MCAv / % SpO_2 desaturation. Breathing reserve was computed as 40 * FEV_1 – $\dot{V}_E$ at end-exercise.

4.4 Discussion

The main finding in the current randomized trial in lowlanders with moderate to severe COPD (GOLD grade 2 – 3) was a major reduction in endurance during constant load bicycle exercise at 2’590 m compared to baseline values at 490 m. The performance decrements at 2’590 m were associated with arterial hypoxemia, deoxygenation of muscle and cerebral tissues and an impaired cerebral blood flow response to the exercise-induced decline in CTO. The breathing reserve was reduced more at 2’590 m compared to 490 m with associated higher ventilatory equivalents for $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ and dynamic hyperinflation. Therefore, the greater degree of dyspnea and impairment of exercise performance that lowlanders with COPD experience at moderate altitude is multifactorial, likely involving impairments in systemic and cerebral availability of oxygen, as well as in pulmonary gas exchange.

In 51 healthy young men ascending from 490 m to 2’590 m within a few hours, we previously observed a decrease in resting SpO_2 from 95 % to 91 % associated with a decrease in $P_{ET_{CO_2}}$ (the surrogate of the Pa_{CO_2}) from 5.3 to 4.8 kPa.[117] This was consistent with an increase in ventilatory drive, and thus alveolar ventilation, induced by the hypobaric hypoxia. Exercise tests were not performed in that study. Investigations in 8 elite cyclists at sea level and after 1 day of exposure to 2’340 m revealed a decrease in maximal work capacity by 14 %, $\dot{V}_{O_2}$max

by 13 % and in maximal cycling endurance by 26 % at a constant load of 80 % of sea level maximal work capacity.[118] Similar data on the physiologic effects of altitude in COPD patients have not been available. One uncontrolled case study in 18 COPD patients (mean FEV_1 42 % predicted) ascending within 2 – 3 hours from sea level to 2’086 m revealed a reduction in 6-minute walk distance within one hour after arrival at 2’086 m by 52 % in association with drops of SpO_2 to 75 %.[75] Participants in the current study had a slightly higher FEV_1 (60 % predicted, Table 4-1) than those in the cited study, but they were exposed to a higher altitude of 2’590 m, which may explain the similar reduction in exercise endurance by 54 % of the base value at 490 m. Differences in the timing and type of exercise hamper further comparisons between the two studies. To our knowledge, the current randomized trial provides for the first time robust quantitative data on the reduction of exercise performance and the underlying physiological mechanisms in lowlanders with COPD travelling to moderate altitude.

Our data recorded at low altitude (490 m) are consistent with those of previous studies showing a reduced breathing reserve and exercise-induced hypoxemia in patients with severe COPD.[119] Although the breathing reserve of the patients in the current study was not exhausted at any of the two altitudes it was reduced more at 2’590 m than at 490 m (Table 4-2), most likely due to hypoxic ventilatory stimulation, as well as a more pronounced ventilatory inefficiency for $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ at 2’590 m. The increases in ventilatory equivalents for $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ were mainly due to the reduced barometric pressure, since increases in these variables after adjustment for changes in gas density at 2’590 m were minor. Thus, effects of altitude-related changes in Pa_{CO_2} and alveolar P_{CO_2} and of V_D / V_T on $\dot{V}_E$ / $\dot{V}_{CO_2}$ seem to be small. The exercise-induced increase in alveolar-arterial P_{O_2} difference ($DAaP_{O_2}$)[116] at 2’590 m may have contributed to the increased $\dot{V}_E$ / $\dot{V}_{O_2}$. Despite the higher $\dot{V}_E$ at end-exercise at 2’590 m, dynamic hyperinflation was not greater at high altitude than at 490 m, which is possibly related to the reduced air density and its effect on airflow resistance at the higher altitude[120] even though FEV_1 and FEV_1 / FVC were similar at both measured altitudes. Consistently, IRV and EILV at end-exercise were similar at both altitudes suggesting that the higher $\dot{V}_E$ at 2’590 m was not associated with higher operational lung volumes. Therefore, the impairment in exercise performance and excessive dyspnea in COPD patients travelling to high altitude were more likely due to a reduced oxygenation of the brain than to mechanical ventilatory constraints. In terms of clinical implications, these findings may suggest that the reduced exercise endurance of COPD patients

at altitude might be alleviated by oxygen supplementation rather than by pharmacological bronchodilation.

The reduced $P_{I_{O_2}}$ at 2’590 m exacerbated the hypoxemia at rest and during exercise despite the hypoxic stimulation of $\dot{V}_E$ that was reflected in a lower Pa_{CO_2} at 2’590 m. In healthy subjects, cerebral deoxygenation recorded by NIRS during exposure to simulated altitude was associated with reduced exercise performance.[98] These data and improvements in CTO and exercise performance with oxygen supplementation at high altitude suggest that cerebral hypoxia plays a role in exercise limitation.[121] In the current study in COPD patients, CTO remained stable throughout the exercise tests at 490 m. However, CTO dropped significantly at 2’590 m (Table 4-1, Figure 4-3). Moreover, the response of the cerebral blood flow to hypoxemia was reduced, possibly related to hypocapnia-induced cerebral vasoconstriction at 2’590 m.[19] Cerebral hypoxia may therefore have contributed to exercise limitation in the COPD patients at 2’590 m. In contrast to CTO, MTO was similar at end-exercise at both altitudes suggesting that impairment of MTO was not a main factor in the reduced performance at 2’590 m.

Heart rates at end-exercise were similar at both altitudes. It is conceivable that hypoxemia may have restricted the maximum heart rate during exercise at 2’590 m, as reported at higher altitudes in healthy individuals.[122] Hypobaric hypoxia has been associated with an elevation of pulmonary artery[123] and systemic blood pressure.[124] Therefore, cardiovascular mechanisms may have contributed to the reduced exercise performance at 2’590 m in the COPD patients.

In terms of the clinical relevance of our findings it is important to note that, despite performing physical work to exhaustion, none of the patients with a severity grade of COPD (GOLD 2 – 3) that usually allows to be still active and consider travel experienced a serious adverse event. The selected study altitude of 2’590 m is of particular interest because it is similar to altitudes visited during recreational walking or skiing and not far off the maximal cruising altitude-equivalent permitted in commercial air flight (8’000 ft or 2’438 m). The results are therefore reassuring for COPD patients considering altitude or air travel.

4.5 Conclusions

In conclusion, our results demonstrate that COPD patients travelling to moderate altitude experience a considerable limitation of exercise performance that seems relevant to activities of daily life. The results of a comprehensive physiological evaluation performed in the current study are consistent with a reduced exercise performance, due to combined adverse effects of hypobaric hypoxia on dyspnea, pulmonary gas exchange and cerebral hypoxia. These data may help to counsel patients with COPD planning high altitude travel.

5 Efficacy of dexamethasone in preventing AMS in COPD patients

The author's contribution

MF was involved in writing the study protocol (with KEB), was involved in writing grant applications, wrote the ethic application including case report forms, was involved in the recruitment of COPD patients, was responsible for the transport of all study material from Switzerland to Kyrgyzstan, taught the procedure of examinations to Swiss and Kyrgyz investigators, supervised all examinations during 36 out of 47 (77 %) consecutive study days, processed the raw data, performed all statistics, created all figures, and drafted the manuscript.

Citation

Furian M, Lichtblau M, Aeschbacher SS, Estebesova B, Emilov B, Sheraliev U, Marazhapov NH, Mademilov M, Osmonov B, Bisang M, Ulrich S, Latshang TD, Ulrich S, Sooronbaev TM, Bloch KE. Efficacy of dexamethasone in preventing acute mountain sickness in COPD patients. Randomized trial. CHEST 2018;154(4):788-797.[125]

5.1 Introduction

AMS, the most common of the altitude-related illnesses, has been observed in 10 to 40 % of healthy lowlanders ascending rapidly to altitudes of 3'000 to 3'500 m.[36,126-128] Symptoms include headache, gastrointestinal discomfort, fatigue, weakness and dizziness. Untreated AMS may progress to HACE with loss of consciousness and eventually death.[4] Three to five percent of otherwise healthy individuals ascending rapidly to altitudes >3'500 m experience an excessive rise in pulmonary artery pressure, promoting HAPE with severe hypoxemia, dyspnea and exercise limitation. Both acetazolamide and dexamethasone are used to prevent and treat AMS and HACE while nifedipine is recommended for prevention and treatment of HAPE.[3]

As mountain tourism is increasingly popular, many patients with respiratory diseases such as COPD are also expected to be among travelers to high altitude regions worldwide. COPD is characterized by chronic airflow obstruction related to airway inflammation, remodeling and parenchymal destruction of the lung. This causes dyspnea, impaired exercise performance, hypoxemia, elevated pulmonary artery pressure and other morbidities.[48] Previous observations have raised concerns that the reduced inspiratory oxygen partial pressure during altitude travel in the presence of impaired pulmonary gas exchange may predispose patients with lung disease such as COPD to pronounced hypoxemia and thus AMS[62] and other ARAHE although this has not been conclusively studied. Moreover, measures to prevent AMS / ARAHE in COPD patients have not been evaluated. In healthy individuals dexamethasone has been shown to reduce the incidence of AMS,[127,129-131] and glucocorticoids are prescribed to treat exacerbations in COPD patients.[48] Therefore, we designed the current randomized, placebo-controlled trial to test the hypothesis that dexamethasone prevents or reduces AMS / ARAHE in lowlanders with COPD travelling to high altitude.

5.2 Materials and Methods

5.2.1 Design

This randomized, placebo-controlled, double-blind, parallel-group trial was conducted from 30.4. – 6.8.2015 at the National Center for Cardiology and Internal Medicine, Bishkek (760 m), and the high-altitude clinic Tuja-Ashu (3'100 m), Kyrgyzstan. The clinical trial was registered at www.clinicaltrials.gov NCT02450968.

5.2.2 Participants

Men and women, aged 20 to 75 years, with mild to moderate COPD diagnosed according to the GOLD guidelines[48] (post bronchodilator FEV_1 / FVC <0.7 and FEV_1 >50 % predicted) living below 800 m were recruited in the Bishkek area. Patients with SpO_2 <92 % at 760 m, unstable condition requiring systemic glucocorticoids, suffering from unstable cardiovascular disease or previous myocardial infarction or stroke were not admitted. Patients did not stay at altitudes >1'500 m within 4 weeks before study entry. Participants gave written informed consent and the protocol was approved by the institutional ethics committee in Bishkek, Kyrgyzstan, (01-8/405) and endorsed by the ethics committee Zurich, Switzerland (46-2015).

5.2.3 Interventions

After undergoing baseline evaluation in Bishkek (760 m), participants travelled to the altitude clinic (3'100 m) by minibus within 3 – 5 hours and stayed there for 2 days / nights. On the day before ascent and while staying at 3'100 m participants took oral dexamethasone, 2 x 4 mg capsules / day, or identically looking placebo capsules.

5.2.4 Assessments

A medical history was obtained, and a clinical examination performed. The New York Heart Association (NYHA) functional class and COPD symptoms (COPD Assessment Test, CAT)[132] were determined.

AMS was assessed in the morning and evening by the Environmental Symptoms Questionnaire cerebral score (AMSc) comprising 11 questions on AMS symptoms rated from 0 (not at all) to 5 (extreme). The weighted sum of responses ranges from 0 to 5. Scores ≥0.7 are considered to reflect clinically relevant AMS.[133] AMS was additionally evaluated by the Lake Louise self-assessment score (LLS).[134] During baseline evaluation at 760 m and on the second day at 3'100 m, arterial blood gas analysis (RapidPoint 405; Siemens, Zurich, Switzerland), spirometry (EasyOne; NDD, Zurich, Switzerland), sniff nasal inspiratory pressure measurements[135] and a 6-minute walk test[136] with assessment of perceived effort by the Borg CR-10 scale[137] were performed.

To detect significant hypoxemia, SpO_2 was continuously monitored during nocturnal rest and walk tests, and measured in participants complaining of any discomfort.

5.2.5 Outcomes

The primary outcome was the difference in the combined incidence of clinically relevant AMS and / or ARAHE between participants receiving dexamethasone and placebo during the stay at 3'100 m. Clinically relevant AMS was defined as an AMSc score ≥0.7, ARAHE were defined as any of the following: severe resting hypoxemia (SpO_2 <75 % for >30 min or <70 % for >15 min), severe hypertension (blood pressure systolic >200 mmHg or diastolic >110 mmHg), any intercurrent illness or condition requiring oxygen, pharmacological therapy, or evacuation to lower altitude according to the decision of an independent physician responsible for medical care of participants, or desire of a participant to withdraw from the study. For safety reasons, the protocol required that any patient with AMS / ARAHE had to be treated with oxygen, drugs or other means as appropriate. These patients were transported to low altitude at the earliest convenience.

Secondary outcomes were AMS severity, arterial blood gases, lung function and the 6-minute walk distance.

5.2.6 Sample size

In the absence of conclusive data from previous studies, sample size estimation was based on several assumptions: We reasoned that the Pa_{O_2} was a major determinant of the incidence of AMS in lowlanders ascending within a few hours to high altitude. Moreover, we assumed that the incidence of AMS in COPD patients would be at least as high as that in healthy individuals ascending to an altitude that induced a corresponding degree of hypoxemia.[62] In a previous study in patients with COPD GOLD grade 2 – 3, we measured a mean Pa_{O_2} of 6.7 kPa within 24 hours of arrival at 2'590 m.[68] In another study using linear regression to predict Pa_{O_2} in COPD patients at different altitudes, a Pa_{O_2} of 6.0 kPa was predicted for an altitude of 3'050 m[138] which is similar to the altitude of 3'100 m to which COPD patients were exposed in the current study. In healthy individuals, a Pa_{O_2} of 5.7 kPa was observed within 24 hours after arrival at 4'559 m and the corresponding incidence of AMS was 53 %.[16] Taking into account that participants in the current study ascended to 3'100 m within only 3 – 5 hours and that AMS and ARAHE such as severe hypoxemia, any intercurrent illness, and the desire to withdraw from the study, were also included in the main outcome, we estimated the combined incidence of AMS / ARAHE in COPD patients of the current trial as 60 %. A minimal important difference in the cumulative incidence of AMS / ARAHE was assumed to be a reduction

by 50 %.[127] Based on these premises we intended to include at least 100 patients (50 in each group) to achieve a power of 80 % (alpha of 0.05).

5.2.7 Randomization and measures to prevent bias

Participants were randomized 1:1 to dexamethasone or placebo treatment by a computer algorithm minimizing for differences in sex, age ≤ or >50 years, FEV_1 < or ≥80 % predicted.[139]

Study drugs were dispensed by an independent pharmacist in sets of capsules labeled with a concealed code. Participants and investigators remained blinded until completion of data analysis.

