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Effect of high altitude on human postprandial ^{13}C-octanoate metabolism, intermediary metabolites, gastrointestinal peptides, and visceral perception

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Abstract

Objective: At high altitude (HA), acute mountain sickness (AMS) is accompanied by neurologic and upper gastrointestinal symptoms (UGS). The primary aim of this study was to test the hypothesis that delayed gastric emptying (GE), assessed by ^{13}C-octanoate breath testing (OBT), causes UGS in AMS. The secondary aim was to assess post-gastric mechanisms of OBT, which could confound results under these conditions, by determination of intermediary metabolites, gastrointestinal peptides, and basal metabolic rate.

Methods: A prospective trial was performed in 25 healthy participants (15 male) at 4559 m (HA) and at 490 m (Zurich). GE was assessed by OBT (428 kcal solid meal) and UGS by visual analogue scales (VAS). Blood sampling of metabolites (glucose, free fatty acids (FFA), triglycerides (TG), beta-hydroxyl butyrate (BHB), L-lactate) and gastrointestinal peptides (insulin, amylin, PYY, etc.) was performed as well as blood gas analysis and spirometry. Statistical analysis: variance analyses, bivariate correlation, and multilinear regression analysis.

Results: After 24 h under hypoxic conditions at HA, participants developed AMS ($p < 0.001$). $^{13}CO_2$ exhalation kinetics increased ($p < 0.05$) resulting in reduced estimates of gastric half-emptying times ($p < 0.01$). However, median resting respiratory quotients and plasma profiles of TG indicated that augmented beta-oxidation was the main predictor of accelerated $^{13}CO_2$-generation under these conditions.

Conclusion: Quantification of ^{13}C-octanoate oxidation by a breath test is sensitive to variation in metabolic (liver) function under hypoxic conditions. ^{13}C-breath testing using short-chain fatty acids is not reliable for measurement of gastric function at HA and should be considered critically in other severe hypoxic conditions, like sepsis or chronic lung disease.

KEYWORDS
acute hypobaric hypoxia, beta-oxidation, gastric emptying, stable isotope breath tests

1 | INTRODUCTION

Acute mountain sickness (AMS) is a common syndrome of mountaineers, which develops after ascent to heights over 2500 m.[1] Upper gastrointestinal symptoms (UGS) like loss of appetite, nausea, and vomiting are common in this condition, as are neurologic symptoms like headache, malaise, and insomnia.[1-3] Meta-analysis of physiological studies shows that the degree of delayed GE is one factor associated with the severity of symptoms in patients with functional dyspepsia and chronic nausea and vomiting referred for investigation.[4] Therefore, it can be proposed that UGS in AMS could also be associated with delayed GE. This is supported by the inhibitory effects of hypobaric hypoxia on GE and intestinal motility observed in rats,[5-7] and also in humans in hypobaric chambers simulating hypoxic conditions at 2500 m.[8] However, to date, measurements of gastric function have not been obtained in subjects experiencing AMS in a real HA mountain setting. Scintigraphy, the gold standard for measurement of GE, is not feasible outside medical centers.[9,10] GE breath tests using ^{13}C-labeled marker molecules (^{13}C-acetate, ^{13}C-octanoate) for solid and liquid phases are an established alternative to scintigraphy that have been validated in a number of settings.[11,12] Advantages of this method include user-friendly technical equipment, no radiation exposure, and non-invasive sampling.[10-12] In addition, ^{13}C-octanoate breath test (OBT) can be combined with a high caloric solid test meal, which induces postprandial symptoms and a measurable post-gastric GI peptide hormone and metabolic response that simulates a more physiological and holistic model of the GE process[10,12,13]

As OBT has already been used for tests in hypobaric chambers and for other physiologic investigations under extraordinary conditions, like microgravity,,[8,12,14] we selected this technique to quantify GE at HA. The primary hypothesis of this study was that hypoxia at HA can delay GE and that this is a cause of UGS at HA. To test this hypothesis, the primary aim was to correlate measurements of GE obtained by OBT with AMS and UGS. The secondary aim was to identify possible post-gastric effects on ^{13}C-octanoate metabolism by correlating postprandial plasma levels of intermediary metabolites, postprandial GI peptide levels, and metabolic basal rate measurements with typical OBT parameters. This secondary aim was considered important because OBT does not measure GE directly but relies on the assumption that GE is the rate-limiting step that determines recovery of the ^{13}C-marker in the breath.[10,12,15] This process involves multiple steps and may be influenced by variation in demographic, physiological, and metabolic parameters.[10,12,15,16] For example, in the context of this study, hypoxia at HA influences blood gas hemostasis and hepatic lipid metabolism.[17,18] These effects have rarely been studied under these conditions in humans[17] but in rats, acute hypobaric exposure can enhance fatty acid oxidation in the liver.[19-22] If changes in fatty acid metabolism related to hypoxia occur in HA, then this disturbance of post-gastric metabolism could confound the results of OBT.

2 | MATERIALS AND METHODS

2.1 | Study design

This prospective non-randomized trial was part of a series of studies assessing different aspects of AMS and HA physiology. This investigation focused on GE and UGS at HA. Other parts of the study have been reported separately.[2,23-27] Participants underwent blood sampling of postprandial metabolites, blood gas analysis, and OBT after a defined test meal at 490 m (ZH) and on 2 test days at the Capanna Regina Margherita (MG) high-altitude laboratory (d2/MG2 and d4/MG4) in the Alps (4559 m). The study conformed to the declaration of Helsinki and was approved by the Ethics Committee of the Canton of Zurich (EK-1677). All subjects gave written informed consent before inclusion in the study.

