Safety and exercise tolerance of acute high-altitude exposure (3454 m) in patients with coronary artery disease

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ABSTRACT

Objectives - The aim of the study was to assess the safety and cardiopulmonary adaptation of high altitude exposure in coronary heart disease patients.

Background - The response to exercise and safety of maximal physical stress at altitudes > 3000 m above sea level have not been studied in patients with coronary artery disease so far.

Methods - 22 patients (20 males/2 females), mean age 57 ± 7 years, effectuated a maximal, symptom-limited exercise stress test in Bern (540 m) and after a rapid ascent at the “Jungfraujoch” (3454 m). The study population included 15 patients after ST-elevation myocardial infarction (STEMI) and 7 after a non-STEMI, 12 ± 4 months after the acute event; all patients were revascularized either by percutaneous coronary angioplasty (n=15) or by coronary artery bypass surgery (n=7). Ejection fraction was 60 ± 8%. Betablocking agents were withheld for 5 days before exercise testing.

Results - At 3454 m, peak VO$_2$ decreased by 19% (p<0.001), maximal work capacity by 15% (p<0.001) and exercise time by 16% (p<0.001); heart rate, ventilation and lactate were significantly higher at every level of exercise, except for maximal exertion. No electrocardiographic signs of myocardial ischemia or significant arrhythmias were noted.

Conclusions - Although oxygen demand and lactate levels are higher during exercise at high altitude, a rapid ascent and submaximal exercise can be considered safe at an altitude of 3454 m in low risk patients 6 months after revascularization for an acute coronary event and a normal exercise stress test in the plain.
INTRODUCTION

Leisure time activities at moderate or high altitude are very popular in mountain areas. An increasing number of recreational facilities with easy access even to high altitudes allows a broad public, including sedentary subjects, elderly people and patients with various diseases to be exposed to altitudes beyond 3000 m. In patients with coronary artery disease (CAD), the safety of high-altitude exposure has been of concern for a long time. Until today, recommendations for exposure to or activities at high altitude in this group of patients are based rather on empirical than scientific data, since only a few reports on high altitude exposure with a very limited number of cardiac patients have been published1-5.

The reduction in the inspired O₂ pressure (P\textsubscript{O₂}) with increasing altitude leads to several important circulatory changes. These changes lead to an increase in cardiac work and cardiac oxygen consumption6, which may put cardiac patients at risk, and therefore rises concern about safety of high altitude exposure. In patients with CAD, Wyss et al. observed a significant decrease in exercise-induced coronary flow reserve during inhalation of a hypoxic gas mixture corresponding to an altitude of 2500 m compared to baseline measurements at 450 m7. This could indicate that compensatory mechanisms which suffice at lowland, might be exhausted even at moderate altitudes in patients with CAD.

Therefore, we studied cardiopulmonary adaptation to exercise and safety of a rapid but realistic touristic ascent to an altitude of 3454 m, which corresponds to the altitude of the highest located tourist attraction in the Swiss alpine region with easy access by mountain cogwheel railway (“Jungfraujoch”, Bernese Oberland), visited by > 500’000 people per year.
METHODS

Study population

The study population included 22 patients (2 female, 20 male), mean age 57 ± 7 years, with a BMI of 26 ± 4 kg/m². All patients had a history of an acute coronary event, which was an ST-elevation myocardial infarction (STEMI) in 15 and a non-STEMI in 7 patients. During the acute event, mean peak CK mass was 65 ± 91 µg/L, peak troponin-I 124 ± 239 µg/L and ejection fraction 58 ± 11%. 6 patients suffered from 3-vessel, 6 patients from 2-vessel and 10 patients from 1-vessel disease. 15 patients were treated by percutaneous coronary angioplasty and 7 patients by coronary artery bypass grafting. It remained 3 vessels with a stenosis < 30% and 3 vessels with a stenosis < 50% which were not revascularized. The culprit lesion was the left anterior descendartery in 7, the circumflex artery in 5 and the right coronary artery in 10 cases. After the acute event, all patients participated in an 8 to 12 week ambulatory rehabilitation program. 22 consecutive patients willing to participate were recruited 6 to 18 months after the acute event (mean 12 ± 4 months). At study entry, left ventricular systolic function, measured by echocardiography, was normal with an ejection fraction of 60 ± 8% and a BNP of 50.1 ± 62.1 pg/ml.