5.2.8 Data analysis

Data are summarized by medians and quartiles. The difference between the combined incidence of AMS / ARAHE in the dexamethasone and placebo group was evaluated by Pearson's Chi-Square statistics according to the intention-to-treat principle. Kaplan-Meier and Cox proportional hazards analyses were performed to evaluate the proportion of participants free of AMS / ARAHE at 3'100 m. Altitude- and medication-induced median changes in outcomes (95 % CI) were computed. Effects of dexamethasone were further evaluated by multivariable logistic regression analyses controlling for age, sex, FEV_1, body mass index and SpO_2 at 760 m. A probability of $P < 0.05$ was considered statistically significant.

5.3 Results

124 patients underwent randomization. 6 patients in whom baseline examination revealed that they did not fulfill inclusion criteria were excluded post randomization. Thus, 118 patients were included in the intention-to-treat analysis of the primary outcome (Figure 5-1, Table 5-1). Of these 118 patients, 27 patients (23 %) experienced AMS / ARAHE, received oxygen and other treatment as appropriate and were relocated to lower altitude. 91 patients were able to stay for 2 days / nights at 3'100 m.

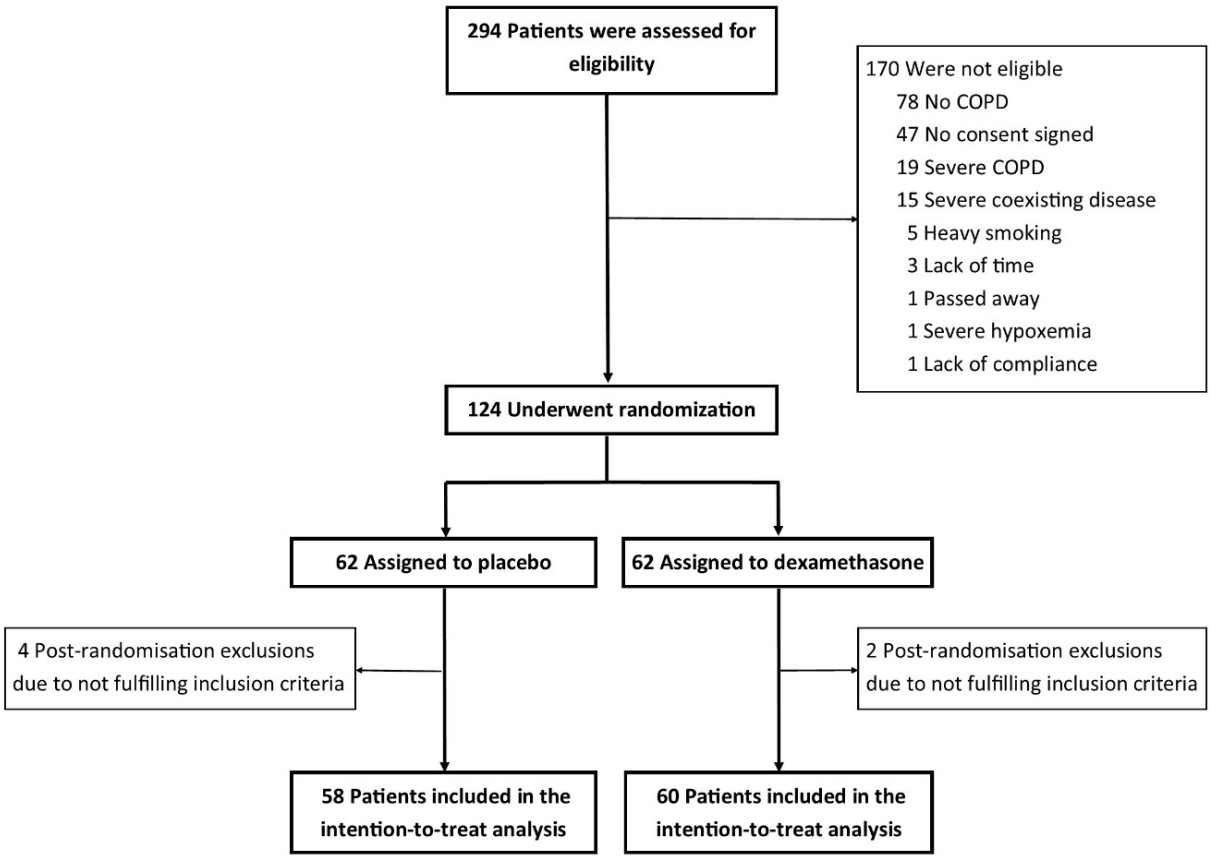

Figure 5-1. Patient flow in the study.

Table 5-1. Patient characteristics.

	Placebo group	Dexamethasone group
N, (males / females)	58 (50 / 8)	60 (50 / 10)
Age, years	60 (53;64)	57 (50;62)
BMI, kg/m^2	25.5 (22.7;27.5)	25.7 (23.4;27.7)
FEV_1, % predicted	94 (76;103)	86 (70;104)
COPD, GOLD grade 1 / 2, n	41 / 17	37 / 23
Smoking, pack years	24 (2;35)	20 (0;34)
NYHA functional class	2 (1;2)	2 (1;2)
CAT score	7 (3;11)	7 (5;11)
Medication		
Inhaled beta-adrenergics, n (%)	1 (2)	1 (2)
Inhaled anticholinergics, n (%)	3 (5)	2 (3)
Inhaled corticosteroids, n (%)	1 (2)	0 (0)
Antihypertensive drugs, n (%)	8 (14)	5 (8)
Beta-blocker, n (%)	2 (3)	3 (5)
Antidiabetic drugs, n (%)	1 (2)	0 (0)

Values are shown in numbers or median (quartiles). BMI = Body mass index; FEV_1 = Forced expiratory volume in the first second; NYHA = New York Heart Association classification; CAT = COPD Assessment Test.

AMS / ARAHE occurred in 14 of 58 participants using placebo (incidence 24 %) and in 13 of 60 participants using dexamethasone (incidence 22 %, P = 0.749 vs. placebo). Timing of AMS and type of ARAHE were similar in the dexamethasone and placebo groups (Figure 5-2, Table 5-3). AMSc scores were highest in the evening on the day of arrival and decreased subsequently (Figure 5-3) with medians well below the value of 0.7 considered to represent clinically relevant AMS.

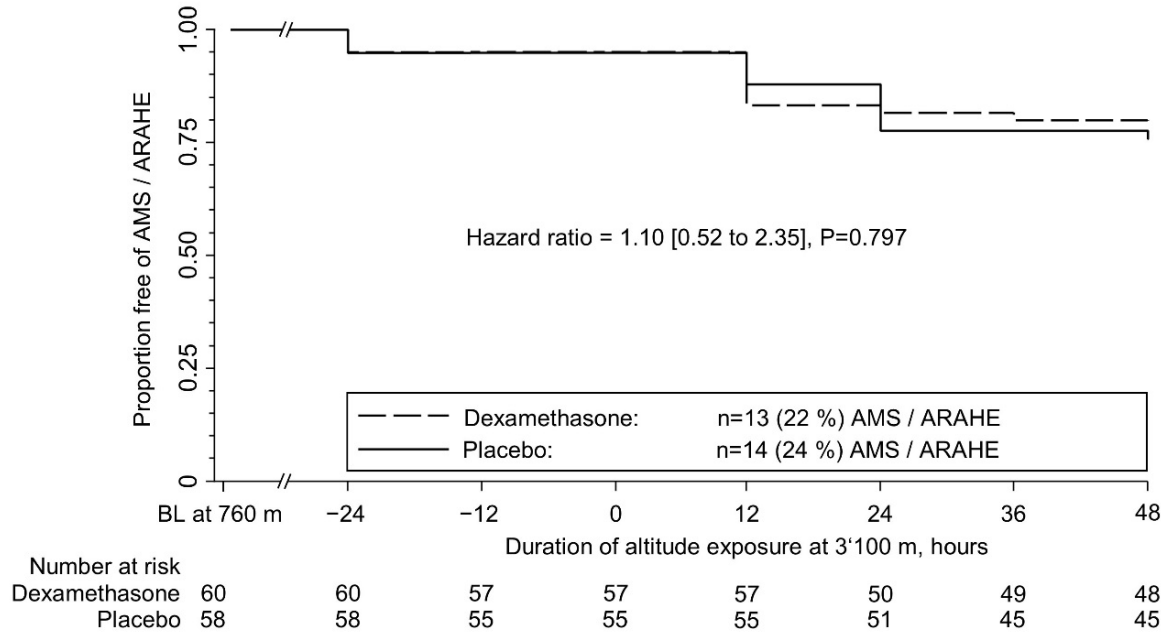

Figure 5-2. Kaplan-Meier-curve of the proportion of study participants remaining free of AMS/ARAHE*. Participants started the study medication on the day before ascent to high altitude (time −24 hours). Time zero on the x-axis represents the time of departure from 760 m to the high-altitude clinic at 3'100 m where participants arrived within 3 − 5 hours. The stay at 3'100 m lasted until the end of the study at time 48 hours. HR = Hazard ratio and 95 % CI calculated by Cox proportional hazards model.*

Table 5-2. Incidence of AMS and ARAHE in lowlanders with COPD during a stay at 3'100 m.

Type of ARAHE	Placebo group, n=58	Dexamethasone group, n=60	P value
Clinically relevant AMS (AMSc score ≥0.7)	5 (9 %)	8 (13 %)	0.414
Severe hypoxemia (SpO_2 <75 % for >30 min or <70 % for >15 min)	4 (7 %)	1 (2 %)	0.159
Intercurrent illness or condition requiring oxygen or pharmacological therapy, evacuation to low altitude, or resulting in study withdrawal according to the decision of the independent physician	4 (7 %); of these 2 (3 %) had elevated blood pressure and 2 (3 %) had elevated temperature and / or shivering	4 (5 %); of these 1 (2 %) had elevated blood pressure, 2 (3 %) complained of chest tightness, 1 (2 %) had pronounced asymptomatic hyperglycemia resulting in study withdrawal by the independent physician	0.960
Desire of the participant to withdraw from the study	3 (5 %)	3 (5 %)	1.00
Combined incidence of AMS / ARAHE*	14 (24 %)	13 (22 %)	0.749

*Some patients experienced more than one type of ARAHE.

Among the 27 participants with AMS / ARAHE (Table 5-2), all received supplemental oxygen and were relocated to low altitude at the earliest convenience. In addition, 13 participants with clinically relevant AMS and / or severe hypoxemia received paracetamol for headaches, 3 participants with arterial hypertension received an ACE inhibitor, 2 participants with elevated temperature and shivering received paracetamol, 1 participant with hyperglycemia received intravenous fluids, 1 participant with chest tightness received nebulized bronchodilators. All these participants recovered completely within a few hours to one day after arriving at low altitude (<800 m).

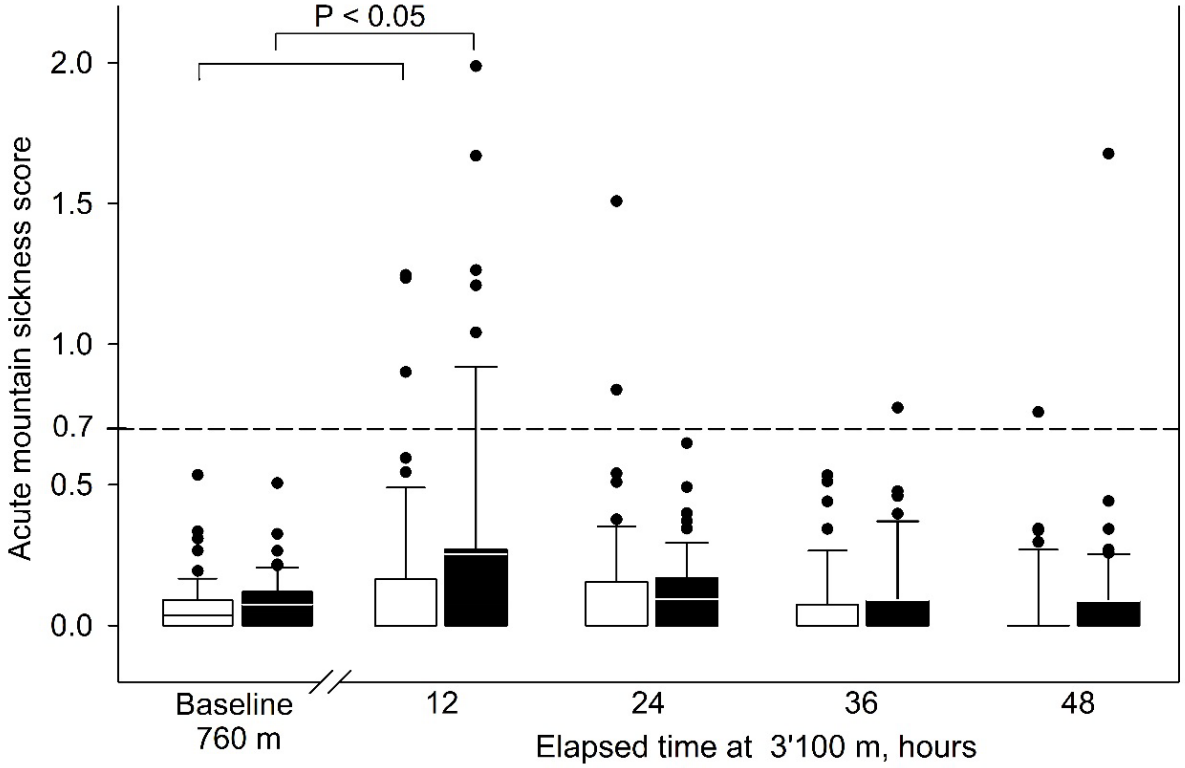

Figure 5-3. AMS severity during 48 hours at 3'100 m assessed by the Environmental Symptom Questionnaire cerebral score. *A score ≥0.7 is considered to reflect clinically relevant illness. Boxes with horizontal line represent 25th, 50th and 75th percentiles, whiskers are the 90th percentile and dots individual values beyond this range for the placebo (white boxes) dexamethasone group (black boxes).*

Table 5-3. Incidence of AMS and ARAHE over the time course of the stay at 3'100 m using different AMS criteria.

		Placebo group, n=58		Dexamethasone group, n=60	
Altitude	Time at 3'100 m	AMS / ARAHE (AMSc ≥0.7)	AMS / ARAHE (LLS ≥4)	AMS / ARAHE (AMSc ≥0.7)	AMS / ARAHE (LLS ≥4)
760 m	-	5 %	5 %	5 %	5 %
3'100 m	Day 1, evening	12 %	17 %	17 %	22 %
3'100 m	Day 2, morning	22 %	34 %	18 %	30 %
3'100 m	Day 2, evening	22 %	36 %	20 %	32 %
3'100 m	Day 3, morning	24 %	36 %	22 %	33 %

Values are percentage from patients assigned to either placebo or dexamethasone. AMS = Acute mountain sickness; ARAHE = Altitude-related adverse health effect; AMSc = Environmental symptoms questionnaire cerebral score; LLS = Lake Louise questionnaire score. An AMSc ≥0.7 corresponds to severe AMS; LLS ≥4 corresponds to moderate AMS.