2.2 | Sample size calculation

We calculated a sample size of 24 and thus decided that a sample of 25 healthy volunteers would be high enough to detect a difference for our endpoint (detection of a significant effect of hypoxia on OBT). For further information, see supplemental file.

2.3 | Subjects and exposure

The study population included 25 healthy volunteers (15 males; 10 females) with susceptibility to high-altitude pulmonary edema (HAPE), described in detail elsewhere[26] and in supplemental Table 1. To avoid acclimatization, participants were only allowed to stay three nights above 2500 m within a month before the rapid ascent (exclusion criteria no 1). Subjects had to be healthy without chronic diseases or regular medication (exclusion criteria no 2). Special diets were not allowed. Initial experiments were performed at ZH (490 m, $P(O_2)$ 140–150 mmHg) to generate baseline values. Exposure to hypoxia took place in groups of 4–5 participants, each using a fixed schedule. The participants were transported by cable car from Alagna Valsesia (Italy, 1205 m) to 3000 m, then ascended to the Gnifetti hut at 3600 m ($P(O_2)$ 94–103 mmHg) in the Monte Rosa region and stayed for one night. On day one, they arrived at the Capanna Regina Margherita in the morning (MG1, 4559 m, $P(O_2)$ 81–91 mmHg), where all HA experiments were performed.[2,23-27]

2.4 | AMS assessments, safety issues, and AMS medication

Manifestation of AMS was assessed using the Lake Louise Score (LLS>4) as well as through medical examination by experienced physicians.[28] For safety reasons, subjects with either significant HAPE susceptibility, or LLS greater than 5 in the morning or evening of MG2, or necessity as identified by participating physicians, were

TABLE 1 Cardiorespiratory parameters, AMS scores, upper gastrointestinal symptoms by AUCs of visual analogue scales, calorie intake, and ^{13}C-octanoate breath test results. Data are given as median and 25th/75th percentile (not normally distributed) or as mean and standard deviation (normally distributed).

		Zurich baseline 446 m			Capanna Margherita day 2 1st examination day, 4559 m			Capanna Margherita day 4 2nd examination day, 4559 m		
parameter	unit	n	median/ mean	25th–75th percentile/ SD	n	median/ mean	25th- 75th percentile/SD	n	median/ mean	25th–75th percentile/SD
Cardiorespiratory parameters and AMS scores										
LLS	-	25	1.00	1.00–2.00	25	5.00***	3.00–7.00	25	3.00 $^{*/+}$	1.50–4.00
P(CO_2)	kPa	25	5.1	0.4	24	3.8***	0.3	24	3,3***/$^{+++}$	0.3
SaO_2	%	25	95.8	95.0–96.2	24	76.8***	74.4–79.0	24	82.1***	76–85
P(O_2)	kPa	25	12.3	11.1–13.5	24	5.2***	5.1–5.6	24	5.8***	5.5–6.5
pH	-		7.424	7.408– 7.440		7.470***	7.460– 7.490		7.485***	7.470– 7.500
HR	1/min	21	71.0	62.0–81.5	20	81.5**	77.0–92.3	24	74.5	68.8–90.8
BF	1/min	22	16.5	14.0–18.3	20	19.0	17.0–21.8	24	20.0*	14.0–24.0
RQ	-	22	0.83	0.81–0.89	20	0.72***	0.68–0.76	24	0.73***	0.68–0.76
Upper gastrointestinal symptoms										
Fullness	mm*min	25	420	61.88–1459	21	1358	0–4806	25	315	0–1949
Bloating	mm*min	25	62.50	0–438.8	21	237.5	0–3893	23	188.8	0–1858
Nausea	mm*min	25	0	0–123.8	21	23.75	0–1815	25	0	0–168.8
Hunger	mm*min	25	8001	5132–16669	21	6104	710.6–16516	25	11391	2611–16901
Calories	kcal	22	861	422.8	20	582.7*	275.9	21	825.1	274.3
^{13}C-Octanoate breath test										
AUC $DOB_{0\text{-}240min}$	o/oo*min	25	2684	551	21	3011	574	25	3117*	386
GEC	-	25	3.610	3.315– 3.945	21	4.046*	3.812– 4.236	25	4.094**	3.820– 4.258
t_{50}	min	25	123.0	114.0–167.5	21	127.2	101.3–149.6	25	107.7**	96.61–121.0

Significant differences versus ZH are indicated by * and versus MG2 by $^{+}$ (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, $^{+}$: $p < 0.05$, $^{++}$: $p < 0.01$, $^{+++}$: $p < 0.001$). LLS, Lake Louise score; P(CO_2), partial pressure of CO_2; P(O_2), partial pressure of O_2; SaO_2, arterial saturation of O_2; HR, heart rate; BF, breath frequency; RQ, respiratory quotient; DOB, delta over baseline; GEC, gastric emptying coefficient; T_{50}, gastric half-emptying time

treated with dexamethasone (total number of interventions was 14 (56%)). For further information, see our supplemental file.

2.5 | Assessing UGS and food intake

UGS (feeling of fullness, nausea, and abdominal bloating) were determined by visual analogue scale (VAS) measurements (similar to[29-31]) in the morning after overnight fasting (t_{-60}), immediately before consumption of two muffins (t_0), 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes thereafter (t_{15} – t_{240}). Total food intake in kcal was measured in the evening. Subjects were offered a dinner consisting of pasta, bolognese sauce, and parmesan cheese as well as biscuits *ad libitum*. Individuals were free to choose the relative amounts of different food components.