Exclusion criteria were an age > 70 years, left ventricular ejection fraction < 45%, an abnormal stress test (chest pain or significant ST-segment depression), uncontrolled arterial hypertension (> 160/95 mmHg at rest), peripheral arterial occlusive disease (> IIb according to Fontaine classification), functionally relevant valvular disease or significant lung pathologies (maximal VC or FEV₁ < 70% of predicted value).

Study protocol

After an initial stress test for screening, all patients underwent a symptom limited cardiopulmonary exercise stress test (CPX) at our cardiovascular centre (540 m). Betablocker
therapy was stopped 5 days before the test for the whole study period. Within less than 3 weeks after the first CPX, patients started their excursion to the “Jungfraujoch” at 7:00 h am and reached the altitude of 3454 m with public transportation at 10:30 h am. The stay at the “Jungfraujoch” lasted 4 hours and included a regular sight seeing programme and a light meal. CPX was performed indoor in a conference room at the tourist complex between 1 and 3 hours after arrival at this altitude.

The patients were informed about the experimental procedures and possible risks related to the present study and informed-consent was obtained. The study protocol was reviewed and approved by the local Ethical Committee.

**Exercise testing**

CPX testing with breath-by-breath gas exchange measurements was performed on a computer-controlled, rotational speed independent bicycle ergometer (Cardiovit CS-200 Ergo-Spiro®, Schiller AG, Baar, Switzerland). Gas calibration was effectuated each day taking into account the ambient barometric pressure (494 mmHg). Calibration of the flow sensor was done before each test. A 12 lead ECG was recorded continuously. Each test consisted of a baseline gas exchange measurement at rest during 1 minute, a 3 minute reference phase during which patients cycled without workload, and a test phase with a 15W/min ramp protocol. The following parameters were measured every 2 minutes: blood pressure, heart rate, subjective rating of perceived exertion (Borg scale) for dyspnea and muscle fatigue and lactate concentration (capillary blood samples from the earlobe; Lactate Pro®, Arkray Inc., Kyoto, Japan). Gas exchange parameters included oxygen consumption ($\text{VO}_2$), carbon dioxide output ($\text{VCO}_2$), tidal volume ($\text{VT}$) and breathing rate (BR). From these data, minute ventilation ($\text{VE}$) and respiratory exchange ratio ($\text{VCO}_2/\text{VO}_2$) were calculated. Peak oxygen uptake ($\text{VO}_2$) was defined as the highest $\text{VO}_2$ achieved during the last 30 seconds of peak exercise. The anaerobic threshold ($\text{VO}_{2\text{AT}}$) was defined using three criteria: the point
after which the respiratory gas exchange ratio becomes 1.0, the V slope method and the point at which the ventilatory equivalent for oxygen ($V_{E}/VO_{2}$) and $P_{ET}O_{2}$ was minimal, followed by a steady increase.

**Statistical analysis**

All data are expressed as mean ± SD. The Wilcoxon signed ranks test was used to calculate p-values for the comparison of the means. A p-value <.05 was considered statistically significant. Data were analysed using SPSS software version 10.0 (SPSS Inc. Chicago, Illinois, USA).
RESULTS

Figure 1 and table 1 show the results for heart rate, blood pressure, ventilation, oxygen consumption, subjective rating of perceived exertion and lactate level with cardiopulmonary exercise testing at 540 m and 3454 m.

Heart rate: At 3454 m, heart rate at rest was increased by 19% compared to lowland (67 ± 9 vs 83 ± 13; p<0.001). For every stage of exercise, heart rate was significantly higher at altitude, except for peak heart rate at maximal effort. At 3454 m, peak heart rate was significantly lower than at 540 m (159 ± 11 vs 163 ± 11, p=0.021).

Blood pressure: There was no significant difference between systolic and diastolic blood pressure values at 3454 m and 540 m at rest and at maximal exercise. During the other stages, systolic blood pressure was significantly higher at altitude, whereas there was no significant difference in diastolic blood pressure.