Arterial blood gas analyses revealed significant altitude-related decreases in Pa_{O_2} and Sa_{O_2} associated with a decrease in Pa_{CO_2} and an increase in pH in both groups (Table 5-4). In patients receiving dexamethasone, the altitude-induced decreases in Pa_{O_2} and in Sa_{O_2} were smaller compared to patients receiving placebo, and the decrease in Pa_{CO_2} and increase in pH were greater while the $DAaP_{O_2}$ remained unchanged.

Table 5-4. Effects of altitude and of dexamethasone on exercise performance, lung function and arterial blood gases.

	Placebo group, n=55			Dexamethasone group, n=57			Difference in change between-groups (95 % CI)
	760 m	3'100 m	Change within group (95 % CI)	760 m	3'100 m	Change within group (95 % CI)	
6-minute walk test							
6-minute walk distance, m	510 (450;550)	495 (450;525)	−20 (−36 to 10)	513 (463;545)	500 (461;535)	−16 (−35 to 0)*	−2 (−27 to 23)
SpO_2 rest, %	95 (94;96)	91 (90;93)	−4 (−4 to −4)*	95 (94;96)	92 (90;94)	−4 (−4 to −3)*	0 (−1 to 1)
MAP rest, mmHg	89 (82;97)	91 (85;102)	4 (1 to 6)*	89 (83;96)	91 (87;96)	2 (−1 to 5)	−1 (−5 to 2)
HR rest, 1/min	77 (70;85)	80 (74;89)	4 (−3 to 6)	77 (67;82)	76 (67;83)	2 (−1 to 3)	−2 (−6 to 3)
SpO_2 end, %	96 (94;97)	85 (82;88)	−10 (−12 to −8)*	95 (94;96)	88 (86;90)	−7 (−8 to −6)*	3 (1 to 4)†
MAP end, mmHg	97 (88;108)	99 (90;108)	3 (−2 to 6)	94 (88;102)	98 (92;102)	3 (−1 to 7)	0 (−4 to 4)
HR end, 1/min	100 (90;106)	107 (97;117)	7 (−1 to 14)	96 (85;105)	103 (95;113)	9 (4 to 18)*	1 (−6 to 9)
Perceived dyspnea, Borg CR10 score	2 (1;3)	2 (1;3)	0 (0 to 1)*	1 (1;3)	2 (1;3)	0 (0 to 1)*	0 (0 to 1)†
Arterial blood gas							
pH	7.40 (7.38;7.41)	7.42 (7.41;7.44)	0.02 (0.02 to 0.03)*	7.40 (7.39;7.42)	7.43 (7.42;7.45)	0.04 (0.03 to 0.04)*	0.01 (0.0 to 0.02)†
Pa_{CO_2}, kPa	5.1 (4.8;5.4)	4.6 (4.4;4.9)	−0.5 (−0.6 to −0.3)*	5.2 (4.8;5.4)	4.4 (4.1;4.7)	−0.7 (−0.9 to −0.7)*	−0.3 (−0.4 to −0.1) †
Pa_{O_2}, kPa	10.0 (9.1;10.5)	8.0 (7.5;8.4)	−1.8 (−2.0 to −1.5)*	9.6 (9.2;10.0)	8.2 (7.9;8.6)	−1.5 (−1.7 to −1.0)*	0.4 (0.0 to 0.8)†
$DAaP_{O_2}$, kPa	3.20 (2.65;4.00)	1.16 (0.61;1.66)	−2.24 (−2.61 to −1.86) *	3.57 (2.97;3.91)	1.11 (0.63;1.41)	−2.25 (−2.55 to −2.13)*	−0.18 (−0.56 to 0.24)
Sa_{O_2}, %	95 (93;95)	89 (87;90)	−5 (−6 to −5)*	94 (93;95)	90 (89;91)	−4 (−5 to −3)*	1 (1 to 2)†
COHb, %	0.8 (0.4;2.4)	0.9 (0.5;3.3)	0.2 (0.1 to 0.6) *	0.8 (0.5;2.0)	1.2 (0.5;2.9)	0.3 (0.2 to 0.6) *	0.0 (−0.2 to 0.3)
Hb conc., g/L	148 (135;156)	149 (138;157)	2 (−1 to 3)	150 (138;158)	150 (141;161)	2 (0 to 5)*	1 (−1 to 3)
Glucose, mmol/L	7.0 (6.0;8.0)	7.3 (6.0;8.5)	0.3 (−0.4 to 0.8)	6.9 (5.9;7.9)	9.4 (7.8;11.4)	2.2 (1.7 to 3.5) *	2.3 (1.4 to 3.4)†
Lung function							
FEV_1, % predicted	96 (76;105)	92 (73;102)	0 (−1 to 2)	84 (70;103)	86 (73;103)	2 (−1 to 4)	2 (−1 to 5)
FVC, % predicted	119 (104;134)	119 (100;136)	0 (−3 to 2)	114 (97;126)	114 (96;125)	−1 (−4 to 2)	−1 (−4 to 2)
FEV_1 / FVC	0.65 (0.59;0.68)	0.65 (0.59;0.68)	−0.00 (−0.00 to 0.01)	0.63 (0.56;0.66)	0.63 (0.60;0.69)	0.01 (−0.00 to 0.03)	0.01 (−0.01 to 0.03)
SNIP, mmHg	75 (63;91)	65 (55;83)	−11 (−13 to −4)*	80 (64;99)	67 (57;89)	−6 (−11 to −1)*	2 (−7 to 9)

Per protocol analysis of data from patients with complete data sets. Values are medians (quartiles) and median changes (95 % confidence intervals). *p <0.05 vs. values at 760 m in the same group; †p <0.05 changes in dexamethasone vs. placebo group. SpO_2 = Arterial oxygen saturation measured by pulse oximetry; MAP = Mean arterial blood pressure; HR = Heart rate; Pa_{CO_2} = Partial pressure of CO_2 in arterial blood; Pa_{O_2} = Partial pressure of O_2 in arterial blood; $DAaP_{O_2}$ = alveolar-arterial P_{O_2} difference; Sa_{O_2} = Arterial oxygen saturation measured by co-oximetry; COHb = Carboxyhemoglobin concentration; Hb conc. = Hemoglobin concentration; FEV_1 = Forced expiratory volume in the first second; FVC = Forced vital capacity; SNIP = Sniff nasal inspiratory pressure.

Upon ascent to high altitude, there was an increase in resting blood pressure in the placebo but not in the dexamethasone group. Resting heart rate remained unchanged in both groups. Spirometry did not significantly change but there was a slight reduction in the sniff nasal inspiratory pressure in both groups at 3'100 m.

The 6-minute walk distance was reduced in both groups to a similar degree at 3'100 m vs. 760 m. The exercise-induced arterial oxygen desaturation was less pronounced in the dexamethasone compared to the placebo group.

Blood analysis after lunch revealed a higher serum glucose concentration in the dexamethasone than in the placebo group and 16 patients (28 %) in the dexamethasone group but only 1 (2 %) in the placebo group had a glucose concentration above 11.1 mmol/L indicating a blood sugar imbalance (P <0.001).[140] One patient in the dexamethasone group was treated for asymptomatic hyperglycemia of 41.4 mmol/L and was therefore withdrawn from the study based on the decision of the independent physician.

Multivariate logistic regression analysis indicated that a low Pa_{O_2} at 760 m, female sex and a low body mass index were predictors of AMS / ARAHE (Table 5-5).

Table 5-5. Predictors of the combined incidence of AMS and ARAHE in mixed logistic regression analysis.

R^2 entire model = 0.189, P <0.01	Odds ratio	95 % CI	P value
Dexamethasone (vs. placebo)	0.68	0.22 to 2.15	0.515
Age, years	0.97	0.91 to 1.04	0.422
Body mass index, kg/m^2	0.80	0.67 to 0.96	0.015
FEV_1, % predicted	0.99	0.95 to 1.02	0.513
Female sex (vs. male)	7.37	1.14 to 47.76	0.036
Pa_{O_2} at 760 m, kPa	0.39	0.20 to 0.76	0.005

FEV_1 = Forced expiratory volume in the first second; Pa_{O_2} = Partial pressure of O_2 in arterial blood; Odds ratios refer to the ratio of the probability of AMS / ARAHE occurrence divided by 1 minus that probability (p / [1 – p]) associated with every one-unit increase in the corresponding independent predictor variable while keeping other variables constant.[141,142]

Exploratory analyses between COPD patients GOLD grade 1 vs. 2 under placebo revealed a similar incidence of AMS / ARAHE (Table 5-6, P = 0.201).

Table 5-6. Incidence of ARAHE in COPD patients with different severities of airflow obstruction.

	Placebo group, n=58	Dexamethasone group, n=60	P value
GOLD grade 1, n (%)	8 of 41 (20)	7 of 37 (19)	0.947
GOLD grade 2, n (%)	6 of 17 (35)	6 of 23 (26)	0.530
All patients combined, n (%)	14 of 58 (24)	13 of 60 (22)	0.749

FEV_1 = Forced expiratory volume in the first second; GOLD grade 1 = FEV_1 / FVC <0.7 and FEV_1 ≥80 % predicted; GOLD grade 2 = FEV_1 / FVC <0.7 and FEV_1 ≥50 % and <80 % predicted.

To evaluate the robustness of the negative conclusions regarding effectiveness of dexamethasone in preventing AMS / ARAHE it was assumed that among the 6 patients desiring to withdraw from the study (Table 5-2), i.e., reaching an endpoint, before arrival at altitude, all 3 randomized to placebo but none of the 3 randomized to dexamethasone would have experienced an AMS / ARAHE. Even in this scenario, the incidence of AMS / ARAHE would not have been significantly different between groups, i.e., 10 of 60 (17 %) in the dexamethasone group and 14 of 58 (24 %) in the placebo group, P = 0.365.

Incorporating less stringent criteria for clinically relevant AMS (LLS ≥4 or ≥3 instead of AMSc score ≥0.7) increased the incidence of AMS alone and of the combined incidence of AMS / ARAHE but the difference in the incidences between patients randomized to dexamethasone and placebo remained statistically nonsignificant (Table 5-7).

Table 5-7. Effect of different criteria for AMS on its incidence and on the incidence of AMS/ARAHE.

	Placebo group, n=58			Dexamethasone group, n=60			P value for AMS / ARAHE
	AMS alone	ARAHE alone	AMS / ARAHE	AMS alone	ARAHE alone	AMS / ARAHE	
AMSc ≥0.7, n (%)	5 (9)	11 (19)	14 (24)	8 (13)	8 (13)	13 (22)	0.749
LLS ≥4, n (%)	13 (22)	11 (19)	21 (36)	15 (25)	8 (13)	20 (33)	0.743
LLS ≥3, n (%)	19 (33)	11 (19)	25 (43)	23 (38)	8 (13)	27 (45)	0.836

The data represent the incidence in numbers (percent). AMSc = Environmental symptoms questionnaire cerebral score; LLS = Lake Louise questionnaire score.

5.4 Discussion

The current randomized, placebo-controlled, double-blind trial has evaluated the efficacy of preventive dexamethasone treatment in reducing the incidence of AMS / ARAHE in lowlanders with mild to moderate COPD travelling to and staying for 2 days at high altitude (3'100 m). The results suggest that dexamethasone was not superior to placebo in preventing AMS / ARAHE although the drug mitigated the altitude-induced hypoxemia by stimulating ventilation. Since dexamethasone is associated with side effects including hyperglycemia, our data do not support the use of dexamethasone for prevention of AMS / ARAHE in patients with mild to moderate COPD ascending to altitudes similar to that reached in the current study, which is representative for many mountain tourism destinations worldwide.

Health effects of altitude travel in COPD patients have not been extensively studied. In a systematic literature search, we did not identify any randomized trial performed in COPD patients at altitude. Three observational studies[56,70,75] evaluated clinical manifestations in lowlanders with COPD travelling to altitudes of 1'472 m to 2'086 m. As observed in the current study, the main findings were a reduction in Pa_{O_2} and in the 6-minute walk distance (Table 5-4). In our own recent study on exercise performance of lowlanders with moderate to severe COPD ascending to 2'590 m we found that endurance was reduced by more than half in comparison to baseline measurements at 490 m, which was related to a reduced systemic and cerebral oxygen availability.[68]

To our knowledge, no studies evaluating the incidence of AMS / ARAHE, or measures to prevent them, have been performed in COPD patients. The current trial addresses this gap by investigating AMS / ARAHE in a large cohort of COPD patients ascending rapidly to 3'100 m, a higher altitude than that in the cited studies.[56,68,70,75] The combined incidence of AMS / ARAHE of 22 % and 24 % in our 2 study groups was moderately high. It was slightly higher than the AMS prevalence of 16 % (defined by an AMSc score $\geq$0.7) estimated for individuals ascending to 3'100 m by a recent meta-analysis of data from 91 published original studies including 66'944 participants.[36] In the current investigation in COPD patients, we observed clinically relevant AMS alone (defined by an AMSc score $\geq$0.7, independent of ARAHE) in only 13 % and 9 % of participants taking dexamethasone and placebo, respectively (Table 5-7). How can we explain the apparent discrepancy in the AMS incidence in the current compared to previous studies included into the cited meta-analysis? One likely explanation relates to our safety rules requiring that all COPD patients suffering from severe hypoxemia (according to

our ARAHE criteria) had to be treated with oxygen, irrespective of whether they had clinically relevant AMS (AMSc score ≥0.7) or not. Consequently, several patients with severe hypoxemia but with no or only mild AMS symptoms received oxygen and had to be withdrawn from the study. This prevented a more prolonged exposure to hypoxia with subsequent development of AMS. In line with this reasoning, the incidence of AMS defined by more liberal criteria (LLS ≥4) was 25 % and 22 % in the dexamethasone and placebo group, respectively (Table 5-7), i.e., only slightly lower than the AMS prevalence of 29% predicted by meta-analysis using the LLS ≥4 criterion. Other potential explanations for a relatively low incidence of AMS in our COPD patients are a possible selection bias in favor of individuals more resistant to altitude illness, genetic factors of Kyrgyz compared to other ethnicities, a higher age and a lower proportion of women than in many previous studies.[36,143] Theoretically, some degree of physiological adaptation to mild, chronic hypoxemia might have rendered COPD patients more resistant to altitude-induced hypoxia. However, a previous study[62] has suggested that lung disease may increase the risk of AMS (odds ratio of 1.6 compared to individuals without lung disease). The current study revealed an association of lower values of Pa_{O_2} at 760 m with a higher incidence of AMS / ARAHE at 3'100 m in logistic regression analysis (Table 5-5) which does not support the assumption that chronic hypoxemia due to COPD protects from AMS / ARAHE. Regression analysis further indicated that female sex and a lower body mass index were associated with an increased risk of AMS / ARAHE, findings that were not consistently reported in healthy individuals.[62,143,144] Differences in design, setting and definition of AMS hamper a detailed quantitative comparison among various studies.[145] Nevertheless, the relatively moderate incidence of AMS / ARAHE that we observed in COPD patients taking placebo at 3'100 m is an important and intriguing result of our study. It suggests that compared to healthy subjects, patients with mild to moderate COPD were not excessively susceptible to AMS / ARAHE despite their lung disease associated with gas exchange impairment and hypoxemia.