2.6 | ^{13}C-sodium octanoate breath test

OBT was performed at 01:00 p.m.. Octanoic acid is an unsaturated fatty acid, which is present in the normal diet. The substance was provided by Euriso-Top (Parc des Algorithms, Bâtiment Homère Route de l'Orme F-91194 Saint-Aubin Cedex). It was produced with a quality assurance program that guarantees the production of *in vivo* products according to Good manufacturing practices (GMP). All volunteers received a solid test meal (muffin, 12.5 g protein, 18.1 g fat, 52.9 g carbohydrates, 428,4 kcal) containing 125 mg sodium ^{13}C-octanoate, as described previously.[13,14] Breath samples were collected in evacuated 50 ml aluminized breath bags before and after 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 min. The measurement of the ratio of $^{13}CO_2/^{12}CO_2$ in the breath samples was done by non-dispersive isotope selective infrared spectroscopy (NDIRS, IRIS® Lab, Wagner Analysen Technik GmbH, Bremen, Germany), which was validated in comparison with the reference method isotope mass spectrometry (IRMS). The results are expressed as d_s in parts per million (ppm) and delta over baseline (dob=d_s-d_0). Definition of the d-value: ds = (RS/RPDB −1) x 1000 with RS =^{13}C/^{12}C isotope ratio in CO_2 in-breath and R_{PDB} = 0.0112372 = isotope ratio in reference (PDB =Pee Dee Belemnite, South Carolina; d_0 = isotope ratio at baseline). To measure the proportion of the administered substrate that is metabolized and exhaled, the results are expressed as maximal percentage dose of ^{13}C recovered (PDR_{max}

[%/h]) and as cumulative PDR (cPDR [%]), that is, the PDR over time for defined time intervals (15–240 min). The base of the calculations is the formulas of Ravussin et al. and Ghoos et al..[32,33] The emptying process described by the half-emptying time (t_{50}) is modeled using the GE analytical procedure described by Ghoos et al..[33]

2.7 | Spirometry

Data collection was performed at 12:00 p.m. When mountaineers were lying and after resting for one hour. Complete breath collection was achieved by wearing a face mask that covered the mouth and nose. O_2 and CO_2 concentrations were continuously measured by amperometric solid-state electrolyte sensors and results were provided and saved as breath-by-breath values. Before each test, calibration of the used system (ZAN 600 USB, nSpire Health, Louisville, KY, USA) was performed immediately. Heart rate (HR) was measured via ECG analysis (CardioCollect 12, Spacelabs Healthcare, Feucht, Germany).

2.8 | Venous blood sampling and arterial blood gas analysis

Blood gas analysis was performed from blood sampling taken from the radial artery using an ABL 5 blood gas analyzer (Radiometer, Copenhagen). Blood samples were taken at ZH, MG2, and MG4. For repeated postprandial venereal blood sampling, a venous catheter was placed. Blood sampling was then performed in the morning before an ad libitum breakfast at 7 a.m. (fasting GI peptides and metabolites), just before, and 30, 60, 90, 120, 180, 240 min after a test meal of two muffins at 01:00 pm. EDTA-plasma samples were kept frozen in liquid nitrogen or stored at −80°C for further analysis.

2.9 | Plasma L-lactate, glucose, FFA, TG, and ketone plasma levels

Plasma glucose, free fatty acids (FAA), triacylglycerols (TG), L-lactate, and beta-hydroxyl butyrate (BHB) (ketone body) levels were assessed via Cobas Mira Analyzer at the Institut für Tierernährung, University of Zurich.

2.10 | Gastrointestinal peptides and metabolic parameters

Amylin (active) and glucagon were measured using kits from Millipore Corporation (Milliplex MAP Human Endocrine Assay, Millipore, Billerica, MA, USA), CCK-8 (active), and PYY were measured using radioimmunoassay (RIA) Kits (Eurodiagnostica, Burgdorf, Switzerland) by Prof. Christoph Beglinger, University Hospital Basel, and the analysis of gastrin was performed by using immunoassays (Human Gastrin I (1–17), Enzo Life Sciences, Lausen, Switzerland). Insulin was measured by an ultra-sensitive Human Insulin RIA Kit (Millipore).

2.10.1 | Variables

Results of GI peptides and metabolites were expressed as fasting plasma levels and plasma levels over time, and the area under the curve (AUC) was calculated for the whole postprandial period (AUC 0–240 min). The AUC was also calculated for continually assessed VAS of UGS (feeling of fullness, nausea, and abdominal bloating). The glucose-insulin ratio was computed as glucose in mmol/l divided through the insulin concentration in nmol/l, HOMA score (provided by the formula of Matthews et al.[34]) was adopted from the publication of Spliethoff et al..[27]

2.10.2 | Previously published data

Parts of this work, including some GI peptide levels, blood gas measurements, some metabolite plasma levels, AMS assessment, and UGS have already been published but were re-analyzed due to their importance in this study context (see also[2,23-27]).

2.10.3 | Statistical analysis

Statistical analysis is described in supplemental data.

3 | RESULTS

3.1 | Development of acute mountain sickness

On MG2, 52% of subjects (13/25) developed clinically relevant AMS with a LLS>4. The median LLS was 5 ($p < 0.001$) and thereby over the threshold for diagnosis of AMS indicating significant development of AMS compared to ZH (Table 1, Figure S1). On MG4, eight participants had recovered while five had still LLS>4, with the median LLS score remaining at an elevated level compared to ZH (Table 1, Figure S1). Thus, AMS onset occurred by MG2 in the majority of participants and began to resolve by adaption to HA from MG2 to MG4.

