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ORIGINAL ARTICLE

**Wolfgang Schobersberger · Peter Schmid
Monika Lechleitner · Serge P. von Duvillard
Helmut Hörtnagl · Hanns-Christian Gunga
Anton Klingler · Dietmar Fries · Karl Kirsch
Reinhard Spiesberger · Rochus Pokan · Peter Hofmann
Fritz Hoppichler · Gebhard Riedmann
Holger Baumgartner · Egon Humpeler**

Austrian Moderate Altitude Study 2000 (AMAS 2000). The effects of moderate altitude (1,700 m) on cardiovascular and metabolic variables in patients with metabolic syndrome

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Abstract We investigated the changes in the cardiovascular system [resting blood pressure (BP) and heart rate (HR), measured by means of a 24-h ambulatory BP and a holter-electrocardiogram (ECG)], glycemic parameters, and lipid metabolism of subjects suffering from metabolic syndrome during a 3-week sojourn at 1,700 m in the Austrian Alps. A total of 22 male subjects with metabolic syndrome were selected. Baseline investigations were performed at Innsbruck (500 m above sea level). During the 3-week altitude stay the participants simulated a holiday with moderate sports activities. Examinations were performed on days 1, 4, 9, and 19. After returning to Innsbruck, post-altitude examinations were conducted after 7–10 days and 6–7 weeks, respectively. The 24-h ambulatory BP and holter ECG revealed a decrease in average HR, BP, and rate pressure product (RPP: systolic blood pressure × HR) after 3 weeks of altitude exposure. In some patients, an increase in premature ventricular beats was observed at the end compared to the beginning of the exposure to moderate altitude. The ECG revealed no ischemic ST-segment changes. Maximal physical capacity as measured by symptom-limited maximal cycle ergometry tests remained unchanged during the study. Six weeks after the altitude exposure the blood pressure increased again and returned to pretest levels. The Homeostasis Model

H.-C. Gunga (✉) · K. Kirsch
Institut für Physiologie, Zentrum für Weltraummedizin Berlin,
Freie Universität Berlin, Arnimallee 22,
14105 Berlin, Germany
E-mail: gunga@zedat.fu-berlin.de
Fax: +49-30-84451658

W. Schobersberger · D. Fries
Klinische Abteilung für Allgemeine und
Chirurgische Intensivmedizin der Klinik für Anästhesie
und Intensivmedizin, 6020 Innsbruck, Austria

P. Schmid
Rehabilitations- und Kurzentrum "Austria",
4701, Bad Schallerbach, Austria

M. Lechleitner
Universitätsklinik für Innere Medizin,
Universitätsklinik Innsbruck, Anichstrasse 35,
6020 Innsbruck, Austria

S.P. von Duvillard
Human Performance Laboratory,
University of North Dakota,
Grand Forks, ND, USA

H. Hörtnagl
Institut für Sport- und Kreislaufmedizin,
Anichstrasse 35, 6020 Innsbruck, Austria

A. Klingler
Labor für Theoretische Chirurgie,
6020 Innsbruck, Austria

R. Spiesberger · R. Pokan
Institut für Sportwissenschaften,
Universität Wien, Austria

S.P. von Duvillard · P. Hofmann
Institut für Sportwissenschaften,
Karl-Franzens-Universität, Graz, Austria

F. Hoppichler
Krankenhaus der Barmherzigen Brüder,
5020 Salzburg, Austria

G. Riedmann
Österreichische Gesellschaft für Alpin- und Höhenmedizin,
6900 Bregenz, Austria

H. Baumgartner
Institut für Biochemische Pharmakologie,
Universität Innsbruck,
6020 Innsbruck, Austria

E. Humpeler
IHS-Institut Humpeler/Schobersberger Forschungsinstitut
für Urlaubs- und Freizeitmedizin sowie
Gesundheitstourismus, 6900 Bregenz, Austria

Assessment index, which is a measure of insulin resistance, decreased significantly and glucose concentrations obtained after an oral glucose tolerance test were significantly lower after the stay at altitude compared to the basal values. We conclude that after a 3-week exposure to moderate altitude, patients with metabolic syndrome (1) tolerated their sojourn without any physical problems, (2) exhibited short-term favorable effects on the cardiovascular system, and (3) had significant improvements in glycemic parameters that were paralleled by a significant increase in high-density-lipoprotein-cholesterol.

Keywords Altitude · Hypertension · Obesity · Coronary heart disease · Metabolic syndrome

Introduction

Visits and vacations at moderate altitudes of 1,500–2,500 m are very common among people who enjoy mountains and mountainous scenery. Many of these visitors are also patients with known or unknown arterial hypertension, diabetes mellitus, obesity, and disturbances in lipid metabolism, who may exhibit known or unknown signs and symptoms of heart disease. Several studies have addressed the short-term effects of moderate altitude in patients with known cardiovascular problems (Morgan et al. 1990; Hultgren 1992; Alexander 1994; Pokan et al. 1994; Roach et al. 1995; Levine et al. 1997; Erdmann et al. 1998; Steinacker et al. 2000), suggesting a small risk of acute cardiac events for patients with stable, treated heart disease and arterial hypertension. However, only limited data are available on long-term effects and associated changes in cardiovascular variables at moderate altitude in this population. A significant reduction in systolic blood pressure (SBP) at rest (Inama and Halhuber 1975; Halhuber et al. 1985) and during submaximal exercise (Nikolowa et al. 1989) was reported in patients with coronary heart disease (CHD) after a sojourn of several weeks duration at moderate altitude. Since cardiovascular and metabolic disorders are most frequent in western civilized populations, and are on the increase (Björntorp 1999), it can be assumed that among these mountain vacationers quite a large percentage show the signs and symptoms of metabolic syndrome. Metabolic syndrome is classified as a disease where patients exhibit a combination of obesity, hypertension, dyslipoproteinemia, and glucose intolerance (Reaven 1996). This syndrome is strongly related to an increase in sympathetic nervous activity (Reaven 1996; Björntop 1999) leading finally to an increased cardiovascular risk (DeFronzo and Ferrannini 1991). Acute hypoxia is known to increase SBP and diastolic blood pressure (DBP) and heart rate (HR) via stimulation of sympathoadrenergic activity under resting conditions (Hultgren 1992; Mazzeo et al. 1998; Duplain et al. 1999), while acclimatization under conditions of moderate hypoxia may cause a reduction in sympathetic tone, contributing to the decrease in blood pressure (BP) observed in hypertensive patients (Inama and Humpeler 1981). Remarkably, there are no reports to date on how tourists with metabolic syndrome adapt to and tolerate prolonged hypobaric-hypoxic exposure combined with moderate physical exercise.