Efficacy of dexamethasone in prevention of AMS in healthy individuals is supported by a few randomized trials.[127,129-131] In the current study in COPD patients, dexamethasone did not reduce the incidence of AMS / ARAHE, nor did it reduce AMS symptoms. These negative results may be explained in several ways. Our study applied a relatively rigorous definition of clinically relevant AMS (AMSc score ≥0.7) and was therefore underpowered (post hoc power of 30 %) to exclude a significant reduction in AMS / ARAHE from a relatively low incidence of 24 % to 12 %. In the absence of data from previous studies, we had based our sample size estimation

on the assumption that COPD patients would be similarly susceptible to AMS as healthy individuals at a corresponding degree of hypoxemia (that occurred in healthy individuals at higher altitude). We further assumed that including safety endpoints into the main outcome such as severe hypoxemia, would increase the combined incidence of AMS / ARAHE to 60 %, above that of AMS alone. In exploratory analyses of our data using more liberal criteria for clinically relevant AMS (LLS ≥4 or ≥3) resulting in a higher incidence of AMS / ARAHE, the difference between the dexamethasone and placebo groups remained nonsignificant (Table 5-4).

The lack of efficacy of dexamethasone in the current study may also be related to underdosing. We choose to administer 4 mg dexamethasone every 12 hours as this was successfully used in healthy individuals in the study by Zheng CR et al.[127] and as it is recommended in current guidelines.[3,4] We were reluctant to use 4 mg every 6 hours as in the study by Montgomery J et al.[129] and in some other trials [146] because of the greater risk of side effects. In fact, several participants in the current study had considerable hyperglycemia. Compared to the daily dose of 40 mg prednisone that is recommended for treatment of COPD exacerbations in the GOLD guidelines,[48] the dose of 8 mg dexamethasone per day corresponds to a higher glucocorticoid action of about 53 mg prednisone.

The physiological mechanisms responsible for the effectiveness of dexamethasone in preventing AMS in healthy individuals remain speculative. However, a reduction in vascular permeability and in sympathetic tone, anti-inflammatory effects, and improvement in oxygenation have all been proposed.[78] In this regard, it is interesting to note that the COPD patients using dexamethasone in the current study experienced a milder altitude-induced hypoxemia that was associated with a similar change in the $DAaP_{O_2}$ but a greater reduction in Pa_{CO_2} than in patients using placebo (Table 5-4). These findings, together with the increase in pH, suggest that dexamethasone in the dose of 8 mg/day improved the Pa_{O_2} of COPD patients by stimulating ventilation through an enhanced ventilatory drive, although this did not result in a reduced incidence of AMS / ARAHE.

For safety considerations, our study included patients with predominantly mild forms of COPD that did not require treatment. Moreover, patients with unstable cardiovascular disease, previous myocardial infarction or stroke were excluded from study participation. Further studies are required to evaluate whether patients with more severe COPD or with relevant comorbidities are at excessive risk of experiencing adverse health effects when travelling to altitude.

5.5 Conclusions

We found that lowlanders with mild to moderate COPD who are not severely hypoxemic at low altitude and devoid of unstable cardiovascular disease or other relevant comorbidity tolerate a stay at a high altitude of 3’100 m relatively well. About one of four patients experienced clinically relevant AMS or severe hypoxemia and other ARAHE, independent of the use of preventive dexamethasone treatment. Considering that at least 8 patients would (theoretically) have to be treated with dexamethasone to prevent one case of AMS / ARAHE under the conditions of the current study, and considering the risk of side effects such as severe hyperglycemia, the current results do not support the use of dexamethasone for prevention of AMS / ARAHE in patients with mild to moderate COPD travelling to 3’100 m.

6 Effect of dexamethasone on nocturnal oxygenation in COPD at 3’100 m

The author’s contribution

This investigation was part of the second study described in chapter 5, MF’s tasks were the same as described for chapter 5, including drafting the manuscript.

Citation (Submitted)

Furian M, Lichtblau M, Aeschbacher SS, Estebesova B, Emilov B, Sheraliev U, Marazhapov NH, Mademilov M, Osmonov B, Bisang M, Ulrich S, Latshang TD, Ulrich S, Sooronbaev TM, Bloch KE. Effect of dexamethasone on nocturnal oxygenation in lowlanders with chronic obstructive pulmonary disease travelling to 3’100 m. A Randomized Clinical Trial. (submitted)

6.1 Introduction

Worldwide, millions of people live in or travel to mountain areas.[61] Even though moderate hypobaric hypoxia at altitudes of 1’500 – 3’500 m is generally well tolerated by healthy individuals, nocturnal hypoxemia, periodic breathing, disturbances of sleep structure measured during polysomnography and impairment of subjective sleep quality are commonly noticed.[8,32-34] According to recent studies, patients with pre-existing respiratory diseases such as OSAS[81] or COPD seem to be particularly susceptible to altitude-related hypoxemia, sleep and breathing disturbances (data from COPD currently submitted). In patients with OSAS, continuous positive airway pressure therapy combined with acetazolamide was effective in preventing exacerbation of sleep apnea during altitude sojourns.[80,81] In patients with COPD, mechanical ventilatory constraints combined with the stimulation of ventilation by acetazolamide and hypobaric hypoxia at altitude may promote dyspnea.[82] The use of supplemental oxygen is hampered for logistical reasons, because its use is cumbersome and difficult to be justified for travelers with mild COPD. Therefore, other means to prevent altitude-related adverse health effects in COPD patients are warranted. In healthy mountaineers, dexamethasone, a drug with potent glucocorticoid action, has been suggested to prevent AMS[146] and to reduce pulmonary artery pressure and stimulate ventilation in persons susceptible to high altitude pulmonary edema.[147] In COPD patients, glucocorticoids are used to treat exacerbations. Therefore, the current randomized, placebo-controlled trial was performed in lowlanders with mild to moderate COPD to evaluate the hypothesis that preventive dexamethasone treatment would mitigate nocturnal hypoxemia, periodic breathing and impairments of sleep quality during a stay at high altitude.

6.2 Materials and Methods

6.2.1 Design

This trial was part of the second project of this thesis evaluating the effect of dexamethasone on the incidence of ARAHE in COPD patients. The study design is described in section 5.2.1. This trial and the primary outcome have been separately registered at www.ClinicalTrials.gov NCT02450968.

6.2.2 Participants

Participant recruitment, inclusion and exclusion criteria are described in section 5.2.2

6.2.3 Interventions

Interventions are described in section 5.2.3.

6.2.4 Assessments

General assessments are described in section 5.2.4. Respiratory sleep studies (AlicePDx, Philips AG Respironics, Zofingen, Switzerland) including SpO_2, nasal cannula pressure swings, thoracic and abdominal movements, snoring, electrocardiogram and body position were monitored. According to previous studies,[81,148] apneas / hypopneas were defined as a >50 % reduction in nasal pressure swings or chest wall excursions during ≥10 sec;[149] obstructive events were scored if asynchronous or paradoxical chest wall excursions suggested continued effort or if a flattened inspiratory portion of the nasal pressure curve suggested flow limitation; central apneas / hypopneas were scored in the absence of criteria of obstructive events. If central apneas / hypopneas occurred as part of a periodic breathing pattern for at least 3 consecutive cycles with minimal duration ≥5 sec they were also scored. CTO was monitored with NIRS sensors (NIRO 200NX, HAMAMATSU Photonics, Solothurn, Switzerland) placed bilaterally, high on the forehead[150] during the first night at 760 m and 3'100 m. The apnea / hypopnea index (AHI) and the oxygen desaturation index (ODI >3 % SpO_2 dips/hours, and cerebral ODI >3 % CTO dips / hours) were calculated as mean number of events per hour of time in bed. Subjective sleep quality was rated on a visual analogue scale ranging from 0 (extremely bad) to 100 mm (excellent), insomnia was evaluated by asking subjects to estimate the number of awakenings and time spent awake at night. The Karolinska Sleepiness Scale was administered. It rates current sleepiness from 1 "very awake" to 9 "very tired".[151] Vital signs, spirometry (EasyOne, NDD, Zurich, Switzerland) and arterial blood gas analysis (RapidPoint 405, Siemens, Zurich, Switzerland) were obtained. During the psychomotor vigilance test (PVT) subjects were sitting in a quiet room and had to press a button in response to light signals appearing at irregular intervals during 10 min while the reaction time was recorded.[152]

6.2.5 Outcomes

The primary outcome was the between-group difference in altitude-induced changes in mean nocturnal SpO_2 during the 1st night at 3'100 m. Secondary outcomes were effects of dexamethasone during the 1st and 2nd night at 3'100 m on SpO_2, other variables from sleep studies and daytime evaluations, and effects of altitude in the two groups.

6.2.6 Sample size

The sample size estimation was calculated for the project evaluating the effect of dexamethasone on ARAHE in COPD patients and required 100 patients with COPD. This sample size allows detecting a mean difference in nocturnal SpO_2 of 2 % (SD, 3.5 %) with a two-sided significance level of 0.05 and a power of 80 %.

6.2.7 Randomization & Blinding

Randomization and blinding are described in section 5.2.7

6.2.8 Data analysis

Data are presented as medians (quartiles) and median differences (95 % CI) to account for the non-normal distribution. The primary outcome was analyzed according to the intention-to-treat principle, missing values were filled by multiple (20) imputations using regression models with chained equations including the following predictors:[153] drug assignment, study night, anthropometrics, daytime SpO_2, FEV_1 % predicted, and body mass index at 760 m. Between-group comparisons were performed by Mann-Whitey-U tests, and by computing median differences with 95 % CI, intra-group comparisons were performed by Wilcoxon signed rank tests. Multivariable regression analysis was performed to elucidate independent predictors of SpO_2 in the 1st night at 3’100 m. A p-value <0.05 was considered statistically significant.

6.3 Results

Two-hundred ninety-four individuals were screened and 124 were randomized (Figure 6-1); 6 patients were excluded post randomization as they did not fulfill inclusion criteria. Therefore, the intention-to-treat analysis included 118 patients, 58 randomized to placebo and 60 to dexamethasone. Of these, 10 patients in the placebo group and 4 in the dexamethasone group (P = 0.092, Fisher’s Exact test) had incomplete data for various reasons (Figure 6-1). Their missing primary outcome data were imputed for the intention-to-treat analysis. In all patients requiring oxygen therapy and relocation to lower altitude according to safety rules, the corresponding adverse health effect such as excessive hypoxemia, elevated blood pressure or discomfort for other reasons resolved within a few hours without sequelae. Baseline characteristics of patients receiving dexamethasone and placebo were similar, i.e., they had mild to moderate airflow obstruction, were non-obese and moderately symptomatic (for patient characteristics see Table 5-1).

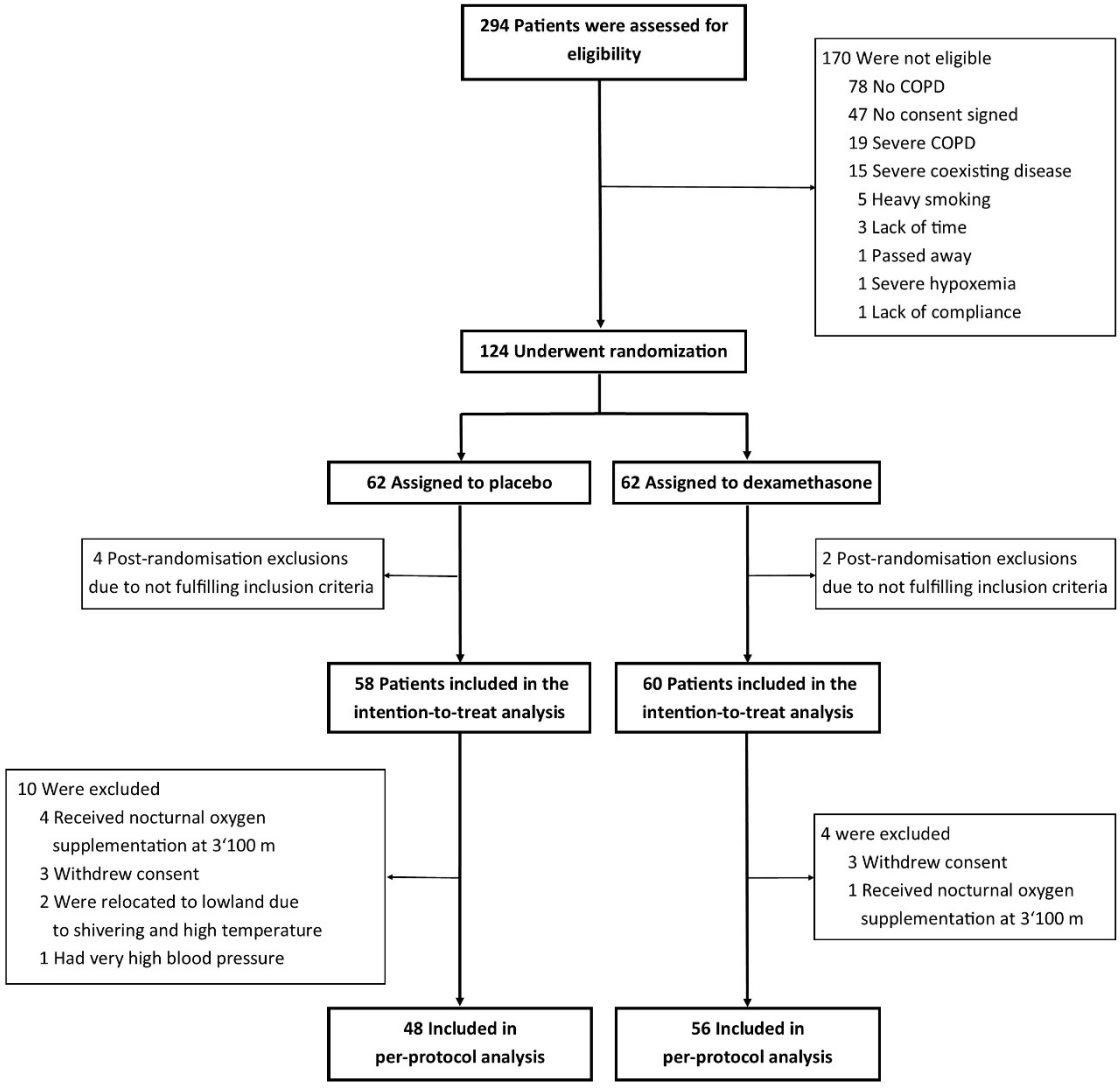

Figure 6-1. Patient flow in the study.