3.2 | Development of upper gastrointestinal symptoms

The median perception of fullness, abdominal bloating, nausea, and hunger after ingestion of the test meal showed no significant

differences between ZH and MG2 (Table 1, Figure S2). However, despite physical activity, the mean food intake decreased after short exposure to HA (Table 1). Bloating, nausea, and fullness showed a high inter-correlation: fullness vs. nausea ($r = 0.8$, $p < 0.01$), vs bloating ($r = 0.748$, $p < 0.01$), nausea vs. bloating ($r = 0.811$, $p < 0.01$). Food intake and hunger had also a high inter-correlation ($r = 0.5$, $p < 0.01$).

3.3 | Cardiorespiratory adaption on HA

Due to acute hypobaric hypoxia exposure, median O_2 blood partial pressure declined during the first two days as well as the median oxygen saturation and showed a compensatory but not statistically significant improvement on day 4 (Table 1, Figure S3). Participants' median heart rates increased transiently on day 2 while on day 4, no significant difference between lowland level and HA could be detected (Table 1, Figure 1). Median breath rate also presented a constant increase from ZH to MG4 with a significant difference on MG4 compared to lowland levels (Table 1, Figure 1). This hyperventilation reduced mean CO_2 blood partial pressure, which consecutively elevated median blood pH (Table 1, Figure S3). The mean resting respiratory quotient (RQ) dropped during the stay at HA despite this hyperventilation (Table 1, Figure 1). These findings demonstrate cardiorespiratory stimulation following hypobaric hypoxia resulting in activation of circulation and ventilation with consecutive alteration of the blood gas levels. Decline of the resting RQ might indicate a crucial switch in intermediary metabolism.

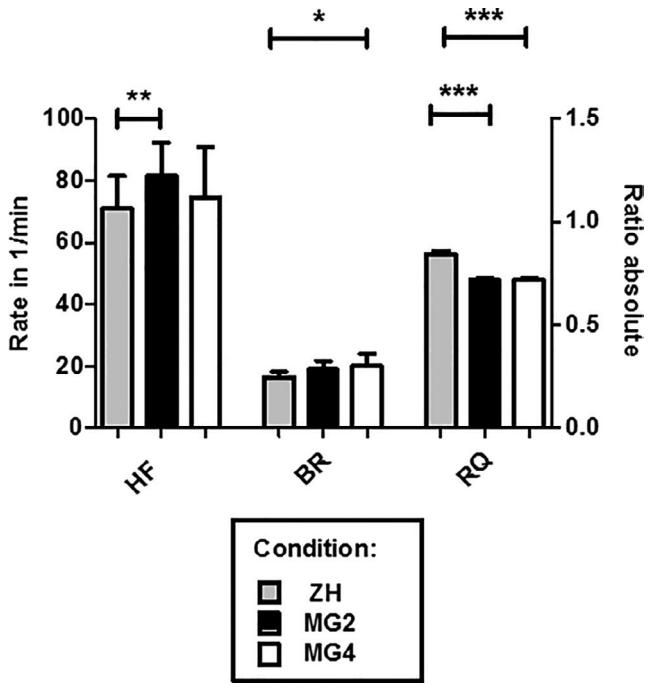

FIGURE 1 Heart rate and breath rate are accelerated at high altitude; respiratory quotients are decreased. High altitude-induced stimulation of sympathetic nervous system leading to increase of mean heart rate and breath frequency. Despite hyperventilation, resting RQ decreased high significantly during the stay on MG, which indicates a metabolic shift toward fat/ fatty acid oxidation (ZH: Zurich baseline 446 m; MG2/4: Capanna Margherita day 2/4 4559 m). HR, heart rate; BF, breath frequency; RQ, respiratory quotient; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

3.4 | ^{13}C-octanoate short-chain fatty acid metabolism

The mean $^{13}CO_2$ exhalation after ingestion of the test meal, expressed as delta over baseline (DOB), was lower at ZH compared to MG and increased progressively during the stay at HA. In the analysis of the $^{13}CO_2$ excretion curve as a GE process, the calculated median half-emptying time (T_{50}) and the GEC were consecutively lower or higher, respectively (Table 1, Figure 2).

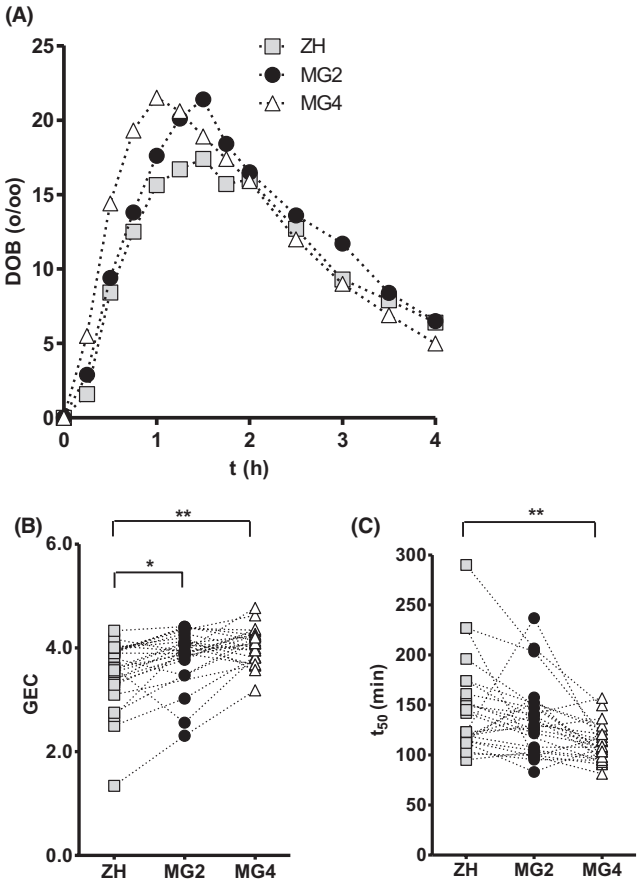

FIGURE 2 ^{13}C-octanoate breath test shows accelerated $^{13}CO_2$ clearance at high altitude $^{13}CO_2$ exhalation (parameterized as mean DOB values (a)) increased computed GEC (b) and decreased gastric half-emptying time (c) after ingestion of a solid ^{13}C-octanoate containing meal under hypoxic conditions (ZH: Zurich baseline 446 m; MG2/4: Capanna Margherita day 2/4, 4559 m). DOB, delta over baseline; GEC, gastric emptying coefficient; T_{50}; half-emptying time of breath test; *: $p < 0.05$; **: $p < 0.01$.