Therefore, the purpose of the AMAS-2000 study was to investigate (1) 24-h HR and BP changes via electrocardiogram (ECG)-holter monitoring, (2) changes in physical capacity, and (3) metabolic changes focusing on insulin resistance using the Homeostasis Model Assessment (HOMA) index in patients with metabolic syndrome before, during, and 1 and 6 weeks after a prolonged stay at 1,700 m in the Austrian Alps.

Methods

Study participants

In the area of Innsbruck, a city that is located 500 m above sea level, volunteers were invited via a local newspaper to participate in our pilot project evaluating the effect of a 3-week stay at moderate altitude at Oberlech, Austria (1,700 m). Body-weight, body composition, BP, HR, and metabolic variables were measured. Forty men were scheduled to participate, but due to acute infections and schedule conflicts, and after laboratory and ergometric screening, only 22 participated in this study. The Ethics Committee of the Leopold-Franzens-University of Innsbruck approved the study and written informed consent to participate was obtained from all subjects before the commencement of our study.

Baseline investigations (t_1) were conducted at the end of August in Innsbruck, 1–2 weeks before the altitude sojourn. All participants were driven by bus to an altitude of 1,700 m (Oberlech, Austria), where they remained for 3 weeks, simulating a holiday in a comfortable resort hotel with moderate sports activities such as mountain hiking (at an altitude between 1,500–2,500 m, 4–5 guided mountain tours of 4–5 h duration per week). The sleeping altitude was 1,700 m. Non-alcoholic fluid intake was allowed *ad libitum* and nutrition was balanced with no specific dietary restrictions. For technical reasons related to the time schedule of the investigations, the subjects arrived at the health resort hotel in groups every 3 days in the late afternoon (5 p.m.–7 p.m.). During the altitude stay, four additional examinations were performed: after the first night at altitude (15–17 h after arrival at 1,700 m; t_2), on day 4 (t_3), day 9 (t_4), and day 19 (t_5). All examinations were performed between 8 a.m. and 10 a.m. After the volunteers returned to Innsbruck, post-altitude examinations were conducted after 7–10 days (t_6) and 6–7 weeks (t_7).

The baseline characteristics of the study participants are given in Table 1. Four patients suffered from type 2 diabetes mellitus and were being treated with oral antidiabetics, nine patients were on antihypertensive medication (six with angiotensin-converting enzyme inhibitors, three with beta-blockers), nine patients took aspirin, six took allopurinol, and nine were on statin therapy.

Cardiovascular measurements

At 1–2 weeks before ascent to moderate altitude (t_1), and 7–10 days (t_6) and 6 weeks [40.0 (2) days; t_7] after exposure to altitude, all patients were subjected to a bout of symptom-limited sitting cycle ergometry (Ergoline, Germany) at increasing increments of 25 W every 2 min. ECG recordings were monitored throughout all testing at an altitude of 500 m (Innsbruck, Austria). The subjects performed a 5-min effortless warm-up on the cycle ergometer. Room temperature was comparable at all tests (18–20°C). Blood pressure at rest was measured manually in the morning with the

Table 1 Anthropometric data and baseline metabolic profile of the AMAS-2000 volunteers ($n = 22$ patients with metabolic syndrome; data are presented as median and range). (*BMI* Body mass index, *BP* blood pressure, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *Apo* apoprotein, *[Lp(a)]* concentration of lipoprotein a, *ApoA1* apolipoprotein A1, *ApoB100* apolipoprotein B100)

Variable	Median	Range
Median age (years)	54	40–65
Median BMI ($kg \cdot m^{-2}$)	30.3	23.7–50.5
BP systolic (mmHg)	140	112–172
BP diastolic (mmHg)	87	80–115
Cholesterol ($mg \cdot dl^{-1}$)	205.5	152–282
Triglycerides ($mg \cdot dl^{-1}$)	176.5	91–655
HDL-C ($mg \cdot dl^{-1}$)	43.5	36–72
LDL-C ($mg \cdot dl^{-1}$)	125.7	62–201
ApoA 1 ($mg \cdot dl^{-1}$)	135.5	113–177
ApoB 100 ($mg \cdot dl^{-1}$)	122.5	81–187
[Lp(a)] ($mg \cdot dl^{-1}$)	9.0	6.0–114.0
Fasting plasma glucose ($mg \cdot dl^{-1}$)	95.0	80–226
HbA1c (%)	5.7	4.8–9.5

subjects in an upright sitting position according to the sixth report of the Joint National Committee on the prevention, detection, evaluation, and treatment of high BP (1997). During the 1st and 2nd day, and on the last 2 days of the 3 weeks of altitude exposure, all patients underwent a 24-h continuous ECG-holter monitoring (Delmar, Model 363, Digital recorder 483, USA) and 24-h continuous BP monitoring (Mobilgraph, IEM, UK) in randomized order. From the 24-h continuous ECG holter monitoring, we measured HR, the number of ventricular extrasystoles (VES), and ST-segment changes. For the determination of myocardial ischemia, we used ECG recordings to determine episodes of horizontal and descending ST-segment changes of 0.1 mV that lasted longer than 1 min. From the 24-h continuous BP monitoring, we also measured changes in HR, SBP, and DBP.