The Table 6-1 and Figure 6-2 summarize the effects of altitude travel and of dexamethasone on outcomes assessed during sleep studies. The mean nocturnal SpO_2 was significantly reduced in nights 1 and 2 at 3’100 m compared to 760 m by medians of 7 % to 8 % in patients treated with placebo and by 4 % to 6 % in patients taking dexamethasone. Thus, dexamethasone attenuated the altitude-induced drop in SpO_2 by a median of 3 % in the first and second night at 3’100 m (Figure 6-2). Patients in the placebo group spent more time of the night with low SpO_2 than patients in the dexamethasone group (Figure 6-3). The ODI increased in both groups with altitude ascent; however, dexamethasone mitigated this effect and prevented an altitude-induced increase in the AHI, mainly by preventing a major increase in the central AHI and, to a lesser extent in the obstructive AHI. Dexamethasone significantly reduced the nighttime spent with

periodic breathing compared to placebo. In the first night at 3’100 m, patients using placebo revealed a slight reduction in CTO and an increase in the cerebral ODI, similar changes were observed in the dexamethasone group (Table 6-1). At 3’100 m, heart rate was increased in both groups compared to 760 m.

Table 6-1. Polygraphic sleep studies and subjective sleep assessments.

	Placebo group, n=48			Dexamethasone group, n=56			Treatment effect on night 1 at 3'100 m	Treatment effect on night 2 at 3'100 m
	760 m	3'100 m night 1	3'100 m night 2	760 m	3'100 m night 1	3'100 m night 2		
Time in bed, min	545 (527;557)	513 (496;529) *	507 (484;521) *	533 (502;561)	517 (506;528) *	518 (502;530) *¶	15 (1 to 29)	20 (6 to 34)
SpO_2 mean, %	92 (91;93)	84 (83;85) *	86 (84;87) *	92 (91;93)	86 (84;88) *¶	87 (86;89) *¶	3 (2 to 3)	3 (2 to 3)
ODI, 1/h	2.8 (0.5;8.1)	18.5 (6.8;47.0) *	20.2 (5.0;44.5) *	3.3 (1.6;7.9)	8.1 (4.3;20.2) *¶	7.6 (3.3;14.6) *¶	−15.4 (−21.4 to −9.3)	−15.7 (−21.8 to −9.5)
AHI, 1/h	20.5 (12.3;48.1)	39.4 (19.3;66.2) *	38.0 (15.6;63.2) *	25.9 (16.3;37.1)	24.7 (13.2;33.7) ¶	21.6 (13.4;38.7) ¶	−18.7 (−25.3 to −12.0)	−17.7 (−24.3 to −11.0)
Central AHI, 1/h	1.6 (0.3;2.8)	13.2 (3.1;27.7) *	11.1 (2.7;32.1) *	1.5 (0.5;2.5)	3.7 (2.0;8.3) *¶	4.2 (1.4;11.8) *¶	−12.0 (−18.5 to −5.5)	−12.1 (−18.7 to −5.5)
Obstructive AHI, 1/h	18.2 (11.1;38.2)	19.2 (9.3;35.8)	14.1 (8.6;36.1)	23.2 (15.6;36.0)	17.4 (7.1;24.8) *	15.6 (8.5;27.0) *	−6.7 (−11.5 to −1.8)	−5.5 (−10.4 to −0.6)
Periodic breathing, min	0 (0;0)	26 (4;70) *	22 (3;85) *	0 (0;0)	4 (0;15) *¶	4 (0;24) *¶	−40 (−63 to −16)	−41 (−64 to −17)
Cerebral tissue oxygen., %	70.1 (66.7;73.0)	67.1 (62.1;70.0) *	-	67.6 (65.1;73.9)	67.3 (61.4;71.5) *	-	0.9 (−1.9 to 3.8)	-
Cerebral ODI, 1/h	0.7 (0.1;2.0)	3.6 (0.6;11.4) *	-	0.8 (0.1;1.9)	2.0 (0.4;4.9) *	-	−4.5 (−0.9 to −8.1)	-
Heart rate, 1/min	65 (59;70)	69 (63;73) *	67 (60;72) *	64 (60;68)	69 (62;75) *	60 (54;67) *¶	2 (0 to 4)	−5 (−8 to −3)
Subjective sleep quality, %	58 (43 to 82)	55 (30 to 71)	55 (40;69)	50 (38 to 73)	57 (39;75)	64 (45;78) *	11 (−1 to 22)	12 (0 to 23)
Sleep latency, min	30 (10;45)	30 (10;55)	30 (10;30)	30 (10;30)	30 (10;60)	30 (10;60)	1 (−20 to 21)	−1 (−22 to 19)
Awakenings at night, n	2 (1;3)	2 (1;3)	2 (1;3)	2 (1;3)	2 (1;3)	2 (1;3)	0 (−1 to 1)	0 (−1 to 1)
Waketime at night, min	13 (5;30)	10 (5;25)	10 (5;20)	5 (5;15)	15 (8;30) *	10 (5;30) *	22 (−2 to 47)	5 (−20 to 30)

Values are shown in median (quartiles); Treatment effects shown as mean differences and 95 % CI; SpO_2 = Arterial oxygen saturation measured by pulse oximetry; ODI = Oxygen desaturation index; AHI = Apnea / hypopnea index; * p <0.05 vs. 760 m; ¶ p <0.05 dexamethasone vs. placebo at the same corresponding altitude & day.

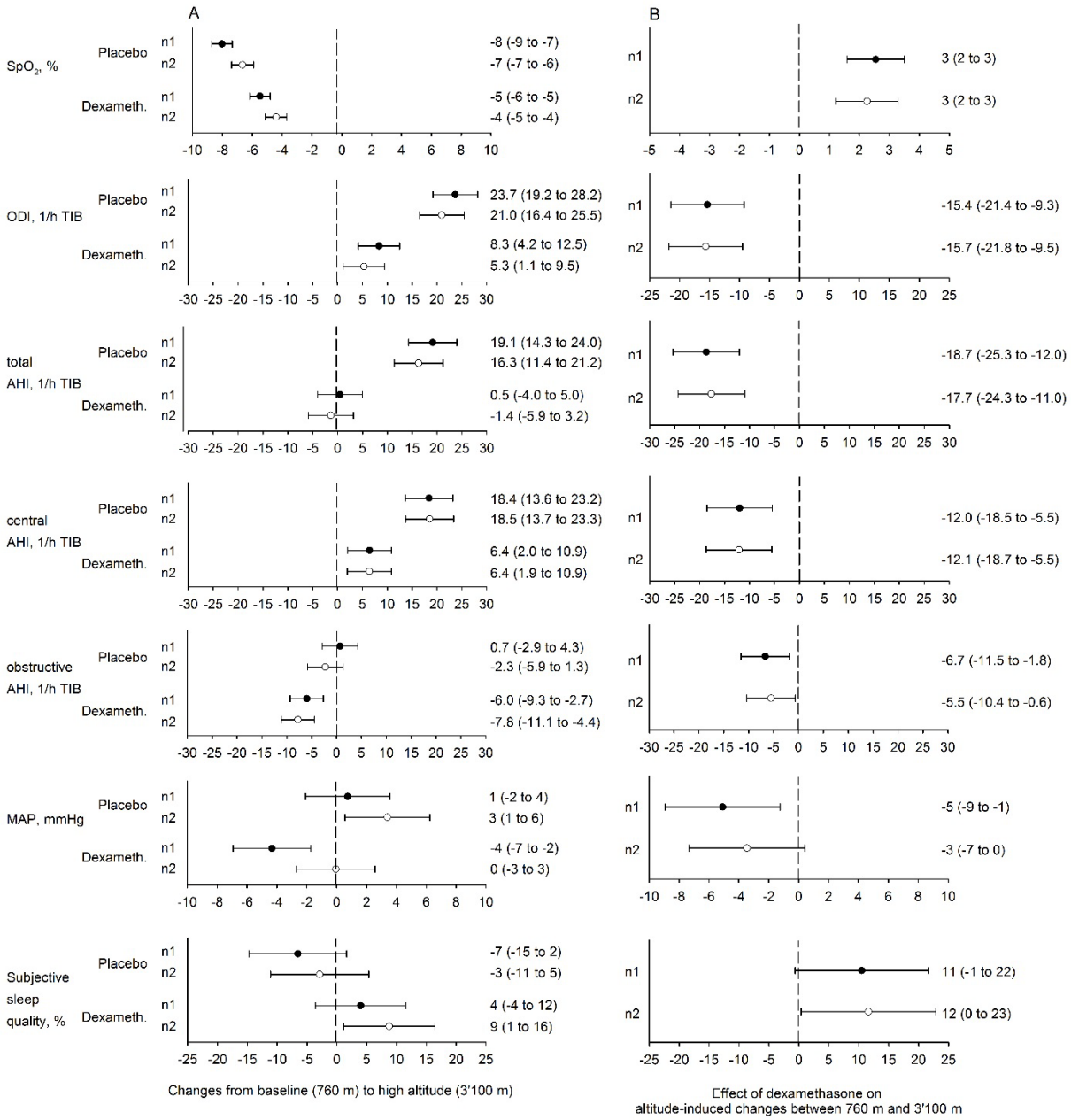

Figure 6-2. Altitude- and dexamethasone-induced changes in breathing pattern and morning assessments after the 1st and 2nd night at 3’100 m. *Panel A: Altitude-induced changes in placebo and dexamethasone group. Dots represent mean difference and horizontal bar the 95 % CI. Altitude-induced change is significant when the value zero is not part of the 95 % CI. Panel B: Effect of dexamethasone is significant when the value zero is not part of the 95 % CI. n1 / 2 = Night 1 / night 2; SpO_2 = Nocturnal oxygen saturation measured by pulse oximetry; ODI = Oxygen desaturation index; AHI = Apnea / hypopnea index; Subjective sleep quality was assessed by visual analog scale in the morning after the night examination.*

Patients using dexamethasone perceived a better sleep quality compared to patients using placebo (Table 6-1, Figure 6-2). There were no significant differences in subjective estimates of sleep latency, nocturnal time awake and awakenings between two groups. The PVT reaction time was similar at low and high altitude and no between-group difference was noted (Table 6-2). Subjective sleepiness assessed was also similar in both groups.

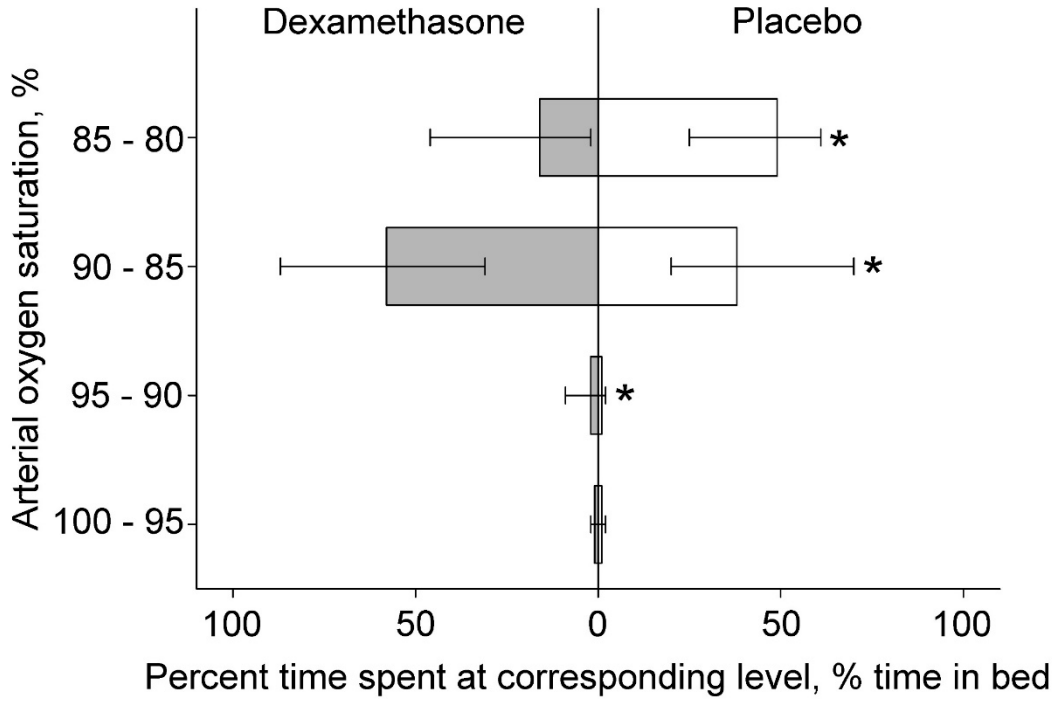

Figure 6-3. Effect of dexamethasone on time spent in different levels of hypoxemia during the first night at 3’100 m. *Whiskers represent the 25th and 75th percentile. Asterisks indicate a significant effect of dexamethasone compared to placebo.*

There were trends of an increase in mean arterial blood pressure in the placebo group and reduction of blood pressure in the dexamethasone group, so that the net effect of dexamethasone was a reduced blood pressure at altitude (Table 6-2). Arterial blood gas analyses revealed an altitude-induced hypocapnia and an increase in pH that was more pronounced in patients taking dexamethasone, though less altitude-induced hypoxemia compared to patients using placebo. Spirometry did not change over the course of the study. 28 % of all patients assigned to dexamethasone had asymptomatic hyperglycemia (Table 6-2).

Table 6-2. Daytime assessments.