TABLE 2 Pre- and postprandial changes of metabolites. Data are given as median and $25^{th}/75^{th}$ percentile (not normally distributed) or as mean and standard deviation (normally distributed).

		Zurich baseline 446 m			Capanna Margherita day 2 1^{st} examination day, 4559 m			Capanna Margherita day 4 2^{nd} examination day, 4559 m		
parameter	unit	n	median/ mean	25^{th}–75^{th} percentile/ SD	n	median/ mean	25^{th}- 75^{th} percentile/SD	n	median/ mean	25^{th}–75^{th} percentile/SD
Fasting metabolites										
L-lactate	mmol/l	21	0.9010	0.2327	21	1.046	0.2119	20	1.286**	0.5312
Glucose	mmol/l	21	5.240	5.130–5.790	21	5.680	5.175–6.085	20	6.045**	5.158–7.368
FFA	mmol/l	21	0.4640	0.3945–0.8925	21	0.6950	0.5545–0.9695	20	0.6600	0.4930–0.9410
TG	mmol/l	21	0.8300	0.6550–1.035	21	0.6800*	0.5350–0.7900	20	0.5600*	0.4925–0.7325
BHB	mmol/l	21	0.0570	0.0445–0.1740	21	0.2570**	0.0595–0.6400	20	0.1065	0.07525–0.1638
Postprandial metabolites (0-240min)										
L-lactate	mmol/l* min	21	217.6	32.74	21	301.6**	52.39	21	373.2***/+	133.1
Glucose	mmol/l* min	21	1404	1318–1532	21	1428	1330–1576	21	1589*	1371–1706
FFA	mmol/l* min	21	92.96	84.16–108.0	21	143.9**	113.0–174.0	21	126.2**	107.5–180.7
TG	mmol/l* min	21	214.2	59.85	21	197.6	48.42	21	193.6	49.42
BHB	mmol/l* min	21	26.54	18.89–36.01	21	44.22	24.27–74.60	21	38.79	18.77–48.93

Significant differences versus ZH are indicated by * and versus MG2 by + (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, +: $p < 0.05$, ++: $p < 0.01$, +++: $p < 0.001$). FFA, free fatty acids; TG, triacylglycerides; BHB, beta-hydroxyl butyrate.

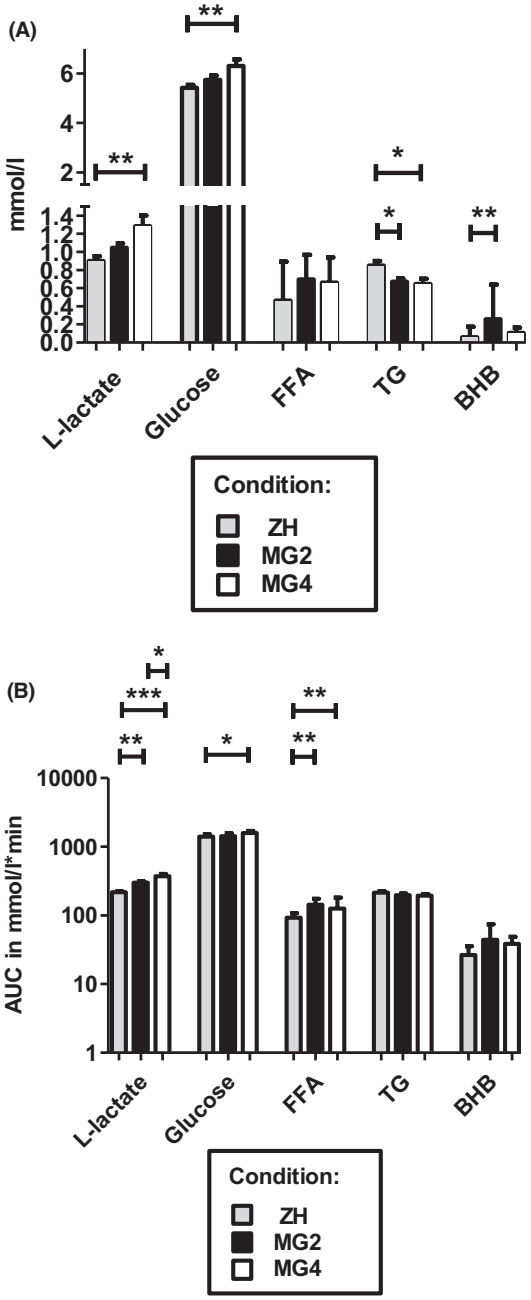

FIGURE 3 High-altitude exposure affects intermediary metabolism Acute hypobaric hypoxia affects fasting (a) as well as postprandial (b) metabolism: Mean L-lactate and glucose are increased in order to provide metabolites for exercise. To spare glucose, energy production uses TG, which lowers plasma TG levels and increases FFA levels. Increased liver beta-oxidation of free fatty acid increases plasma ketone body levels (BHB) (ZH: Zurich baseline 446 m; MG2/4: Capanna Margherita day 2/4 4559 m). FFA, free fatty acids; TG, triacylglycerols; BHB, beta-hydroxyl butyrate; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

3.5 | Changes of intermediary metabolism at HA

Exposure to HA had a major impact on fasting as well as on postprandial intermediary metabolism: Mean fasting blood L-lactate levels progressively inclined during the stay at 4559 m as well as mean fasting blood glucose levels. The mean of fasting TG dropped due to hypobaric hypoxia exposure and remained lower during the stay at HA. Median of fasting ketone bodies (BHB) levels inclined transiently during the first two days of HA exposure before falling back to a not significantly elevated level compared to ZH (Table 2, Figure 3(A)).