Laboratory measurements

Metabolic parameters were measured in Innsbruck before the stay at moderate altitude (t_1) and 7–10 days (t_6) after return from 1,700 m. Blood samples were taken from an antecubital vein in the morning after a 10-h overnight fasting period. Serum samples from all study participants were stored at –70°C. Plasma glucose was measured, and liver and kidney function tests were performed according to routine procedures.

Glycosylated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (HPLC; Diamat; Bio-Rad; Richmond, Calif., USA), with a reference range of 4.2–6.0%. Cholesterol and triglyceride levels were determined by enzymatic methods (Cholesterol PAP, MA Kit 100; Roche; Triglyceride PAP, UNi-Kit II, Roche), and high-density lipoprotein cholesterol (HDL-C) was assayed using a precipitation procedure with dextran sulfate and manganese chloride (Patsch et al. 1989). Levels of low-density lipoprotein cholesterol (LDL-C) were calculated according to the Friedewald equation (Friedewald et al. 1972). Plasma concentration of lipoprotein a [Lp (a)] was determined by an enzyme-linked immunosorbent assay (ELISA; Immuno, Vienna, Austria).

Plasma apolipoproteins (apo) A1 and B100 were determined by immunoturbidometric tests (Tina-quant, Boehringer Mannheim, Mannheim, Germany). A Cobas Mira Autoanalyzer (Roche, Basel, Switzerland) was used for all above-mentioned plasma measurements. Insulin was determined by the IMX Insulin assay (Abbott, Vienna, Austria) and C-peptide by a radioimmunoassay (C-PEP-RIA-CT, Biosource, Belgium).

The oral glucose tolerance test was performed after measurement of capillary fasting glucose by ingestion of 75 g glucose dissolved in 250 ml tea. Capillary glucose values were determined after 30, 60, 90, and 120 min. The oral glucose tolerance test was not carried out for the four patients with manifestation of type 2 diabetes mellitus. HOMA was measured for determination of insulin resistance according to Matthews et al. (1985) and Bonora et al. (2000): fasting plasma glucose ($mmol \cdot l^{-1}$) × fasting serum insulin ($U \cdot ml^{-1}$)/25.

Statistics

Anthropometric and metabolic data are presented as median values and the range; cardiovascular variables are shown as mean (SD). Repeated measures analysis of variance was applied to significant time effects with subsequent evaluation of linear contrasts to baseline. A significance level of 5% ($P < 0.05$) was applied in all studies.

Results

Cardiovascular measurements

Figure 1 shows the time course of changes in SBP and DBP at rest. A significant decrease of resting SBP was measured on day 4 at altitude and remained decreased in the first post-altitude examination (t_6). DBP did not change. The results of the 24-h monitoring of SBP and DBP, HR, and RPP at the start and at the end of the 3-week altitude sojourn are shown in Figs. 2, 3 and 4. For all variables, the measured values were lower at the end compared to the start of altitude exposure, which was significant mainly between the hours of 6 p.m. and midnight. In several participants, three of whom had documented CHD, we observed a small yet significant increase in VES. However, we did not observe any couplets, triplets, ventricular tachycardia, ventricular and atrial flutter, or ischemic ST-segment changes during the 24-h monitoring. The maximal cycle ergometry expressed in Watts (W) in absolute (W_{max}) and relative ($W_{max} \cdot kg^{-1}$) values was unchanged during the study [baseline values: 180 (52) W and 1.9 (0.5) W, respectively]. The total time of cycle ergometry also remained unchanged [t_1: 863 (250) s; t_2: 875 (286) s; t_3: 901

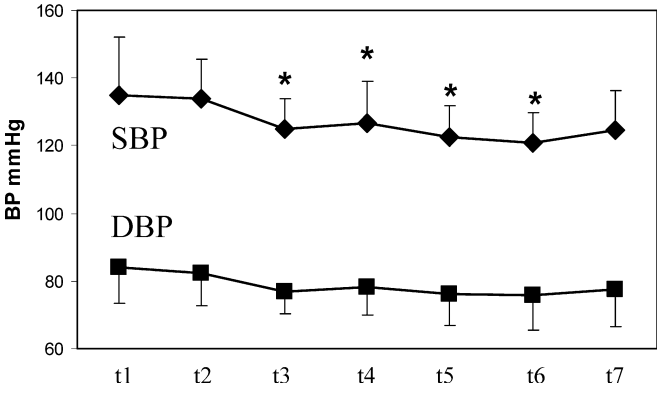

Fig. 1 Time course of changes in blood pressure (BP) before (t_1), on day 1 (t_2), day 4 (t_3), day 9 (t_4) and day 19 (t_5) at altitude and 1 week (t_6) and 6 weeks (t_7) post-altitude. (*SBP* Systolic blood pressure, *DBP* diastolic blood pressure). *$P < 0.05$ compared to baseline values (t_1)