	Placebo group, n=48			Dexamethasone group, n=56			Treatment effect on night 1 at 3'100 m	Treatment effect on night 2 at 3'100 m
	760 m	3'100 m night 1	3'100 m night 2	760 m	3'100 m night 1	3'100 m night 2		
Karolinska sleepiness score	3 (3;5)	3 (3;5) *	3 (3;5)	3 (3;5)	3 (3;5)	3 (3;5)	−1 (−2 to 0)	0 (−1 to 0)
Reaction time, ms	344 (297;422)	327 (286;393)	-	317 (279;408)	336 (287;401)	-	38 (−28 to 104)	-
Weight, kg	73.0 (65.6;80.9)	72.1 (65.7;79.2)	73.2 (66.0;80.2)	72.0 (63.0;80.0)	70.5 (62.6;80.0)	72.4 (63.3;80.7)	0 (−1 to 1)	0 (−1 to 0)
Morning BPs, mmHg	131 (111;141)	128 (118;141)	134 (120;142) *	130 (112;142)	126 (113;134)	129 (120;141)	−5 (−10 to 0)	−3 (−9 to 3)
Morning BPd, mmHg	82 (73;89)	82 (74;86)	82 (75;89)	79 (73;87)	77 (69;84) *¶	81 (74;85)	−5 (−9 to −1)	−4 (−7 to 0)
Morning MAP, mmHg	98 (87;105)	96 (89;104)	101 (91;107) *	95 (87;107)	91 (86;101) *¶	97 (91;104)	−5 (−9 to −1)	−3 (−7 to 0)
Heart rate, 1/min	64 (59;70)	68 (62;73) *	66 (60;73)	63 (58;70)	67 (60;71) *	59 (55;69) ¶	0 (−3 to 3)	−4 (−7 to −1)
pH, []	7.39 (7.38;7.41)	7.42 (7.41;7.44) *	-	7.40 (7.39;7.42)	7.43 (7.42;7.45) *¶	-	0.01 (0.00 to 0.02)	-
Pa_{CO_2}, kPa	5.1 (4.8;5.4)	4.6 (4.4;4.9) *	-	5.2 (4.8;5.4)	4.4 (4.1;4.7) *¶	-	−0.2 (−0.4 to −0.1)	-
Pa_{O_2}, kPa	10.0 (9.2;10.7)	8.0 (7.8;8.4) *	-	9.6 (9.2;10.0)	8.2 (7.9;8.7) *	-	0.5 (0.1 to 0.9)	-
Sa_{O_2}, %	95 (93;95)	89 (88;90) *	-	94 (93;95)	90 (89;91) *¶	-	1 (0 to 2)	-
$DAaP_{O_2}$, kPa	3.1 (2.5;4.0)	1.1 (0.5;1.5) *	-	3.6 (3.0;3.9)	1.1 (0.6;1.4) *	-	−0.2 (−0.6 to 0.2)	-
HCO_3−, mmol/L	23.3 (21.7;24.4)	22.1 (20.8;23.0) *	-	23.2 (22.0;24.4)	21.4 (20.6;22.8) *	-	−0.6 (−1.4 to 0.1)	-
Hct, %	44 (40;46)	44 (41;46)	-	44 (41;46)	44 (41;47) *	-	0 (0 to 0)	-
tHb, g/dL	14.8 (13.5;15.7)	14.9 (13.8;15.6)	-	15.0 (13.8;15.8)	14.9 (14.1;16.1) *	-	0.1 (−0.1 to 0.3)	-
Glu, mmol/L	7.0 (6.0;8.0)	7.4 (6.1;8.5)	-	6.7 (5.9;7.9)	9.3 (7.8;11.4) *¶	-	2.9 (1.7 to 4.1)	-
FEV_1, L	2.7 (2.3;3.0)	2.6 (2.3;3.0)	2.6 (2.1;2.9)	2.5 (1.9;2.9)	2.6 (1.9;2.9)	2.5 (2.0;2.9)	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.2)
FEV_1, % predicted	96 (77;109)	93 (73;105)	90 (79;105)	85 (73;102)	87 (74;103)	90 (70;100)	3 (−1 to 6)	2 (−2 to 5)
FVC, L	4.3 (3.7;4.9)	4.1 (3.5;4.8)	4.1 (3.5;4.8) *	4.1 (3.3;4.5)	4.2 (3.5;4.5)	4.0 (3.3;4.6)	0.1 (−0.1 to 0.2)	0 (−0.1 to 0.1)
FVC, % predicted	122 (104;137)	118 (99;136)	121 (102;129)	115 (98;125)	114 (98;125)	115 (97;126)	2 (−2 to 5)	0 (−3 to 4)
FEV_1 / FVC, []	0.65 (0.60;0.68	0.65 (0.60;0.68)	0.65 (0.59;0.68)	0.63 (0.56;0.66)	0.63 (0.60;0.68) *	0.63 (0.58;0.68)	0.01 (−0.01 to 0.03)	0.01 (0.00 to 0.03

Values are shown in median (quartiles); Treatment effects shown as mean differences and 95 % CI; BPs / BPd = Blood pressure systole / diastole; MAP = Mean arterial pressure; Pa_{CO_2}= Partial pressure of CO_2 in arterial blood; Pa_{O_2} = Partial pressure of O_2 in arterial blood; Sa_{O_2} = Arterial oxygen saturation measured by co-oximetry; $DAaP_{O_2}$ = Alveolar-arterial P_{O_2} difference calculated by the equation of Crapo RO et al.[116]; HCO_3− = Bicarbonate concentration; Hct = Hematocrit; tHb = Total hemoglobin concentration; Glu = Glucose; FEV_1 = Forced expiratory volume in the first second; FVC = Forced vital capacity; * p <0.05 vs. 760 m; ¶ p <0.05 dexamethasone vs. placebo at the same corresponding altitude & day.

Multivariable regression analysis revealed that altitude, exposure time to 3'100 m, dexamethasone intake, baseline (760 m) awake SpO_2, Pa_{CO_2}, and AHI were independent predictors of the mean nocturnal SpO_2 (Table 6-3).

Table 6-3. Predictors of nocturnal SpO_2 in multivariable regression analysis.

	Coefficient	Std. Err	P value	95 % CI
Night 1 at 3'100 m vs. 760 m	−7.00	0.24	<0.001	−7.48 to −6.53
Night 2 at 3'100 m vs. 760 m	−5.61	0.25	<0.001	−6.11 to −5.11
Dexamethasone (vs. placebo)	1.50	0.34	<0.001	0.84 to 2.16
Age, years	−0.03	0.02	0.144	−0.07 to 0.01
Female sex (vs. male)	−0.11	0.60	0.848	−1.28 to 1.05
760 m: Arterial oxygen saturation, %	0.42	0.12	<0.001	0.19 to 0.65
760 m: $DAaP_{O_2}$, kPa	−0.29	0.19	0.117	−0.65 to 0.07
760 m: Pa_{CO_2}, kPa	−1.36	0.42	0.001	−2.18 to −0.53
760 m: FEV_1, % predicted	0.02	0.01	0.118	−0.00 to 0.04
760 m: Apnea / hypopnea index, 1/h	−0.03	0.01	0.013	−0.05 to −0.01
760 m: Body mass index kg/m^2	−0.05	0.04	0.223	−0.13 to 0.03
Intercept	61.20	12.01	<0.001	37.66 to 84.75

$DAaP_{O_2}$ = Alveolar-arterial P_{O_2} difference calculated according to Crapo RO et al.[116]; Pa_{CO_2} = Partial pressure of CO_2 in arterial blood; FEV_1 = Forced expiratory volume in the first second.

6.4 Discussion

The current randomized, placebo-controlled, double-blind trial in lowlanders with mild to moderate COPD (GOLD grade 1 – 2) demonstrates that preventive dexamethasone treatment mitigated the altitude-induced decrease in the nocturnal SpO_2 and ODI and prevented an increase in AHI in the first 2 nights at 3'100 m. These favorable effects were associated with improvements in subjective sleep quality, though reaction time in a psychomotor vigilance test during daytime was not changed. Some patients taking dexamethasone had asymptomatic hyperglycemia. Dexamethasone thus may be used in some COPD patients undergoing altitude travel to prevent severe nocturnal hypoxemia.

In healthy lowlanders, an altitude-dependent reduction in nocturnal SpO_2, emergence of periodic breathing, sleep disturbances and impaired cognitive performance have been reported in several observational studies and in a few randomized trials.[30] For example, in 51 healthy lowlanders (median age 24 years) the median nocturnal SpO_2 in the first night after ascent from 490 m to 2'590 m was 90% and the AHI 13.1 /hour.[8] In 40 healthy volunteers (mean age

40 years) ascending from 555 m to 3'150 m, the mean SpO_2 during the first night at high altitude was 83 %, the AHI 7.4 /hour.[33]

In COPD patients, effects of altitude travel have not been reliably studied. In a previous investigation in 32 lowlanders with moderate to severe COPD (median FEV_1 59 % predicted) ascending from 490 m to 2'590 m, we observed a median nocturnal SpO_2 of 85 % and emergence of predominantly central sleep apnea (increase in the median AHI from 15.4 /hour to 58.6 /hour, data in preparation for submission). This degree of nocturnal hypoxemia and central sleep apnea was similar to that in the current patients with less severe COPD (placebo group) but exposed to a higher altitude of 3'100 m. Although the nocturnal hypoxemia of these patients was not more pronounced than that reported in healthy individuals at 3'150 m,[33] the AHI in the COPD patients at 3'100 m was much higher than that in the healthy individuals (i.e. 38.8 /hour, vs. 7.4 /hour). It is uncertain whether exclusion of 14 / 58 individuals in the placebo group with severe hypoxemia requiring oxygen therapy due to safety rules has raised the median SpO_2 although the missing data were replaced by multiple imputation. The greater altitude-induced increase in the AHI in COPD patients (placebo group) compared to healthy individuals in previous studies suggests a reduced stability of control of breathing in COPD patients compared to healthy, possibly due to their older age and / or their lung disease which might have promoted central apnea by an increased ventilatory drive.[154,155] However, as we did not measure ventilatory drive, and as arterial blood gas analyses are not available from the cited investigations in healthy individuals, we have no data to corroborate this hypothesis. The baseline AHI at 760 m of the patients in the current study of 20.5 /hour and 25.9 /hour with predominantly obstructive events is within the quartile range of values reported in a sample of the general population older than 40 years (i.e., 7.2 /hour to 27.1 /hour).[156] In the absence of symptoms of sleep apnea syndrome, we have no evidence that the participants of the current study suffered from the obstructive sleep apnea syndrome, a condition known to predispose to an exacerbation of sleep apnea during altitude sojourns.[148]

The current trial is the first to evaluate prevention of altitude-related nocturnal hypoxemia and breathing disturbances in COPD patients. We selected dexamethasone for this trial for two main reasons: Dexamethasone has been shown to prevent AMS in healthy individuals, and glucocorticoids are used to treat COPD exacerbations, as they reduce airway inflammation and improve airflow obstruction. Moreover, in otherwise healthy susceptibles to high altitude pulmonary edema ascending rapidly to 4'559 m, dexamethasone improved nocturnal oxygenation and reduced high altitude periodic breathing in addition to reducing pulmonary artery pressure;[84,147]

the reduction in high altitude periodic breathing was related to a reduced eupneic $P_{ET_{CO_2}}$ (the surrogate of Pa_{CO_2}). As the apnea threshold was also reduced, the CO_2 reserve (the difference between eupneic Pa_{CO_2} and apnea threshold of Pa_{CO_2}), one of the determinants of breathing stability, was maintained. In the current study, COPD patients using dexamethasone had a greater altitude-related hypocapnia than patients using placebo indicating a reduced eupneic Pa_{CO_2} (Table 6-2). Assuming no change in the CO_2 reserve by dexamethasone, the lower AHI at 3'100 m in patients using dexamethasone might therefore be related to a greater ventilatory overshoot required to cross the apnea threshold because of the hyperbolic shape of the alveolar ventilation vs. Pa_{CO_2} relationship.[31,147] A reduced hypoxic ventilatory drive due to the higher Pa_{O_2} in patients using dexamethasone might have additionally stabilized their control of breathing. There is increasing evidence that pulmonary hypertension is associated with breathing instability.[6,157,158] Reducing the hypoxic pulmonary hypertension by dexamethasone[84] might additionally have contributed to the stabilizing effect on ventilation reflected in the reduced AHI.

Patients using dexamethasone perceived a better sleep quality at altitude compared to patients using placebo, in which a trend for an altitude-related impairment of subjective sleep quality was noted. In both groups, subjective sleepiness and reaction time in the psychomotor vigilance test during daytime remained unchanged with ascent to altitude. It is uncertain whether the relatively mild altitude-induced reduction in cerebral tissue oxygenation detected by near-infrared spectroscopy was not strong enough to cause measurable effects in these outcomes in both patient groups.

Of note is the fact that 28 % of the COPD patients assigned to dexamethasone had a glucose concentration above 11.1 mmol/L, indicating a blood sugar imbalance[140] ($P < 0.001$ vs. placebo), but no other adverse effects of the drug were noted.

Limitations of this study include the recruitment of predominantly mild COPD patients and investigation during only nights at altitude; results can therefore not be extrapolated to patients with more severe COPD or longer altitude sojourns. A similar fraction of patients using dexamethasone and placebo (22 % vs. 24 %, $P = 0.749$) experienced clinically relevant AMS and / or severe hypoxemia (SpO_2 <75 % for >30 min).[69] Since these patients received oxygen and other appropriate treatment and were withdrawn from the study, the effect of dexamethasone on their nocturnal SpO_2 could not be assessed.

6.5 Conclusions

The results of the current randomized trial reveal that lowlanders with mild to moderate COPD travelling to high altitude suffer from nocturnal hypoxemia and central sleep apnea, which can be mitigated by preventive dexamethasone treatment, which also improves subjective sleep quality and reduces daytime blood pressure. Since the effects of dexamethasone on oxygenation are moderate, and since the drug may predispose to hyperglycemia temporary use for prevention of altitude-related hypoxemia, breathing and sleep disturbances in COPD patients should be limited to selected patients in whom nocturnal oxygen therapy is not feasible during altitude travel.

7 General discussion

The high prevalence of COPD worldwide and the increase in mountain tourism and air travel, as well as the lack of scientific evidence on potential adverse physiological and clinical consequences of altitude exposure in these patients indicate a high need for research studies in this field. In particular, studies evaluating 1) the general health risk and means for prevention of adverse effects of altitude and 2) studies quantifying limitations in exercise performance and related physiological mechanisms and 3) research on effects of altitude on sleep and nocturnal breathing in COPD patients are of high interest and needed in order to obtain targets for prevention and treatment of adverse consequences.

The current thesis investigated for the first time altitude-induced physiological changes and clinical symptoms in COPD patients travelling to and staying for a few days at high altitude. It also evaluated the efficacy of dexamethasone for prevention of AMS and ARAHE, and sleep related breathing disorders. Our results show that patients with moderate to severe COPD (GOLD grade 2 – 3, FEV_1 30 – 80 % predicted) experienced a major reduction (of 54 %) in endurance time of submaximal bicycle exercise. To evaluate potential means to improve the altitude tolerance we performed the first randomized trial of dexamethasone as preventive treatment for AMS and ARAHE in COPD patients staying at 3’100 m. Although dexamethasone did not significantly reduce the incidence of AMS or ARAHE, it improved the nocturnal oxygen saturation, high altitude periodic breathing and subjective sleep quality.

The novel insights gained by this research may serve as a physiological basis to better understand the susceptibility to AMS / ARAHE and the altitude-induced physiological changes in COPD patients, and to better counsel COPD patients undergoing altitude travel. Our findings may guide future research and help identify targets for prevention and treatment of altitude-related illness in patients with respiratory disease.

7.1 Altitude-induced physiological and clinical changes in COPD

Our studies provide detailed data on the physiological and clinical response to acute altitude exposure in COPD patients. We focused on this disease, because it is highly prevalent and associated with impaired pulmonary gas exchange and systemic consequences, including cardiovascular disease and peripheral muscle weakness, that may further impair the tolerance of hypobaric hypoxia at altitude. We focused on three essential aspects of wellbeing in this setting:

exercise capacity, altitude-related illness and control of breathing during sleep. Each of these topics will be discussed in the following paragraphs.