Changes in the intermediary metabolites were also evident after ingestion of the test meal at HA: Mean postprandial serum L-lactate levels were augmented 2 and 3 h after ingestion at MG2 and at each point of time at MG4. The mean postprandial FFA levels at 4 h after ingestion of the test meal were higher at 4559 m compared to lowland level (Figure S4(A)). The total amount of the postprandial determined L-lactate and FFA-plasma levels (AUC 0-240 min) increased at MG2 and remained higher or further increased (L-lactate), respectively, at MG4, while glucose plasma levels only inclined at MG4 (Table 2, Figure 3B). These results demonstrate that the metabolism at HA is changed toward catabolic processes: Provision of small energy-carrying molecules (L-lactate, glucose, FFA, and BHB) and reduction of energy-storing metabolites (TG).

3.6 | Serum levels of GI peptides show no alteration at HA

Postprandial glucagon levels were significantly lower 5 h after eating the test meal at MG2 and, conversely, higher at almost every point of time at MG4 compared to ZH (at 30 min, 60 min, 120 min, and 180 min) (Figure S4(B)). Postprandial median insulin levels on MG2 were lower than ZH and MG4 at 30 Min after the meal (Figure S4(B)). No differences could be identified between insulin levels of ZH and MG4 (Figure S4(B)). Postprandial CCK-, gastrin-, PYY-, and amylin levels did not differ between ZH and MG2, and MG4, respectively. Fasting as well as total postprandial distribution levels of GI peptides (AUC 0-240 min) showed no significant changes between HA and ZH (Table S2, Figure S5).

3.7 | Predictive analysis of ^{13}C-octanoate metabolism at HA

Multiple linear regression analysis was applied to the data set to generate a surrogate model for the prediction of the observed increase of $^{13}CO_2$ exhalation (parameterized as dependent variable by DOB AUC 0-240 min) from changes of postprandial metabolite levels (FFA-, TG-, glucose-, L-lactate-, and BHB levels), of the postprandial feeling of fullness, of the postprandial GI peptide levels (amylin-, gastrin-, CCK-, insulin-, PYY-, and glucagon levels), of cardiorespiratory parameters (SaO_2, $P(CO_2)$, HR, and BR), of food intake, hunger, and of body height (Table 3). Covariates were included based on *a priori* knowledge of physiological and biochemical considerations. Other rational variables like RQ or glucose/insulin ratios were not included due to multicollinearity. The applied model has a high significance ($p = 0.0001$) that can explain 68% of the variance (adjusted

variables	unstandardized	standard error	standardized	partial correlation r
Intercept***	11647.548***	2057.844		
Food intake	.245	.243	.171	.211
Hunger AUC 0-240 min*	−.020*	.009	−.290*	−.420
Fullness AUC 0-240 min	−.039	.034	−.152	−.238
SaO2*	−16.847*	7.337	−.386*	−.440
PCO2	−25.652	115.554	−.040	−.047
Breath rate	−1.073	12.127	−.010	−.019
Heart rate	−3.903	5.504	−.100	−.149
Height***	−36.828***	7.378	−.649***	−.729
L-lactate AUC 0-240 min	−.281	.860	−.051	−.069
Glucose AUC 0-240 min	.454	.437	.168	.216
FFA AUC 0-240 min	−.520	.828	−.075	−.133
TG AUC 0-240 min***	−5.117***	1.159	−.530***	−.685
BHB AUC 0-240 min	−.003	.003	−.143	−.196
Glucagon AUC 0-240 min	−.018	.010	−.247	−.359
Insulin AUC 0-240 min	−.014	.016	−.127	−.180
Gastrin AUC 0-240 min	.006	.020	.035	.065
CCK AUC 0-240 min	.003	.043	.010	.016
PYY AUC 0-240 min	.009	.017	.081	.108
Amylin AUC 0-240 min	.010	.006	.261	.344

Overall model $p < 0.001$, R^2: 0.826, adjusted R^2: 0.68, F(d, f = 19,41) 5.514*** *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 3 Multilinear regression analysis of predictors for observed increased $^{13}CO_2$ clearance (DOB AUC 0-240 min) after ingestion of a ^{13}C-octanoate labeled solid meal. Height, hypoxemia, hunger, and TG levels were best predictors. The negative correlations of TG levels and hypoxia with enhanced ^{13}C-octanoate metabolism suggest hypoxia-induced hepatic beta-oxidation and not changes in GE explain the observation that $^{13}CO_2$ clearance is increased under hypoxic conditions at HA.