Ventilation: At rest and at peak exercise, there was no significant difference at altitude or at lowland in regard to the ventilation. During the test, ventilation was significantly increased at altitude at all stages.

Oxygen consumption: Oxygen consumption increased equally with similar values for VO₂ during submaximal exercise at both altitudes. At 3454 m, oxygen consumption began to be retarded with increasing work load after 6 minutes at altitude and at exhaustion peak VO₂ was significantly lower (22.9 ± 3.9 vs 28.3 ± 4.4 ml/kg/min., p<0.001). Mean peak VO₂ at lowland corresponded to 96% of the predicted value (63% - 123%).

Subjective rating of perceived exertion (Borg scale): Perceived dyspnea was significantly higher at all stages of exercise, whereas perceived leg fatigue was significantly different only up to 6 min. of exercise.

Lactate: At every stage, lactate levels were higher at 3454 m, except for the maximal value. While at the beginning of exercise differences were only marginal, the values diverged
clearly after 4 minutes. At maximal exercise, lactate levels were 7.1 ± 1.8 at 540 m and 6.9 ±
1.5 mmol/l at 3454 m (p=0.715).

Figure 2 shows the results of cardiopulmonary exercise testing in regard to exercise
capacity, oxygen consumption and exercise time. At exhaustion, maximal power output
decreased from 189 to 160 watt (-15%, p<0.001), peak VO₂ decreased from 28.3 to 22.9
ml/kg/min. (-19%, p<0.001), and exercise duration decreased from 644 to 538 sec (-17%,
p<0.001).

All patients tolerated the rapid ascent from the plain up to 3454 m and the 4 hour stay
without complications. None of the cardiopulmonary stress tests had to be stopped
prematurely. No evidence of stress-induced ischemia nor significant arrhythmias were noted
during stress test and recovery.
DISCUSSION

Study Findings

To our knowledge, this is the first study of safety and cardiopulmonary response to exercise in patients after a myocardial infarction at an altitude of 3454 m. For this reason we selected a patient group at very low risk (condition after coronary revascularization, normal left ventricular function and no signs of ischemia during an exercise test at lowland).

A rapid ascent and a 4 hour stay in a real life touristic setting have both been well tolerated, and no ischemia or significant arrhythmia occurred during the stress test. In order to eliminate the influence of betablockers on the physiologic adaptation to altitude, this medication was stopped at least 5 days prior to the first exercise test. This fact actually adds further value to the safety issue of the study, since the absence of this medication imposed a higher stress on the cardiovascular system during exercise testing.

It is important to notice, that the data do not apply to patients at a higher risk than the population studied. Especially patients with a reduced left ventricular function, incomplete revascularization or less than 6 months after an acute coronary event represent a different risk population and in such patients there could be a danger in exposing them to such an altitude. This is especially the case for patients presenting symptoms of heart failure. Furthermore our study has been performed inside a building at room temperature, without exposure to extreme weather conditions. Prolonged outdoor physical activity, with low temperatures or hazardous weather conditions, would impose additional physical stress for such patients.

However, we think that the result of this study will allow high altitude exposure of a considerable number of patients who have been discouraged to travel to such an altitude so far.
**Risk of high altitude exposure in patients with CAD**

For patients with stable CAD, there is concern that exposure to high altitude may (1) elicit ischemia, (2) increase the risk of arrhythmias or (3) provoke an acute coronary event.

In this study, at submaximal exercise, rate pressure product was significantly higher at altitude at every specific power output stage, due to a higher heart rate and a higher systolic blood pressure, therefore imposing a markedly increased myocardial oxygen demand. In addition, sympathetic activation associated with hypoxia\(^{10}\) might cause coronary vasoconstriction in regions with abnormal endothelial vasomotor control\(^{7,11,12}\) and further compromise myocardial oxygen delivery. Even though our patients were revascularized, their remained some coronary artery stenoses (3 vessels with a stenosis < 30% and 3 vessels with a stenosis < 50%) which were not revascularized, but none of these caused symptoms or abnormalities in the electrocardiogram.