7.1.1 Exercise performance

In healthy, normally trained individuals, submaximal exercise performance near sea level is mainly determined by $\dot{V}_{O_2}$max, whereas $\dot{V}_{O_2}$max is determined by pulmonary diffusing capacity, maximum cardiac output, oxygen carrying capacity and skeletal muscle characteristics.[27] At higher altitude, maximum aerobic power progressively decreases due to the decrease of atmospheric pressure. In conjunction, we observe a smaller oxygen diffusion gradient between the alveoli and the pulmonary capillary blood, and consequently the arterial blood, muscles and vital organs. Additionally, $\dot{V}_{O_2}$max is reduced due to a hypoxia-induced reduction in the maximum heart rate, redistribution of blood flow from locomotor towards respiratory muscles, and further exercise-induced hypoxemia. As suggested by Fulco CS et al.[159] submaximal and maximal performance are closely linked, although it is difficult to determine the decline of submaximal performance with altitude. Differences in intensities, durations and proportions of aerobic and anaerobic phases of the exercise test influence the outcome. Furthermore, compared to the $\dot{V}_{O_2}$max "plateau" which indicates good motivation and an "all-out" performance, there is no such "all-out" indication for a submaximal exercise performance. Taking these limitations into account, Grover RF et al., estimated that maximum exercise performance was reduced by 8 % for each 1'000 m ascent starting at 700 m.[26] At 2'300 m, Fulco CS et al. assumed a $\dot{V}_{O_2}$max decrement of 15 % and a 7 % prolongation of a fixed distance race that would last for 20 – 30 min near sea level.[159]

In our own research in COPD patients at altitude, we focused on submaximal exercise. Endurance of submaximal work is of particular relevance, as it represents the exercise intensity required to perform many daily activities and it is therefore essential for patients with COPD. Consistent with our hypothesis, we observed a major limitation in submaximal exercise endurance in patients with moderate to severe COPD after ascent to 2'590 m. Even though a quantitative comparison to existing data is hampered for various reasons mentioned above, the reduction in performance by 54 % at 2'590 m seems much greater than that estimated to occur in healthy athletes at 2'300 m by Fulco CS et al. Since exercise intolerance is already a hallmark in COPD patients near sea level, a further relative reduction at higher altitude is even more relevant in terms of practical consequences.

Near sea level, the exercise performance in COPD patients is limited by airflow obstruction, diffusion limitation, ventilatory inefficiency, static and dynamic hyperinflation, arterial hypoxemia and muscle hypoxia, associated pulmonary hypertension and increased work of breathing all contributing to increased dyspnea. Additionally, exercise performance can be negatively influenced by comorbidities, medication, anxiety, sedentary lifestyle and an ongoing exacerbation of COPD.[52]

Our findings in COPD patients indicated that the exercise limitation at higher altitude was mainly related to an inefficient pulmonary gas exchange, reflected in high ventilatory equivalents for CO_2 clearance and O_2 uptake, hypoxemia and muscular hypoxia, and an inadequate cerebral blood flow response to hypoxemia. Similar physiological mechanisms limiting exercise performance, i.e., ventilatory inefficiency and diffusion limitation resulting in hypoxemia, have been identified in COPD patients studied at low altitude. In contrast, dynamic hyperinflation, an important cause of exercise limitation in COPD patients near sea level, was not enhanced at 2'590 m compared to 490 m despite the higher $\dot{V}_E$ (Figure 4-3). A possible explanation for this finding might be the reduction in barometric pressure and air density at the higher altitude that reduced turbulent flow (reduction in the Reynold number) and therefore airflow resistance.[15]

In further studies that were not part of the current thesis we found that COPD patients (GOLD grade 2 – 3) had a reduction of $\dot{V}_{O_2 max}$ of 7 % at 1'650 m, which is similar to the predicted $\dot{V}_{O_2 max}$ decrement in athletes[159] (data accepted for publication in Int J Chron Obstruct Pulm Dis). The modest impairment of maximum performance at 1'650 m compared to 490 m might be due to the only slight reduction in barometric pressure ($P_{B2'590\ m}$ vs. $P_{B490\ m}$ = 0.87) and $P_{I_{O_2}}$.

A comparison of our results obtained in elderly COPD patients to data from healthy individuals of similar age is hampered since previous high altitude studies have included mainly healthy, fit mountaineers or athletes of younger age. To my knowledge, only 2 studies in patients with coronary heart disease have evaluated exercise performance in older persons exposed to altitudes similar to that in the current study. Our data provide therefore long-needed insights into the clinical and physiological response to altitude in older individuals with lung disease. An observational study in 20 US veterans (aged 68 ± 3 years), 50 % with known or high risk for coronary heart disease, investigated the response in these elderly subjects to 2'500 m.[160] The altitude was well tolerated by the veterans, but minute ventilation increased only minimally from 11.0 ± 2.9 L/min to 12.6 ± 5.9 L/min, P = 0.02, while $\dot{V}_{O_2}$max was reduced by 12 %. For

comparison, the COPD patients in our studies reached a higher minute ventilation at 2'590 m of (median of 13.7 L/min but their Pa_{O_2} decreased more during submaximal exercise intensity (to 6.7 kPa) compared to the veterans at maximal exercise (7.2 ± 0.4 kPa). The exercise limitation in COPD patients was most likely due to the gas exchange impairment with lower Pa_{O_2} to the impaired diffusing capacity with high ventilatory equivalent for oxygen was and due to ventilation / perfusion mismatch and dead space ventilation as suggested by an elevated $DAaP_{O_2}$. A more detailed comparison of the impairment of exercise performance in the veterans with a maximal treadmill protocol to the reduced performance of COPD patients in our study is not feasible.

In another uncontrolled study, 23 patients with coronary artery disease and 23 controls (aged 51 ± 9 and 53 ± 6 years, respectively) performed symptom-limited bicycle testing at 1'000 (clinic Gais, baseline) and 2'500 m (Mount Säntis).[161] Both groups performed similarly in regard of exercise capacity and arterial oxygenation, suggesting no disadvantage from coronary artery disease in exercise performance at an altitude of 2'500 m.

When comparing COPD patients in our study to results of the cited study in healthy controls and the patients with coronary heart disease maximal work capacities at low altitude were different (healthy controls: 200 ± 30 Watts; coronary artery disease patients: 162 ± 28 Watts; our COPD patients: 92 (73;120) Watts). The reason for exercise termination at 2'500 m reported by controls and coronary artery disease patients included more often dyspnea and leg fatigue, whereas general fatigue was predominantly the reason for stopping at 1'000 m. These observations are in accordance with our findings in patients with COPD.[105] Actually, in comparison to 2'590 m, patients at 490 m had better ventilatory equivalents, lower RER, similar hyperinflation, better arterial oxygenation and lower perceived dyspnea, therefore the reason for exercise termination are probably due to general fatigue due to exercise duration. Of course, as before mentioned, several exercise limiting factors were present, however they were less expressed compared to high altitude. In COPD patients, especially dyspnea sensation is crucial and at high altitude perceived dyspnea was higher, probably due to higher ventilatory stimulation due to severe hypoxemia, which is in accordance with the reported reasons for exercise termination from the study from Erdmann et al.[161] Furthermore, cerebral hypoxia in the frontal cortices has also been shown to play a role in dyspnea perception.[162]

7.1.2 AMS and ARAHE

According to a recent meta-analysis of data from 66'944 healthy mountaineers, the mean incidence of AMS at altitudes between 2'590 – 3'100 m is estimated to be 21 – 27 % (ranging from 4 – 32 %).[36] The high variability in estimates is due to differences in the definition of AMS in studies using various scores and cut-off values,[36] differences in ascent rates,[163] study designs,[145] fitness degree,[62] smoking status[164] and age[62] of participants. Despite an association of AMS with pre-existing lung disease in some retrospective analyses[62] and a more pronounced hypoxemia in COPD patients at an altitude of 3'100 m compared to that in healthy trekkers at similar altitude, robust evidence on the susceptibility of COPD patients to AMS has been lacking to date. Our prospective, randomized studies address this point by evaluating the incidence of AMS in COPD patients of different severities of airflow obstruction and after rapid ascent to different altitudes that are relevant for mountain tourists. In contrast to expectations based on the previous reports cited above, we did not observe a high incidence of AMS in COPD patients. Thus, only 8 and 9 % of participants in our studies at 2'590 m and 3'100 m respectively, suffered from AMS using the AMSc score and a criterion of $\geq$0.7 points to indicate clinically relevant AMS.

The rather low incidence of AMS in COPD patients can be explained in several ways. It may relate to physiological mechanisms, as well as to some particularities of our study protocols. Thus, it is conceivable that chronic, mild hypoxemia might have induced some degree of physiological "acclimatization" that contributed to a better tolerance of hypobaric hypoxia in COPD patients. However, these patients did not show erythrocytosis or metabolic acidosis to compensate respiratory alkalosis due to increased minute ventilation, two of the markers of acclimatization observed in long-term residents at high altitude.[6] Other potential reasons for a low incidence of AMS in COPD patients participating in our study may be their older age compared to participants in most previous studies on incidence of AMS,[36] as well as their Kyrgyz ethnicity, which might have modified their susceptibility to altitude-related illness. Further studies in age-matched healthy controls and in individuals of different ethnicity are required to evaluate these hypotheses.

Unlike previous studies on AMS in healthy individuals, the protocol of our investigations included distinct safety rules aimed at preventing dangerous complications of exposure to severe hypoxemia in COPD patients, some of them with associated potentially unknown cardiovascu-

lar disease. These safety rules may have induced a "survivor effect", as patients with most pronounced hypoxemia had to be treated with oxygen and were withdrawn from the study at an early stage, before the development of AMS that might have occurred after more prolonged exposure to altitude. The criteria for the safety rules were difficult to determine, and to some degree arbitrary. Their selection was based on clinical reasoning and guidelines. For example, guidelines of the British Thoracic Society for assessment of the fitness for flight suggest that inflight supplemental oxygen be administered to a passenger if SpO_2 fell below 85 % during a hypoxic challenge test.[76] The criteria selected by us to define severe hypoxemia requiring oxygen supply to the patient (i.e., SpO_2 <75 % for >30 min or SpO_2 <70 % for >15 min) represented a compromise aiming at not risking any serious complication but still allowing to simulate real life situations COPD patients may face at altitude. In a systematic search of the scientific literature, we did not identify any studies supporting any particular level of hypoxemia that was clearly associated with an increased risk of complications. Other safety criteria for withdrawal from our studies were symptoms and signs of a critical conditions such as extreme systemic hypertension (>220 mmHg systolic or >120 mmHg diastolic) or signs of emerging cardiac or central nervous system disease.

Even though the safety rules in our studies in COPD patients hamper the comparison with studies in healthy mountaineers in terms of the AMS incidence, our data are clinically important because the results reflect the incidence of a clinically relevant outcome, i.e. ARAHE, which includes AMS and / or a condition judged to be of clinical relevance. Moreover, the evaluation of dexamethasone and other drugs for prevention of this combined outcome is also important, as the goal is to identify measures that prevent harm to patients undergoing altitude travel. We saw that at 2'590 m, 9 of 38 patients (24 %) experienced AMS or ARAHE requiring descent, oxygen or another therapeutic intervention (data accepted for publication in Int J Chron Obstruct Pulmo Dis). Moreover, for patients with mild to moderate COPD (GOLD grade 1 – 2, FEV_1 >50 % predicted) ascending to an even higher altitude of 3'100 m, 27 of 118 (23 %) suffered from AMS or ARAHE, nocturnal hypoxemia, breathing and sleep disturbances. As the degree of airflow obstruction at low altitude was a significant independent predictors of the combined incidence of AMS / ARAHE and exercise endurance at high altitude, our studies provide novel, clinically important evidence for assessing the risk and the expected physical impairment of COPD patients undergoing altitude travel.

7.1.3 Nocturnal arterial oxygenation and breathing stability

In a recent systematic review of the scientific literature, we could identify only two conclusive studies using polysomnography to evaluate the effect of altitude exposure on nocturnal oxygenation, sleep and breathing disturbances in healthy volunteers.[30] In one of these studies involving healthy participants with a mean age of 40 years, the SpO_2 and ODI near sea level were 97.0 ± 1.3 % and 0.7 ± 0.9 /hour and these values changed to 82.1 ± 4.0 % and 12.1 ± 17.1 /hour in a night at 3'150 m.[33] In the other of the two cited studies performed in 51 healthy men (median age 24 years) the nocturnal SpO_2 at 490 m was 96 % and it decreased by 6 % in the first night at 2'590 m; correspondingly the mean low altitude ODI was 0.3 /hour and it increased by 7.8 /hour in the first night at 2'590 m.[8] In COPD patients, GOLD grade 2 – 3, studied in the same setting as the healthy participants mean nocturnal SpO_2 at 490 m was lower (92 %), the ODI higher (5.0 /hour) and the altitude-induced decrease in the SpO_2 (85 %) and the increase in the ODI (39.5 /hour) at 2'590 m were greater as the changes in healthy subjects (data in preparation for submission). These data suggested that the pulmonary gas exchange and control of breathing in COPD patients was altered in comparison to that in the healthy individuals. Consistent with the findings in the previous study in COPD patients mentioned above, the results of the current study performed as part of this thesis indicate that the COPD patients were more hypoxemic and had a higher ODI and AHI than those reported in healthy individuals at low and high altitude. Apart from the airway and parenchymal lung disease tied to COPD that may have impaired ventilation and gas exchange in the COPD patients their nocturnal breathing instability may have been related to an increased ventilatory drive, i.e., an enhanced controller gain, and alterations in ventilatory response time due to cardiovascular compromise that prolonged the circulation time from the lungs to the chemoreceptors. The older age of COPD patients compared to healthy individuals in the cited studies, the presence of cardiovascular disease in some patients and the baseline hypoxemia might have contributed to their greater susceptibility to high altitude periodic breathing.

7.2 Measures to prevent adverse, altitude-related health effects in COPD patients

It seems reasonable to advise COPD patients travelling to high altitude to continue their regular medication and to refrain from smoking. More specific and evidence-based recommendations have so far not been available. Therefore, the aim of the second trial within this thesis was to evaluate the efficacy of preventive dexamethasone intake against AMS and other ARAHE.

7.2.1 AMS and ARAHE

Dexamethasone is recommended as a drug for treating severe AMS and HACE. In contrast, it is used only as a second line drug for AMS prevention in persons allergic to or otherwise not tolerating acetazolamide. Therefore, not many randomized, controlled trials of dexamethasone for prevention of AMS have been conducted. A recent systematic review and meta-analysis[146] including 8 randomized controlled trials (totally including 216 trekkers) using dexamethasone as a preventive therapy,[84,129-131,165-168] concluded that dexamethasone effectively reduced the risk of AMS, however another meta-analysis did not find any risk reduction with dexamethasone.[169]

The mechanisms underlying the preventive effect of dexamethasone for AMS are not well understood. The drug has immediate (non-genomic) and delayed (genomic) effects. When using dexamethasone as a preventive medication, 24 hours before ascending to altitude, both, non-genomic and genomic effects are active and might contribute to protection from AMS. It has been suggested that dexamethasone blocks hypoxia-mediated vascular endothelial growth factor expression in microvascular endothelial cells in the brain and inhibits the accompanying increase in permeability, therefore reducing the formation of cerebral edema and preventing excessive intracranial pressure.[78] Dexamethasone also inhibits inflammatory pathways, reduces reactive oxygen species and has a sympatholytic effect. It should be noted that a higher sympathetic activity has been specifically observed in AMS and HAPE-susceptibles compared to non HAPE-susceptibles.[44] Furthermore, dexamethasone improves arterial oxygenation, another promoter of AMS, through stimulation of ventilation as indicated by our results in COPD patients. The increased Pa_{O_2} in COPD patients taking dexamethasone might also have prevented an excessive altitude-induced rise in pulmonary artery pressure. The observed lack of a beneficial effect of dexamethasone in reducing the incidence of AMS / ARAHE might be due to the unexpectedly low incidence we observed at 3’100 m, reducing the statistical power, and to particularities of our protocol that included safety rules, as discussed above in detail.