$R^2 = 0.68$). The independent variables SaO_2 (regression coefficient b = −16.85, $p = 0.03$), postprandial TG levels (regression coefficient b = −5.12, $p = 0.00$), hunger (regression coefficient b = −0.02, $p = 0.04$), and body height (regression coefficient b = −36.83, $p = 0.00$) predicted significant changes in $^{13}CO_2$ exhalation. All other independent variables, especially the postprandial GI peptide levels, had no significant influence in this model. By comparison of standardized regression coefficients and partial correlation coefficients r, metabolic variables (TG levels) and height have more impact on $^{13}CO_2$ clearance (DOB) than hunger or hypoxemia (SaO_2) (Table 3). In a subsequent, stepwise, multilinear regression analysis with the same variables, only body height, postprandial TG levels, and SaO_2 were integrated in the model. Body height had the biggest portion in the change of R^2 in this analysis (54%), followed by the postprandial TG levels (36%), and finally SaO_2 (10%).

4 | DISCUSSION

Stable isotope breath tests are non-invasive diagnostic tests that can be widely applied for the assessment of gastrointestinal symptoms and diseases.[12] In clinical practice, the ^{13}C-Octanoate Breath Tests (OBT) is an established alternative to scintigraphy for measurement of solid GE; however, the interpretation of OBT findings assumes stable post-gastric absorption, metabolism, and excretion.[10-12,15,16] This study in a real HA setting offers unique insights into these post-gastric aspects of the OBT in human subjects. Specifically, we provide evidence that this technique, using a labeled short-chain fatty acid, is sensitive to variation in metabolic (liver) function under hypoxic conditions. For this reason, the results of OBT could not be used to address the primary hypothesis of this study, specifically that changes to GE at HA are a cause of typical dyspeptic symptoms in acute mountain sickness (AMS). Instead, the results provide insight into important metabolic changes to hepatic lipid metabolism during HA adaption.

On day 2 at HA (4559 m), approximately half (52%) of the participants developed a LLS >4 (MG2: median LLS=5) signifying clinically relevant AMS.[28] This prevalence is higher than those reported from previous studies at MG[28]; likely due to the rapid ascent with no pre-acclimatization in a study group enriched with AMS-susceptible individuals.[17] During the following two days, the median LLS decreased; however, symptoms persisted at an elevated level compared to ZH (MG4: median LLS=3). This improvement followed response to treatment (14 participants received dexamethasone for AMS symptoms) and /or acclimatization with recovery from AMS.[35] The assessment of UGS at HA showed no significant increase compared to baseline; however, it was noted that, despite intense physical activity, the mean food intake decreased (Table 1).

The primary hypothesis of this study was that delayed GE contributes to UGS in AMS. In this context, the finding of accelerated $^{13}CO_2$ clearance expressed as increased GEC and shortened GE half time (t_{50}) was unexpected. GE under hypoxic conditions at HA has

not been examined in humans; however, given that GE is delayed in animals and also in humans studied in a hypobaric chamber, the finding of accelerated GE in this study was questioned.[4-8] Possible confounders of OBT include disorders of the small intestine that impair marker absorption, liver failure and respiratory failure that impacts on marker metabolism and excretion, and also hyperdynamic circulation.[10] Detailed analysis of the comprehensive physiological data shows that metabolic and hemodynamic changes seen at HA confound the key assumption of OBT that GE is the only variable that determines clearance of the ^{13}C-marker from the body after ingestion of a meal enriched with ^{13}C-octanoate.[17]

The mechanism by which hypoxia affects short-chain fatty acid metabolism was further investigated because, if confirmed, this would imply not only that this method was not suitable for this study, but also that the results of OBT should be considered critically in clinical patients with hypoxia. The metabolite that is mainly combusted for energy production can be identified by using the respiratory quotient (RQ) at rest.[18] RQ was estimated during resting spirometry 1 h before starting the OBT: Strikingly, the median RQs decreased during the stay at HA to a very low level (0.72) which indicates a metabolic shift toward fat combustion.[18] Based on these findings, we proposed that the main cause of the observed accelerated $^{13}CO_2$ clearance might be increased beta-oxidation in the liver. To confirm this possibility, we examined the fasting levels and the postprandial levels of the major metabolites for hypoxia-induced changes of metabolism: We discovered in fasting blood samples that L-lactate and glucose progressively increased while TG levels continually dropped during the stay at HA. Fasting BHB levels were transiently increased on day 2 and were declining again on day 4. Postprandial metabolism presented a similar pattern: Glucose, FFA, and L-lactate were increased in the postprandial period, while BHB and TG showed the same trend as in fasting samples (without reaching significance). These findings suggest that increased $^{13}CO_2$ clearance in this study reflects a switch of metabolism toward lipolysis/beta-oxidation and energy storage mobilization. This metabolic adaption to HA with increased lipolysis has been well studied in animal models.[19-22] Similar patterns of lipid metabolism have also been documented in humans taking part in a trial at Mount Everest base camp at an altitude of 5,364 meters.[36] These observations indicate that the metabolic consequence of acute hypobaric hypoxia is activation of the sympathetic nervous system with consecutive lipolysis and inhibition of lipogenesis.[36-39] The global insulin resistance described at HA might also affect lipid metabolism toward increased lipolysis.[17] Reduced insulin-sensitivity as well as enhanced gluconeogenesis from increased L-lactate levels and glycerol from lipolysis would explain the increase of resting glucose levels[17]; however, HOMA and glucose-insulin ratios did not provide significant results. Nevertheless, insulin resistance is well described for HA exposure, so that a relevant influence in carbohydrate and lipid metabolism is likely, even if we could not prove it here.[17] Taken together, the changes in metabolism and RQ indicate that anaerobic energy production increases, glucose is saved for energy production during exercise, and that fatty acids are used as the major energy source at rest. These findings are consistent with our "secondary hypothesis" that accelerated beta-oxidation and not accelerated GE might be the key cause of elevated $^{13}CO_2$ clearance observed in this study.