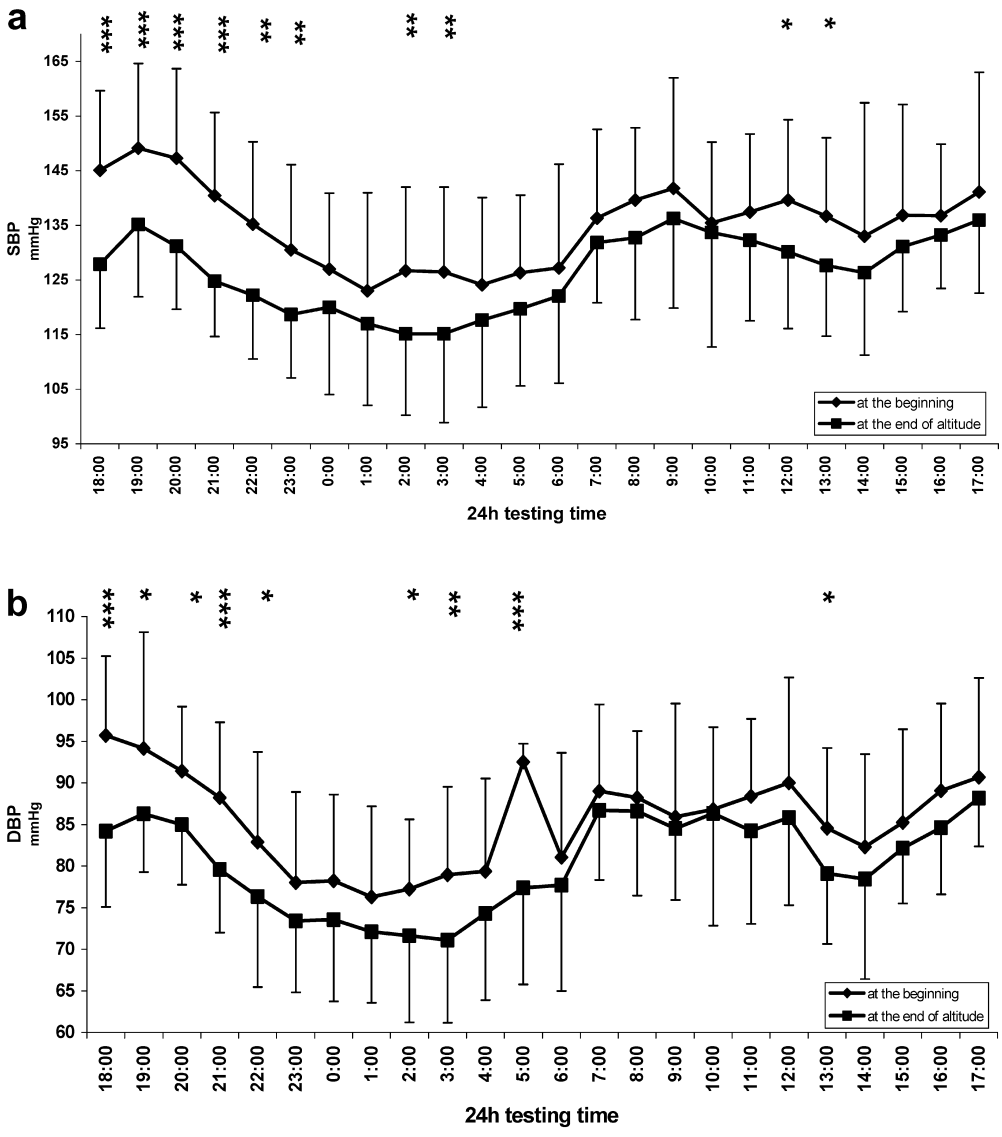

Fig. 2 Time course of changes in (**A**) SBP and (**B**) DBP over a 24-h period before (*closed diamonds*) and at the end (*closed squares*) of 3 weeks exposure to moderate altitude. Asterisks indicate statistically significant differences between the start vs the end of altitude stay: $*P < 0.05$; $**P < 0.01$; $P < 0.001$

(272) s]. Resting HR, submaximal HR (100 W), and maximal HR remained unchanged from t_1 to t_6 and t_7 after altitude exposure [baseline values of HR at rest, submaximal and maximal HR: 83.1 (20.1) beats·min^{-1}; 123.1 (21.0) beats·min^{-1}, and 159.1 (24.4) beats·min^{-1}, respectively]. The SBP during ergometry remained the same between both post-altitude tests compared to pre-altitude ergometry [SBP at t_1 submaximal and maximal: 174.5 (21.0) mm Hg and 208.2 (29.2) mm Hg, respectively]. DBP was unchanged during submaximal and maximal cycle ergometry at t_1 as compared to t_2 (DBP at t_1, submaximal and maximal: 87.5 (12.7) mm Hg and 89.5 (13.1) mm Hg, respectively). At t_3, maximal DBP was significantly higher as compared to t_1 and t_2 ($P < 0.05$). There were no horizontal or descending ST-segment changes present in excess of 0.1 mV during any cycle ergometry tests. In addition, we observed no HR abnormalities. During altitude exposure, we reduced antihypertensive drug therapy in three cases due to symptomatic BP reduction. These reductions in antihypertensive drug therapy remained effective for at least 6 weeks post-altitude. No patient required an increase or intervention of antihypertensive or anti-ischemic drug therapy. Angina pectoris did not occur in any patient at altitude or during maximal (W_{max}) or submaximal (100 W) cycle ergometry.

Biochemical measurements

Fasting plasma glucose, fasting insulin levels, and C-peptide of the study participants did not change during the entire study. HbA1c values were 5.7% (range 4.8–9.5%) at baseline and did not change after the altitude sojourn. The HOMA index as a measure of insulin resistance showed a significant decrease from 4.0 (range 1.1–17.7) before ascent to altitude to 1.9 (range 0.5–8.4) after return ($P < 0.04$). The capillary blood glucose levels obtained in the course of an oral glucose tolerance test were lower after the stay at moderate altitude, a change