7.2.2 Nocturnal arterial oxygenation and breathing stability

Effects of dexamethasone on sleep and breathing have not been conclusively investigated. In a study in HAPE-susceptible mountaineers, dexamethasone (2 x 8 mg/day) administered on day 2 after arrival at 4'559 m resulted in major reductions in AHI and ODI at 4'559 m and an improvement in arterial oxygenation.[147] This suggested that dexamethasone not only prevented HAPE when taken early, before ascent (as shown in another study),[84] but was also effective when subclinical HAPE had already started. To our knowledge, no other study investigating the effect of dexamethasone on nocturnal oxygenation, breathing patterns and sleep has been published.

The improvement in arterial oxygenation during daytime observed in our studies in COPD patients taking dexamethasone at altitude was also preserved at night, perhaps preventing further hypoxia-induced hyperventilation, one of the mechanisms contributing to instability of ventilation. Additionally, dexamethasone may have mitigated high altitude periodic breathing through a reduction in pulmonary artery pressure that was demonstrated by echocardiography (data submitted for publication). It has been previously shown that sleep apnea is common in patients with idiopathic or chronic thromboembolic pulmonary hypertension, suggesting a pathophysiological link. Suggested mechanisms include a prolonged circulation time, increased ventilatory drive and other unknown mechanisms.[157] The observed improvement in sleep quality by dexamethasone might be due to improved arterial oxygenation, less periodic breathing and therefore less apnea-related short awakenings (arousals). We recently observed a stable ratio between apneas and apnea-related arousals of approximately 4 : 1 (data accepted in the Journal *Sleep*), therefore the absolute amount of arousals is assumed to be higher in placebo compared to dexamethasone. The lack of beneficial effects from nocturnal dexamethasone effects on daytime performance remains speculative. The fact that COPD patients generally felt well at 3'100 m might masked the effects of dexamethasone. Maybe at higher altitudes, effects of dexamethasone on nocturnal outcomes would have an impact on daytime performance as well.

7.2.3 Interaction between AMS / ARAHE and nocturnal hypoxemia

It seems reasonable that acute altitude illness including symptoms such as headache, gastrointestinal problems, weakness and dizziness have an impact on nocturnal sleep & breathing pattern or vice versa. Indeed, in the most popular questionnaire for AMS, the Lake Louise symptoms (LLS) questionnaire, there is a question about difficulty sleeping in the previous night,

suggesting a link between sleep and AMS.[134] However, the reason for taking the AMSc questionnaire[133] rather than AMS diagnosed by LLS in the ARAHE composite endpoint was the current debate about this interaction, where it was suggested that this has no or only poor correlation.[170] Finally in 2018, the revised LLS questionnaire omitting the question about disturbed sleep was released confirming the poor correlation.[171]

In healthy individuals there is a clear inverse relationship between hypoxemia and AMS. A study in 16 non-AMS versus AMS-susceptibles showed lower SpO_2, higher $DAaP_{O_2}$, higher heart rate, but similar Pa_{CO_2} values in AMS-susceptibles compared to non-AMS susceptibles.[172] The authors reported a more pronounced hypoxemia after 1 hour of exposure to 4'880 m in AMS-susceptibles that was not related to hypoventilation. They suggested that either diffusion impairment, anatomical right-to-left shunt or ventilation / perfusion mismatch might be the underlying promoter of hypoxemia. Interestingly in COPD patients, oxygenation was worse compared to healthy individuals, however the incidence of AMS was lower than expected, indicating that COPD itself or other associated factors might play a role in developing AMS. In another study performed in healthy mountaineers rapidly ascending to Capanna Regina Margherita, 4'559 m, oxygenation, breathing stability and minute ventilation was measured during the first night to elucidate their role in AMS development, assessed in the morning after. 11 mountaineers developed AMS (AMS+), whereas 10 did not (Controls).[173] AMS+ developed severe nocturnal hypoxemia (59 ± 13 % compared to 73 ± 6 % in Controls) and higher minute ventilation (7.94 ± 2.35 L/min compared to 6.06 ± 1.34 L/min). AHI tended to be higher in AMS+ but was not significantly different (60.1 ± 34.6 /hour compared to 47.1 ± 42.6 /hour). These authors concluded that pronounced nocturnal hypoxemia was a promotor for AMS, whereas this was, again, not related to hypoventilation. Breathing instability seemed to play a minor role in development of AMS, which is in accordance of our findings in COPD patients (mean change of AHI was +19.1 /hand and 0.5 /hours in patients assigned to placebo and dexamethasone, respectively). Interestingly, when performing a post-hoc multivariable regression analysis to elucidate whether nocturnal outcomes play a role in AMS severity in COPD, we saw that nocturnal hypoxemia and female sex are independent predictors, whereas breathing instability reflected in the AHI and other baseline outcomes were not (Table 7-1). This finding supports the observations in previous reports in healthy subjects.[173]

Table 7-1. Predictors of AMS in multivariable regression analysis at 3'100 m.

	Coefficient	Std. Err	P value	95 % CI
Apnea/hypopnea index, events/hour	0.000	0.001	0.741	−0.001 to 0.001
Nocturnal arterial oxygenation	−0.014	0.006	0.021	−0.025 to −0.002
Dexamethasone (vs. placebo)	0.025	0.032	0.435	−0.038 to 0.089
Age, years	−0.001	0.002	0.627	−0.004 to 0.003
Female sex (vs. male)	0.242	0.051	<0.001	0.141 to 0.342
760 m: Arterial oxygen saturation, %	0.003	0.010	0.807	−0.018 to 0.023
760 m: $DAaP_{O_2}$, kPa	0.019	0.016	0.236	−0.012 to 0.050
760 m: Pa_{CO_2}, kPa	0.035	0.038	0.353	−0.039 to 0.110
760 m: FEV_1, % predicted	0.000	0.001	0.923	−0.002 to 0.002
760 m: Body mass index kg/m^2	−0.003	0.004	0.415	−0.010 to 0.004
Intercept	0.575	1.090	0.598	−1.562 to 2.712

$DAaP_{O_2}$ = Alveolar-arterial P_{O_2} difference calculated according to Crapo RO et al.[116]; Pa_{CO_2} = Partial pressure of CO_2 in arterial blood; FEV_1 = Forced expiratory volume in the first second.

Since we found that dexamethasone has improved nocturnal oxygenation by a mean of 3 % (Figure 6-2) but in parallel is not a predictor in this regression analysis might indicate that improvement in nocturnal SpO_2 by dexamethasone was too low to detect an effect in AMS severity, supporting our argument that recommended dexamethasone dosage of 8 mg/d is insufficient in patients with COPD compared to healthy subjects to prevent them from AMS. Study strengths and limitations

A major strength of our studies is that they are the first randomized trials in patients with COPD performed at real altitude. Major logistical challenges encountered in large, clinical field trials may have precluded the execution of similar studies in the past. Mastering these difficulties and creating protocols that were easy to implement and did not result in any harm to participants are further strengths of our research. The two large, well-designed, randomized trials performed as part of this thesis provide for the first time robust and extensive data on physiological and clinical outcomes in patients with COPD and various degrees of airflow obstruction travelling to different altitudes that represent many tourist destinations. Conducting studies in different countries enhanced the generalization of the conclusions, but at the same time may have introduced difficulties in interpretation of the results, because of the different settings in Switzerland and in Kyrgyzstan, and because of the difference in the ethnicity and cultural background of participants in these countries. To overcome the linguistic and cultural challenges in the studies performed in Kyrgyzstan, clinical examinations were performed by Kyrgyz staff. Detailed standard operating procedures were created for all examinations, and the staff was intensively

instructed before and during the trials through regular teaching sessions. In the first trial, an ascent rate of 913 m/hour (from 490 m to 2'590 m within 2.5 hours) was present. A lower ascent rate of 585 m/hour (from 760 m to 3'100 m within 4 hours) in the second and third trial and the inclusion of mild to moderate COPD patients might have influenced the incidence of AMS / ARAHE.[4] Inclusion of a healthy, age-matched control group in our studies may have enhanced the interpretation of the physiological findings, but was not essential, since COPD patients served as their own control. Nevertheless, a healthy control group would have given more insights whether the observed physiological changes were similar in healthy and in COPD, providing more information for future studies in these research areas. In regard to the clinically relevant primary outcomes of the studies included in this thesis, a well-matched control group would have not substantially strengthened the conclusions, since the altitude-induced physiologic changes in COPD might have a different clinical relevance compared to healthy. Similar changes in healthy subjects would not allow the conclusion that patients with COPD were at similar risk of ARAHE as healthy subjects, since COPD is a systemic disease with various organ manifestations that may represent a vulnerability to hypoxia. Furthermore, since healthy subjects have a higher exercise capacity and arterial oxygenation, altitude-induced changes are difficult to compare to corresponding changes in COPD patients. Theoretically, best would be to find add a control group which is also matched for baseline exercise performance, however, these controls would not qualify as healthy controls anymore. The same is true for the assessment of ARAHE or nocturnal hypoxemia. Because obtaining qualitative data in COPD patients were of high priority from a clinical point of view, in order to provide evidence for counselling patients undergoing altitude travel and due to financial and logistical considerations, we have not been able so far to perform similar studies in a healthy, age-matched controls but this will be an important goal in future investigations.

8 General conclusions

This thesis adds novel information about adaptations and maladaptations in COPD patients travelling to high altitude. In these randomized clinical trials it has been shown that patients with mild to severe COPD already at moderate to high altitude experience physiological and clinical changes, including severe exercise intolerance, nocturnal hypoxemia and breathing instability exceeding the severity in healthy at similar altitudes. One out of four COPD patients experienced an ARAHE, forcing the patient to receive treatment and relocation from 3'100 m to lower altitude. Dexamethasone prophylaxis of excessive nocturnal and daytime hypoxemia may be useful in selected COPD patients, in whom hypoxemia is expected to be pronounced at altitude and when close monitoring of side effects including hyperglycemia is performed. The inability of dexamethasone in reducing AMS symptoms stands in contrast with the current guidelines, therefore this large trial in COPD patients provides unique information which should initiate an update of the current guidelines. Indeed, the efficacy of dexamethasone in AMS prevention is under debate,[146,169]and this large trial in COPD patients is in accordance with the up-to-date meta-analysis.

9 Outlook

Further studies in healthy men and women of various ethnicities and matched to COPD patients in terms of age and sex would give important additional insights into the normal physiological and clinical changes at altitudes of 2'590 – 3'100 m. Additionally, a study in healthy subjects older than 40 years might provide valuable information on the altitude effects in an age group that has not been included in previous studies. Such data may also serve as reference for future studies in COPD patients using other preventive treatments. This thesis introduced a new research field with important questions to be answered. For the near future, well-designed randomized trials focusing on the efficacy of a higher dosage of dexamethasone or the prescription of another preventive medication (i.e. acetazolamide, sildenafil) against AMS / ARAHE in COPD patients may help to better understand the physiology and to better counsel such patients considering travel to high altitudes. In the longer term, detailed insights into the physiological and clinical changes with hypobaric hypoxia and into the effect of various treatments may help to identify new targets for therapies against hypoxemia with COPD and possibly other respiratory disease. Exercise intolerance observed in this thesis was related to various limiting factors

(cerebral, muscular and systemic hypoxia, dynamic hyperinflation and pulmonary gas diffusion impairments), however, this thesis was not able to identify or distinguish the importance between these factors for exercise intolerance. This should be addressed in future well-designed physiological studies investigating these factors in great detail, if possible, invasively to avoid negative conclusions due to low sample sizes or high variability due to non-invasive measurement techniques.

10 Literature

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11 Abbreviation list

AHI	=	Apnea-hypopnea index
AMS	=	Acute mountain sickness
AMSc	=	Environmental symptoms questionnaire cerebral score
ARAHE	=	Altitude-related adverse health effect
BBB	=	Blood-brain barrier
BTPS	=	Body temperature, pressure and humidity conditions
CAT	=	COPD assessment test
CI	=	Confidence interval
COPD	=	Chronic obstructive pulmonary disease
CMS	=	Chronic mountain sickness
CTO	=	Cerebral tissue oxygenation
$DAaP_{O_2}$	=	Alveolar-arterial P_{O_2} difference
ECG	=	Electrocardiography
EELV	=	End-expiratory lung volume
EILV	=	End-inspiratory lung volume
FEV_1	=	Forced expiratory volume in the first second
FI_{O_2}	=	Fraction of inspired O_2
FVC	=	Forced vital capacity
FRC	=	Functional residual capacity
GOLD	=	Global Initiative for Obstructive Lung Disease
HACE	=	High altitude cerebral edema
HAPE	=	High altitude pulmonary edema
HAPH	=	High altitude pulmonary hypertension
HVR	=	Hypoxic ventilatory response
IATA	=	International Air Transport Association
IRV	=	Inspiratory reserve volume
LLS	=	Lake Louise score

LTOT	=	Long-term oxygen therapy
MCA	=	Middle cerebral artery
MCAv	=	Middle cerebral artery peak blood flow velocity
MTO	=	Muscle tissue oxygenation
MVC	=	Maximal ventilatory capacity
NIRS	=	Near-infrared spectroscopy
NYHA	=	New York Heart Association functional class
ODI	=	Oxygen desaturation index
OSAS	=	Obstructive sleep apnea syndrome
PVT	=	Psychomotor vigilance test
P_B	=	Barometric pressure
RER	=	Respiratory exchange ratio
Sa_{O_2}	=	Arterial oxygen saturation
SpO_2	=	Arterial oxygen saturation measured by pulse oximetry
STPD	=	Standard temperature, pressure, dry conditions
TLC	=	Total lung capacity
Pa_{CO_2}	=	Partial pressure of CO_2 in arterial blood
Pa_{O_2}	=	Partial pressure of O_2 in arterial blood
$P_{ET_{CO_2}}$	=	Partial pressure of end-tidal CO_2
$P_{I_{O_2}}$	=	Partial pressure of inspired oxygen
V_D	=	Physiological dead space
$\dot{V}_E$	=	Minute ventilation
VEGF	=	Vascular endotherlial growth factor
V_T	=	Tidal volume
$\dot{V}_{CO_2}$	=	CO_2 production
$\dot{V}_{O_2}$	=	O_2 uptake

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13 Publications

1. **Furian M,** Lichtblau M, Aeschbacher SS, Estebesova B, Emilov B, Sheraliev U, Marazhapov NH, Mademilov M, Osmonov B, Bisang M, Ulrich S, Latshang TD, Ulrich S, Sooronbaev TM, Bloch KE. Efficacy of dexamethasone in preventing acute mountain sickness in COPD patients. Randomized trial. Chest 2018; in press.

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