Other explanations for the above-described findings can be postulated but seem unlikely: Impaired absorption of lipids can delay absorption of ^{13}C-labeled fatty acids in intestinal disorders; however, the observations above require *accelerated* absorption of nutrition at HA and this is not consistent with reports in animals and humans, discussed above.[17] Moreover, there is no evidence of an increased postprandial blood flow of the mucosa or the intestine at altitude; mucosal blood flow is decreased in hypoxic conditions, which contributes to the high frequency of mucosal erosions documented in endoscopy at HA.[17,24] In the larger vessels like the hepatic portal vein, the postprandial blood flow is not altered by HA exposure.[17] Hyperventilation and hyperdynamic circulation could also have an impact on OBT results.[10] Pulmonary and circulatory functions were estimated by using BGA and spirometry performed one hour before the test. If there had been increased CO_2 excretion by hyperventilation on day 2, then the RQ would increase to values >1.[18] This was not the case and so that we concluded that hyperventilation did not cause the accelerated $^{13}CO_2$ clearance.[18] Hypobaric hypoxia usually increases cardiac output.[17] An accelerated circulation situation leads also to a higher blood gas turnover, which might accelerate $^{13}CO_2$ clearance. Cardiac output is computed as the product of stroke volume and HR.[18] We did not perform any direct measurement of stroke volume and HR during the OBT. Thus, we only could use the HR from the spirometry one hour before OBT. The median HR was higher at MG2 than at ZH indicating increased cardiac output. Strikingly, at MG4 when the calculated GEC was higher than at ZH and MG2, the median HR was no longer significantly above baseline levels. Therefore, it can be inferred that increased circulation at HA has, if any, only a minor impact on $^{13}CO_2$ clearance. Neurohormonal feedback regulation mediated, in part, by GI peptides modulates GE and the delivery of nutrients to the small bowel.[40,41] Previous studies showed an impact of acute hypoxia at HA on postprandial and fasting GI peptide levels.[42-46] To study the changes of these variables at HA in correlation with GE, fasting levels, and postprandial levels of glucagon, insulin, gastrin, CCK, amylin, and PYY were measured. No significant changes in fasting levels as well as in the integrals/ AUC 0-240 min postprandial were observed. This finding is what one would expect if GE was *not* significantly affected by the study procedures and we concluded that changes of GI peptides do not explain the accelerated $^{13}CO_2$ clearance in OBT.

By using multilinear regression model, we used all the data available to create a model that predicts changes of $^{13}CO_2$ clearance in OBT (expressed as DOB AUC 0-240 min) at HA. Postprandial TG levels, SaO_2, height, and hunger were identified as significant independent variables. The applied model (Table 3) has a high significance ($p = 0.0001$) and explains much of the variance in $^{13}CO_2$ clearance (adjusted $R^2 = 0.68$). Ranking the variables by comparison of the standardized coefficients, body height, and TG levels had the greatest impact on DOB AUC 0-240 min. All parameters were negatively correlated with DOB. The negative correlation between DOB and

body height was expected and explained by the higher ratio of the offered ^{13}C-octanoate substrate (all participants received the same test meal) and the lower distribution volume and lower absolute baseline CO_2 production rate in smaller humans.[18] The connection with the grade of hypoxemia was obvious. The very high negative correlation with the postprandial TG levels appears to confirm that elevated beta-oxidation in the liver is a major cause for increased $^{13}CO_2$ clearance. The negative correlation between plasma TG levels and the grade of beta-oxidation is well described in literature.[47-51] Moreover, a connection between reduced hunger and increased beta-oxidation has also been reported.[52-54] Taken together, augmentation of beta-oxidation by hypoxemia stimulated increase of catecholamines and cortisol is the best explanation for the elevated $^{13}CO_2$ clearance in the OBT observed in this study. Indeed, under these extreme conditions, the OBT could be considered as a quantitative metabolic test of hepatic beta-oxidation and not a GE test. These findings are not consistent with those from studies in hypobaric chambers which simulated conditions at 2500 m[8] and might be explained by more hypoxic conditions at a higher altitude, more prolonged exposure to hypoxia and by further stressors for the sympathetic nervous system with intense physical activity and cold triggering higher release of catecholamines.

5 | LIMITATIONS

This study was primarily designed to examine GE with ^{13}C-octanoate GE breath test (OBT) at a real HA setting in AMS and not to validate the physiological principles of the test itself. However, after initial indications that OBT may not be suitable in our setting, we identified factors which confounded this test. It is for this reason that we did not perform spirometry or ECG analysis at the same time as OBT and have to speculate that physiological parameters like HR, RQ, or BF did not have changed between their assessment during the trial and OBT.

6 | CONCLUSION

This study offers unique insights into the limits of the OBT and the complex changes of human metabolism at HA. The major conclusion from our results is that the interpretation from OBT for GE should be performed with particular care when participants might be in hypoxic condition.

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CONFLICT OF INTEREST

The authors declare no relevant conflict of interest.

AUTHOR CONTRIBUTIONS

MF, MM, MG, HF, TAL, and OG: Study design and conception. PPS, RNVdB, MM, HF, TAL, and OG: Data acquisition. PPS, RNVdB, MF, AG, MM, MG, HF, TAL, and OG: Analysis and interpretation. PPS and OG: Drafting. PPS, RNVdB, MF, AG, MM, MG, HF, TAL, and OG: Revision. PPS, RNVdB, MF, AG, MM, MG, HF, TAL, and OG: Final approval.

DATA AVAILABILITY STATEMENT

More data can be found in our supplemental file. Further information can be requested from the corresponding author.

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