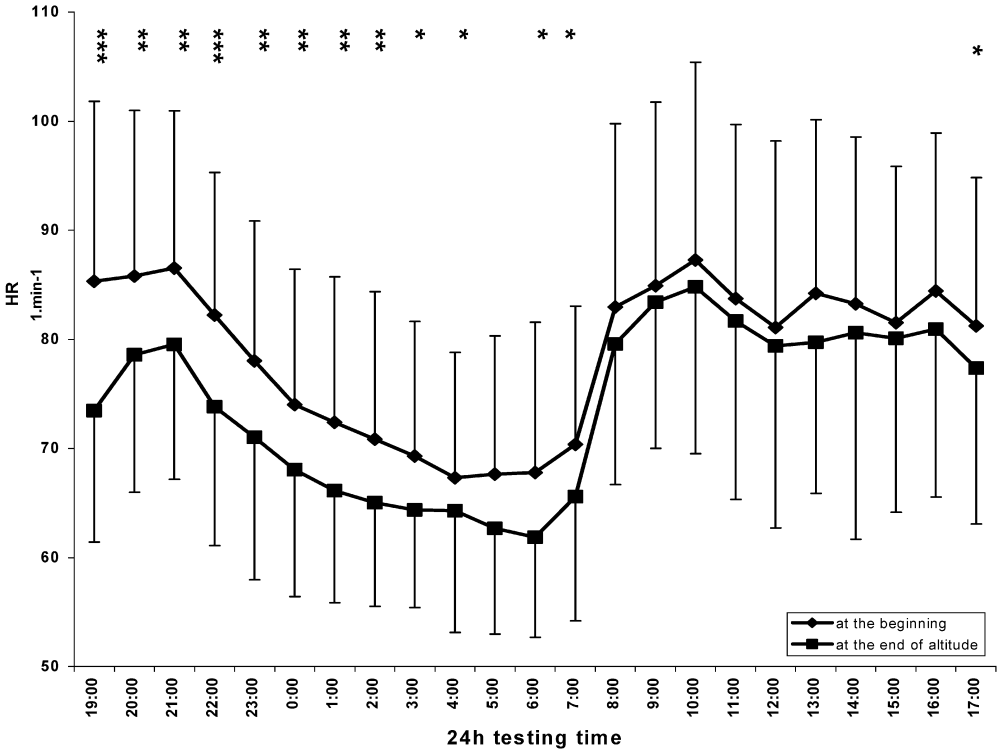

Fig. 3 Average heart rate (*HR*) values measured during 24-h holter electrocardiogram monitoring before (*closed diamonds*) and at the end (*closed squares*) of the 3-week sojourn to moderate altitude. Asterisks indicate statistically significant differences between the start vs the end of altitude stay: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$

that was statistically significant for glucose concentrations measured 60 min and 90 min after glucose ingestion (Table 2). No significant changes were observed in total cholesterol and LDL-C levels when the values obtained before and after the stay at moderate altitude were compared. Serum triglyceride levels did not change. In contrast, HDL-C values increased significantly from 43.5 mg·dl^{-1} (range 26.0–74.0 mg·dl^{-1}) to 48.5 mg·dl^{-1} (range: 26.0–102.0 mg·dl^{-1}; $P < 0.001$). Altitude exposure resulted in an increase in HDL-subfractions, HDL_2-C (from 4.0 mg·dl^{-1}, range 2.0–13.0 mg·dl^{-1}, to 6.0 mg·dl^{-1}, range 3.0–23.0 mg·dl^{-1}; $P < 0.002$) and HDL_3-C (from 39.0 mg·dl^{-1}, range 24.0–59.0 mg·dl^{-1}, to 45.6 mg·d^{-1}, range 34–79 mg·dl^{-1}; $P < 0.03$). Serum levels of apo A 1, apo B 100, and [Lp(a)] exhibited no significant differences comparing baseline values to post-altitude values. Serum concentrations of leptin remained unchanged.

Discussion

The main findings of our AMAS-2000 pilot study were that (1) all patients with metabolic syndrome tolerated the habituation at moderate altitude without any

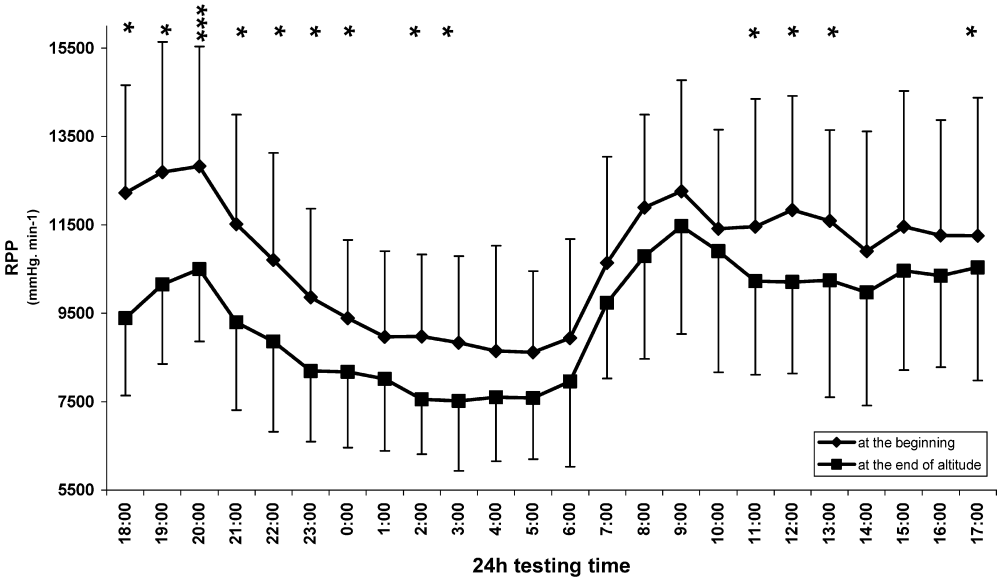

Fig. 4 Rate pressure product (*RPP*: SBP×HR) calculated from 24-h R–R holter monitoring of HR and BP before and after a 3-week of exposure to moderate altitude. Asterisks indicate statistically significant differences between the start vs the end of altitude stay: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$

Table 2 Capillary glucose concentration after oral glucose ingestion. The *P* value compares baseline data (obtained before the altitude sojourn) with post-altitude data (obtained 7–10 days after return from altitude). Data are presented as the median (range) of $n = 22$ patients with metabolic syndrome

Variable	Baseline (t1)	Post-altitude (t6)	*P*-value
Fasting glucose ($mg \cdot dl^{-1}$)	99 (86–163)	98 (84–118)	$P < 0.129$
30 min	164 (106–228)	160 (139–228)	$P < 0.097$
60 min	172 (101–276)	166 (87–276)	$P < 0.031$*
90 min	151 (75–234)	140 (75–162)	$P < 0.021$*
120 min	113 (63–205)	106 (63–207)	$P < 0.145$

*Significant difference

significant cardiovascular and metabolic problems, and (2) that beneficial effects were observed, as evidenced by reductions in HR, BP, and RPP, and by a reduction in the HOMA index as a measure of insulin resistance.