A lot of concern is about the possibility of an increased risk of high-grade ventricular arrhythmias. The absence of any arrhythmic event with maximal sympathetic activation during maximal exercise stress test in combination with increased lactic acid levels in our patients can be regarded as reassuring. However, one has to keep in mind that our patients had normal or only slightly reduced left ventricular function and were fully revascularized.

Exercise is also known to be associated with an increased risk of myocardial infarction, particularly after heavy exertion\(^{13,14}\). Levine et al. reported in a study with a similar design the occurrence of a myocardial infarction in a patient after an exercise stress test at an altitude of 2500m\(^5\). Whether altitude adds to the risk of plaque rupture during exercise remains unknown. Changes in inflammatory activation, platelet aggregability and fibrinolytic activity, the increase of blood pressure and shear forces, changes in the arterial tone and twisting of the arteries during exercise as well as the role of a haemostatic imbalance as a trigger of acute cardiac events has been discussed as promoters of the occurrence of plaque rupture\(^{15}\). We do not expect that altitude would have a major influence on these triggering
mechanisms. In contrast, regular physical activity has been shown to protect against plaque rupture\textsuperscript{13,16,17} and therefore, a history of regular physical activity may be a good predictor of an uneventful stay at high altitude.

**Blood pressure, heart rate and ventilatory response to altitude**

Systemic blood pressure increases in response to hypoxia at the early stages of altitude adaptation\textsuperscript{18}. Our patients, some of them with treated hypertension, did not show significantly higher resting systolic blood pressures at altitude. However during exercise, systolic pressure response was significantly increased during all stages, except for the maximum. The enhanced blood pressure response is attributed to a higher excitability of arterial chemoreceptors and a reactive increase of the sympathetic nervous tone. Adequate blood pressure control seems therefore important for high altitude exposure tolerance and safety.

At altitude, submaximal heart rate and cardiac output can rise as much as 50\% above sea level values, whereas the heart’s stroke volume remains unchanged\textsuperscript{19}. This increase of submaximal exercise blood flow in compensation of arterial desaturation was also observed in our study population. At 3454 m, heart rate at rest was 19\% higher compared to 540 m and remained significantly higher except for the heart rate at maximal effort, which was even significantly lower (158 ± 11 vs 163 ± 11 beats/min; \(p=0.021\)). This effect of hypoxia on peak heart rate has been a matter of debate for a long time. In a review of several studies on maximal heart rate after acute hypoxic exposure, Lundby et al. have highlighted a possible influence of altitude on peak heart rate\textsuperscript{20}. They determined peak heart rate at increasing simulated altitudes in a dose-response study in healthy young males, showing a linear relationship between heart rate and simulated altitude up to 6300 m\textsuperscript{20}. Our CAD patients show a similar heart rate behaviour as the healthy subjects in Lundby’s study and endorse their findings. As a consequence of a decreased peak heart rate in a hypoxic environment, the maximal cardiac output is also reduced, leading to a reduction in maximal \(O_2\) delivery to the
working muscles. Below 3100 m, the reduction of VO₂max is primarily caused by a decrease in arterial oxygen saturation, whereas at higher altitudes, a reduction of cardiac output is likely to contribute to the limitation of maximal oxygen uptake as well. The decrease in peak heart rate seems to be reinforced after days at high altitude and therefore also depends on time of hypoxic exposure.

Hyperventilation due to reduced arterial P O₂ is the most important and most obvious immediate response to altitude exposure. Arrival at altitudes ≥ 2300 m initiates rapid physiologic adjustments to compensate for the “thinner” air with reduction in alveolar P O₂. For any given energy expenditure, ventilation increases proportionately with altitude. At the same time, due to a shift upwards and to the left of the relationship between lactate and workload, lactate levels at altitude are higher at each stage of exercise, which also contributes to exercise hyperventilation.