Altitude exposure and cardiovascular adaptation

Exposure to high altitude induces a stimulation of the sympathetic pathways in healthy subjects that remains elevated for several weeks (for review see Smith and Muenter 2000), resulting in an increase in pulse rate and BP (Bernardi et al. 1998). At altitudes below 3,000 m, sympathoadrenal stimulation is less pronounced, even an initial short-term vagotonia may be detected (Pokan et al. 1994). Thus, in the early phase of altitude adaptation, resting HR and BP were reported to be either increased or unchanged (Palatini et al. 1989; Savonitto et al. 1991; Veglio et al. 1999). During acclimatization to moderate altitude, most hemodynamic variables were reduced towards pre-altitude levels within 1–2 weeks (Inama and Halhuber 1975; Halhuber et al. 1985). Most patients with CHD can expect similar changes in hemodynamic variables to occur because of acute altitude exposure (Pokan et al. 1994). However, the physical capacity of these patients is reduced at altitude. Morgan et al. (1990) investigated nine patients with documented CHD and subjected these patients to ergometry tests at both 1,600 m and 3,100 m. They observed ST-segment changes at both altitudes and the occurrence of RPP at the same intensity as the ST-segment depression. However, they reported both ST-segment depression and RPP at significantly lower intensity during ergometry at 3,100 m. The maximal performance of these patients was 11% below the test conducted at 1,600 m. Levine et al. (1997) studied 20 subjects with an average age of 68 years, 9 of whom were known to be CHD patients. They were exposed to an altitude of 2,500 m for 5 days in a hypobaric chamber and tested at sea level. The cardiocirculatory variables after exposure to altitude were similar to those of healthy subjects. They observed several episodes of VES during the acute phase of adaptation, with no occurrence of arrhythmia. However, after 5 days these changes returned to pre-test level in these subjects. They suggested that older subjects with known CHD should avoid intense physical exertion during the acute phase of altitude exposure. CHD patients who exhibit a reduced physical performance at sea level can be exposed to the upper limits of their aerobic capacity when performing their daily lifestyle activities, especially at higher altitudes (at or above 4,000 m), although they can adapt quite well to moderate altitude (Fischer 1998). Erdmann et al. (1998) compared 23 healthy subjects to 23 CHD patients with reduced left-ventricular function (average ejection fraction of 39%) and without resting ischemia who underwent an ergometry test at 1,000 m and 2,500 m. There were no significant differences between the two groups; however, the maximal performance was reduced as a function of altitude. In a different study, Roach et al. (1995) studied 97 participants (average age 69 years; 21% with asymptomatic CHD) who rapidly ascended to an altitude of 2,500 m and exhibited an initial increase in RPP. Five days later, the RPP returned to pre-altitude level. No abnormal changes in ECG recordings were observed in patients with asymptomatic CHD. The authors concluded that in patients with asymptomatic CHD, a short stay at moderate altitude does not constitute an additional coronary risk. In contrast to Roach et al. (1995), Hultgren (1992) reported 21 coronary episodes, 17 occurrences of angina pectoris, 2 heart attacks, and 2 sudden deaths in patients staying at 2,800 m. Most of these patients had an increased SBP and HR.

In our 3-week study at moderate altitude in subjects with metabolic syndrome, we observed a reduction in pulse rate and BP as well as reduction in RPP (Figs. 1, 2, 3, and 4). Moreover, we demonstrate that the circadian rhythm of these variables was maintained after acclimatization to altitude. We contribute these changes mainly to the effect of altitude exposure rather than physical activity, which can be deduced from the data derived from cycle ergometry. Remarkably, the maximal performance test (W_{max}, $W_{max} \cdot kg^{-1}$) was nearly identical in all three tests, indicating that the degree of intensity of the guided hiking tours was too low to increase maximum physical capacity. Similarly, HR and BP during exercise were unchanged compared to the post-altitude tests with baseline ergometry. One may postulate that the reduction in resting SBP may have resulted from the reduction in body weight (Gunga et al. 2002, this issue). However, this is unlikely since there were further body weight reductions 6 weeks after altitude exposure, but blood pressure returned to pre-altitude values (Fig. 1). Aerobic exercise is known to reduce blood pressures in hypertensive individuals (Whelton et al. 2002), although there are no consistent findings concerning the type and duration of exercise necessary to effect significant changes. Reductions in BP after a bout of exercise have been described in hypertensive middle-aged and older people (''post-exercise hypotension'', PEH; for details see Thompson et al. 2001). PEH may persist for up to 16 h after exercise. Since BP was measured at least 24 h after the hiking tours, PEH as main contributor for our BP findings can be excluded.

Moderate altitude stimulated erythropoiesis in our vacationers similar to healthy subjects, as evidenced by a long-lasting increases in serum EPO and reticulocyte count. We did not measure any changes in iron status (serum-iron, serum-ferritin, transferrin), hemoglobin concentration, packed cell volume (PCV), red cell count, and vascular endothelial growth factor (for details see Gunga et al. 2002, this issue). An increase in hemoglobin concentration, PCV, and red cell count would adversely affect patients with metabolic syndrome since the accompanying changes in blood rheology could reduce cardiac performance.

Altitude exposure and metabolism

The most striking change of the measured metabolic variables was a significant decrease in insulin resistance accompanied by an increase in HDL-C after the 3 weeks at moderate altitude. Our study participants underwent a simulated holiday stay at moderate altitude without special intervention procedures such as strict dietary recommendations or physical fitness program. They performed moderate guided walking tours for several hours 4–5 times per week. Individual physical activity was controlled by pulse rate registration during hiking. Little is known about the effect of moderate hypoxia on insulin sensitivity. A loss of body weight has been described during high mountain expeditions, but it remains to be seen whether this weight loss is due to a loss of appetite at high altitude or a discrepancy between energy intake and energy expenditure following an increased metabolic rate (Kayser 1992). Leptin is known to be a key mediator in the neuroendocrine regulation of energy homoeostasis and appetite (Auwerx and Staels 1998). Recently it was shown that serum leptin increased in mountaineers after climbing to 4,559 m as well as in subjects who were passively transported to 4,559 m (Tschopp et al. 1998). Elevation in serum leptin correlated with loss of appetite. This is in contrast to our observation of unchanged plasma leptin concentrations despite weight loss after the 3-week sojourn at moderate altitude. Whether the degree of hypoxia or physical work is responsible for these differences remains unclear. On ascent to high altitude, fasting blood glucose is reported either to remain unchanged, including normal glucose tolerance curves (Consolazio et al. 1972), or to increase on ascent (Sawhney et al. 1991). Elevated blood glucose in sojourners to 3,500 m was paralleled by high insulin concentrations until day 7 at altitude, and subsequently returned to baseline values (Sawhney et al. 1991). Larsen et al. (1997) described a reduced rate of insulin-stimulated glucose uptake in the early phase of altitude acclimatization, which was partly restored within 1 week of hypoxic exposure. It was concluded that the activity of insulin decreases markedly during acute hypoxia, which was explained partly by changes in counter-regulatory hormones. Acclimatization to 4,300 m resulted in a depressed arterial glucose concentration and an increased resting glucose appearance (Brooks et al. 1991). Corresponding data for moderate altitudes are lacking. In our volunteers, fasting blood glucose remained unchanged during altitude acclimatization. However, after return to 500 m, an improvement in the oral glucose tolerance test was observed and the decrease of fasting insulin concentration was of borderline significance. The mechanism for this improvement in glucose homeostasis remains to be clarified. Whether our improvements in lipid and glucose metabolism are the consequences of the exercise program itself remains questionable. Endurance exercise acutely increases HDL-C and may improve insulin resistance (Thompson et al. 2001). These effects can be observed for at least 48 h after exercise. Thus, we cannot exclude the influence of the exercise bouts on changes in HDL-C and the HOMA index.

Some studies focused on a possible correlation between hypoxia and lipid metabolism: higher levels of serum HDL-C were reported in populations living at high altitude (Sharma 1990) and increases in HDL-C have been observed in a population migrating from lower altitudes to high mountain regions (Aitbaev et al. 1990). This effect of hypoxia on serum HDL-C was not only observed for high altitude but also for lower altitudes. At low altitudes up to 1,500 m, HDL-C levels were linearly and significantly dependent on the residing altitude, indicating that mild sustained hypoxia may induce an increase of HDL-C levels (Dominguez Coello et al. 2000). Ferezou et al. (1993) reported a decrease of triglyceride-rich lipoproteins accompanied by elevated HDL-C concentrations in healthy volunteers who were transported from low altitude to 4,350 m in the Alps. However, the mechanisms underlying these findings are at present unclear. It is possible that hypoxia-induced changes in key enzymes in fat utilization and oxidation are involved (Kennedy et al. 2001).

Limitations of this pilot project

We cannot discriminate between altitude-specific and recreational effects. One needs to consider that the repeated tests and measurements performed in this study could explain the improved metabolic profile in that the patient's compliance including reduction in snacks and alcohol was improved by the medical control procedures. Therefore, a prospective randomized study should be performed using the same or similar protocol at different locations (i.e., moderate altitude and low altitude).

In conclusion, we found that a 3-week exposure to moderate altitude had a short-term favorable effect on the cardiovascular system in patients with metabolic syndrome, and that cardiovascular risk was not increased. The favorable insulin-sensitivity-improving effects of a 3-week stay at moderate altitude are of great importance regarding the increasing number of patients with insulin resistance and their leisure-time activities at moderate altitudes.

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References

Aitbaev KA, Madaminov I, Meimanaliev TS, Shleifer EZ, Kim NM (1990) Study of the effect of migration to high-mountain regions on the blood lipoprotein system. Kosm Biol Aviakosm Med 24:45–46

Alexander JK (1994) Coronary heart disease at altitude. Tex Heart Inst J 21:261–266

Auwerks J, Staels B (1998) Leptin. Lancet 351:737–742

Bernardi L, Passino C, Spadacini G, Calciati A, Robergs R et al (1998) Cardiovascular autonomic modulation and activity of carotid baroreceptors at altitude. Clin Sci (Lond) 95:565–573

Björntorp P (1999). Neuroendocrine perturbations as a cause of insulin resistance. Diabetes Metab Res Rev 15:427–441

Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F et al (2000) Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity. Diabetes Care 1:57–63

Brooks GA, Butterfield GE, Wolfe RR, Groves BM, Mazzeo RS et al (1991) Increased dependence on blood glucose after acclimatization to 4300 m. J Appl Physiol 70:919–927

Consolazio CF, Jonston HL, Krzywicki HJ, Daws TA (1972) Metabolic aspects of acute altitude exposure (4,300 meters) in adequately nourished humans. Am J Clin Nutr 25: 23–29

DeFronzo RA, Ferrannini E (1991) Insulin resistance :a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 14:291–299

Dominguez Coello SD, Cabrera De Leon A, Bosa Ojeda F, Perez Mendez LI, Diaz Gonzalez L, Aguirre-Jaime AJ (2000) High density lipoprotein cholesterol increases with living altitude. Int J Epidem 29:65–70

Duplain M, Vollenweider L, Delebays A, Nicod P, Bartsch P, Scherrer U (1999) Augmented sympathetic activation during short term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. Circulation 13:1713–1718

Erdmann J, Sun KT, Masar P, Niederhauser H (1998) Effects of exposure to altitude on men with coronary artery disease and impaired left ventricular dysfunction. Am J Cardiol 81:266–270