**Impact of altitude on maximal oxygen uptake**

While the atmospheric gas composition between oxygen (20.9%), nitrogen (78%) and inert gases (1.1%) remains the same, the progressive decrease in atmospheric pressure during the ascent (from 760 mmHg at sea level to 697 mmHg at 540 m and 494 mmHg at 3454 m) leads to a fall of the ambient partial pressure of oxygen (from 159 mmHg at sea level to 150 mmHg at 540 m and 104 mmHg at 3454 m). The mechanisms compensating for this reduced oxygen supply per single breath, are able to maintain a sufficient oxygen delivery to the peripheral tissues at submaximal effort independently of elevation. This was also observed in our patients, who during the first 6 minutes of exercise, showed the same oxygen uptake at 540 m and 3454 m. Thereafter, oxygen uptake at altitude began to be restricted and at exhaustion, peak VO₂ was 19% lower compared with lowland.

Compared to sea level, small declines in VO₂ max have been described at an altitude as low as 589 m. Thereafter, arterial desaturation causes VO₂ max of healthy men and women to
decrease at a rate of 7 to 9% per 1000 m altitude up to an altitude of 6300 m, where aerobic capacity declines at an even more rapid, nonlinear rate\textsuperscript{27}. With a decrease of VO\textsubscript{2max} of 6.3% per 1000 m difference in altitude, the reduction of oxygen uptake in our patients with CAD was even lower than the expected rate for normal individuals.

\textbf{Study limitations}

The study population consisted only of patients with revascularized stable CAD without a relevant reduction of left ventricular function and a normal exercise stress test at lowland. Furthermore, the environment during exercise testing was well controlled and strenuous activity was effectuated only during the exercise stress test. Under outdoor environmental conditions and sustained physical activity at this altitude, the study might have led to different results. Therefore, if giving advise to patients in regard to high altitude exposure, recommendations have to be restricted to the patients represented and to the activity effectuated in our study.

\textbf{Conclusion}

Submaximal exercise at high altitude imposes a higher myocardial oxygen demand, ventilatory response and lactate levels to patients with CAD than at lowland. Adaptation to acute altitude exposure and impact on exercise capacity and oxygen uptake were the same as described for healthy subjects.

Based on our data, patients corresponding to the population of our study can be allowed to expose themselves to an altitude up to 3454 m for a touristic trip 6 months after an acute coronary event, provided that a stress test with an appropriate rate pressure product (at least 25000 mmHg ⋅ cpm) is normal and the left ventricular function not compromised. Physical activity at a submaximal level for a duration of 3 to 4 h as in our study can be safely done and also a short maximal effort during this time period turned out to be safe. If patients...
want to hike for several hours or if they are going to be exposed to wind, rain, snow or cold, normal exercise capacity should be demanded (≥ 100% of the predicted value) and patients should be accustomed to regular strenuous physical activities in order to minimize the risk of incidents.
REFERENCES


FIGURE LEGENDS

Figure 1. Results of cardiopulmonary exercise testing in 22 CAD patients at 540m (♦) and at 3454m (□): heart rate, blood pressure, ventilation and oxygen consumption (* p<0.05).

Figure 2. Results of cardiopulmonary exercise testing in 22 CAD patients at 540m and at 3454m. Power output (watt), oxygen consumption (VO₂) and exercise time (sec) at exhaustion.
Table 1. Changes of cardio-respiratory parameters during symptom-limited exercise test at lowland, compared with 3454 m (n = 22). Values are presented as mean ± SD.
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<th>lactate (mmol/l)</th>
<th>540m</th>
<th>3454m</th>
<th>p-value</th>
<th>540m</th>
<th>3454m</th>
<th>p-value</th>
<th>540m</th>
<th>3454m</th>
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<td>1.7 ± 0.5</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
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<td>1.6 ± 0.4</td>
<td>.082</td>
<td>8.7 ± 19</td>
<td>9.9 ± 1.86</td>
<td>.006</td>
<td>8.7 ± 1.3</td>
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<td>.009</td>
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<td>2.0 ± 0.6</td>
<td>.022</td>
<td>10.6 ± 2.3</td>
<td>12.1 ± 2.4</td>
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<td>13.6 ± 2.3</td>
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Figure 1

Heart rate

Systolic & diastolic blood pressure

Ventilation

Oxygen uptake