Ferezou J, Richalet JP, Serougne C, Coste T, Wirquin E, Mathe D (1993) Reduction of postprandial lipemia after acute exposure to high altitude hypoxia. Int J Sports Med 14:78–85

Fischer R (1998) Trekking trotz Herzerkrankung. Fortschr Med 116:42–43

Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 18:499–502

Gunga H-Ch, Fries D, Humpeler E, Kirsch K, Boldt L-E, Koralewski E, Johannes B, Klingler A, Mittermayr M, Röcker L, Yaban B, Behn C, Jelkmann W, AMAS-Res Team, Schobersberger W (2002) Austrian Moderate Altitude Study (AMAS 2000) - fluid shifts, erythropoiesis, and angiogenesis in patients with metabolic syndrome at moderate altitude (≅1,700 m). Eur J Appl Physiol DOI 10.1007/s00421-002-0734-x

Halhuber MJ, Humpeler E, Inama R, Jungmann H (1985) Does altitude cause exhaustion of the heart and circulatory system? Med Sport Sci 19:192–202

Hultgren HN (1992) Effects of altitude upon cardiovascular diseases. J Wilderness Med 3:301–308

Inama K, Halhuber MJ (1975) Der Herz-Kreislaufkranke im Hochgebirgsklima. Untersuchungen im Kühtai (Tirol) und Obertauern (Salzburg) während kombinierter Klima-Terrainkuren in 1.800 bis 2.500 NN in den Jahren 1965 bis 1971. Deutsche Zentrale für Volksgesundheitspflege e.V., Schriftenreihe Heft 25, Frankfurt

Inama K, Humpeler E (1981) Alpine Höhenlagen als Therapiefaktor bei Herz-Kreislauf-Erkrankungen. In: Deetjen P, Humpeler E (eds) Medizinische Aspekte der Höhe. Thieme, New York, pp 91–103

Joint National Committee (1997) The sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 157:2413–2446

Kayser B (1992) Nutrition and high altitude exposure. Int J Sports Med 13:S129–S132

Kennedy SL, Stanley WC, Panchal AR, Mazzeo RS (2001) Alterations in enzymes involved in fat metabolism after acute and chronic altitude exposure. J Appl Physiol 90:17–22

Larsen JJ, Hansen JM, Olsen NV, Galbo H, Delta F (1997) The effect of altitude hypoxia on glucose homeostasis in men. J Physiol (Lond) 504:241–249

Levine BD, Zuckermann JH, Filipi CR (1997) Effect of high-altitude exposure in the elderly: The Tenth Mountain Division study. Circulation 96:1224–1232

Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RL (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419

Mazzeo RS, Child A, Butterfield GE, Mawson JT, Zamudion S, Moore LG (1998) Catecholamine response during 12 days of high-altitude exposure (4,300 m) in women. J Appl Physiol 84:1151–1155

Morgan BJ, Alexander JK, Nicoli SA, Brammel HI (1990) The patient with coronary heart disease at altitude: observations during acute exposure to 3100 meters. J Wilderness Med 1:147–153

Nikolowa P, Dikova M, Dimitrowa D (1989) Klimatotherapie von Kranken mit ischämischer Herzkrankheit in mittelhohen Gebirgen. Z Physiother 41:109–114

Palatini P, Businaro R, Berton G, Mormino P, Rossi G et al (1989) Effects of low altitude exposure on 24 h blood pressure and adrenergic activity. Am J Cardiol 64:1379–1382

Patsch W, Brown SA, Morrisett J, Gotto AM Jr, Patsch JR (1989) A dual precipitation method evaluated for measurement of cholesterol in high-density lipoprotein HDL2 and HDL3 in human plasma. Clin Chem 35:265–270

Pokan R, Eber B, Fruhwald FM, Brusse H, Grisold M, Klein W (1994) Körperliche Aktivität in mittleren Höhenlagen bei Gesunden und Patienten mit Koronarsklerose. Wien Med Wschr 7:121–124

Reaven GM (1996) Pathophysiology of insulin resistance in human disease. Physiol Rev 75:473–486

Roach RC, Houston CS, Honigman B, Nicholas RA, Yaron M et al (1995) How well do older persons tolerate moderate altitude. West J Med 162:32–36

Savonitto S, Cardellino G, Sardina M, Chebat E, Baldi G et al (1991) Effects of a cable car trip on blood pressure and cardiovascular hormones in lowlander and highlander normotensives. Cardiologica 36:385–390

Sawhney RC, Malhotra AS, Singh T (1991) Glucoregulatory hormones in man at high altitude. Eur J Appl Physiol 62:286–291

Sharma S (1990) Clinical, biochemical, electrocardiographic and noninvasive hemodynamic assessment of cardiovascular status in natives at high to extreme altitudes (3000–5500 m) of the Himalayan region. Indian Heart J 42:375–379

Smith ML, Muenter NK (2000) Effects of hypoxia on sympathetic neural control in humans. Respir Physiol 121:163–171

Steinacker JM, Liu Y, Bärtsch P (2000) Going to high altitude: patients with cardiovascular disease. Dtsch Z Sportmed 51:407–411

Thompson PD, Crouse SF, Goodpaster B, Kelley D, Moyna N, Pescatello L (2001) The acute versus the chronic response to exercise. Med Sci Sports Exerc Suppl 33:S438–S445

Tschopp M, Strasburger CJ, Hartman G, Biollaz J, Bartsch P (1998) Raised leptin concentrations at higher altitude associated with loss of appetite. Lancet 352:1119–1120

Veglio M, Maule S, Cametti G, Cogo A, Lussiana L et al. (1999) The effects of exposure to moderate altitude on cardiovascular autonomic function in normal subjects. Clin Autonom Res 9:123–127

Whelton SP, Chin A, Xin X, He J (2002) Effect of aerobic exercise on blood pressure :a meta-analysis of randomized, controlled trials. Ann Intern Med 136:493–503