

RESEARCH ARTICLE

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# Effect of a four-week isocaloric ketogenic diet on physical performance at very high-altitude: a pilot study

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## Abstract

**Background** A ketogenic diet (KD) reduces daily carbohydrates (CHOs) ingestion by replacing most calories with fat. KD is of increasing interest among athletes because it may increase their maximal oxygen uptake ( $VO_2\max$ ), the principal performance limitation at high-altitudes (1500–3500 m). We examined the tolerance of a 4-week isocaloric KD (ICKD) under simulated hypoxia and the possibility of evaluating ICKD performance benefits with a maximal graded exercise bike test under hypoxia and collected data on the effect of the diet on performance markers and arterial blood gases.

**Methods** In a randomised single-blind cross-over model, 6 recreational mountaineers (age 24–44 years) completed a 4-week ICKD followed or preceded by a 4-week usual mixed Western-style diet (UD). Performance parameters ( $VO_2\max$ , lactate threshold [LT], peak power [ $P_{\text{peak}}$ ]) and arterial blood gases ( $PaO_2$ ,  $PaCO_2$ , pH,  $HCO_3^-$ ) were measured at baseline under two conditions (normoxia and hypoxia) as well as after a 4-week UD and 4-week ICKD under the hypoxic condition.

**Results** We analysed data for all 6 participants (BMI 19.9–24.6  $kg\ m^{-2}$ ). Mean  $VO_2\max$  in the normoxic condition was 44.6  $ml\ kg^{-1}\ min^{-1}$ . Hypoxia led to decreased performance in all participants. With the ICKD diet, median values for  $PaO_2$  decreased by – 14.5% and  $VO_2\max$  by + 7.3% and  $P_{\text{peak}}$  by + 4.7%.

**Conclusion** All participants except one could complete the ICKD.  $VO_2\max$  improved with the ICKD under the hypoxia condition. Therefore, an ICKD is an interesting alternative to CHOs dependency for endurance performance at high-altitudes, including high-altitude training and high-altitude races. Nevertheless, decreased  $PaO_2$  with ICKD remains a significant limitation in very-high to extreme altitudes (> 3500 m).

**Trial registration** Clinical trial registration Nr. NCT05603689 (Clinicaltrials.gov). Ethics approval CER-VD, trial Nr. 2020-00427, registered 18.08.2020—prospectively registered.

**Keywords** Ketogenic diet, Low-carbohydrate, High-altitude, Hypoxia,  $VO_2\max$ , Endurance exercise

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## Introduction

High-fat/low-carbohydrate diets or ketogenic diets (KDs) are an innovative strategy to enhance endurance performance if exercise duration is long enough (e.g., > 4 h) and exercise intensity is low enough (50–60% maximal oxygen uptake [ $\text{VO}_2\text{max}$ ]) [1]. This strategy restricts daily carbohydrates (CHOs) consumption while maintaining low to moderate protein content, thus replacing most calories with fat. There is no standard definition of KD to achieve ketosis because of interindividual variability. CHO consumption < 30–50 g  $\text{d}^{-1}$  represents an accurate assessment [2, 3].

From a human evolutionary perspective, fat played a dominant role in energy supply [4]. However, the advent of agriculture shifted the major calorie contributor from fat to CHOs [5].

A century ago, modern science tried to determine the ideal human diet to optimize performance, with several historical studies conducted between 1939 and 1967 [6–8]. Performance was first enhanced in 1939 by giving additional CHOs to individuals with low blood sugar [6]. The association of glycogen depletion with the development of fatigue and glycogen resynthesis with a CHO-rich diet were later shown by the needle biopsy technique [7]. The idea that only a high-CHO diet could optimize performance gained credence, with a major effort for optimising glycogen storage. Over time, this led to the most commonly accepted dietary recommendation among athletes: high-CHO, moderate-protein and low-fat diet [9].

However, in the early 1980s, a link between high-fat diets and exercise capacity was demonstrated. Phinney et al. [10] showed un-impaired performance in patients with a KD [10]. Several studies challenged the approach of glycogen storage optimisation for enhancing endurance performance. There are some indications that high-CHO consumption may limit athlete's performance when competing for an extended time. CHO stores in muscle tissue (300 g), liver tissue (90 g) and the blood stream (30 g) are sufficient for only 1–3 h of activity for endurance athletes [11]. Peak fat oxidation rate occurs in submaximal exercise intensity between 47 and 64% of  $\text{VO}_2\text{max}$  [1, 12]. Also, well above this CHO threshold (> 80%  $\text{VO}_2\text{max}$ ), athlete's performed equally well while eating a high-fat or high-CHO diet [13]. Empiric observations also indicate well-being with a traditional Inuit diet [14] almost exclusively based on fat and proteins. Furthermore, a growing number of keto-adapted ultra-runner athletes are competing at high levels.

In this context, a new paradigm emerges with the idea to use the virtually unlimited fat store for endurance exercises [1, 5, 15]. The body can adapt to use fat as its primary fuel during submaximal exercise [12] with

metabolic adaptation similar to prolonged fasting [4] and increasing the fat oxidation rate (from 0.4–0.6 to 1.2–1.3 g  $\text{min}^{-1}$ ) [16]. This probably functions by affecting the mitochondrial respiratory chain [2, 16–19]. Furthermore, a KD leads to a biological ketosis by forcing the liver to produce ketone bodies (KBs) by diverting acetyl-CoA [2]. KBs may positively affect slow-muscle fibers (type I) and negatively affect fast-muscle fibers (type II), which can potentially also enhance endurance exercises [2, 18]. KBs are also suggested to be more energy-efficient than glucose [15, 20].

The concept of positive effects of keto-adaptation on endurance performance is still strongly challenged. Burke et al. [21] investigated the effect of a high-fat diet during a 3-week intensified training. In this study, increased rate of fat oxidation resulted in increased oxygen demand for a given work load, impairing exercise economy [21]. Still today, exercise and sport nutrition guidelines recommend that endurance athletes eat more CHOs (7–10 g  $\text{kg}^{-1} \text{d}^{-1}$ ) than routine CHO intake (5–7 g  $\text{kg}^{-1} \text{d}^{-1}$ ) to optimise muscle glycogen stores [22–24].

High-altitude mountaineering is said to have been invented in the middle of the eighteenth century by H.B. de Saussure. Originally limited to scientists and conquistadors, mountaineering as a sport that really emerged much later. The first Mount Everest ascent without oxygen in 1978 contributed to this aspect. Since then, a plethora of studies have explored the major performance limitations at high altitude. Indeed, diminished inspiratory oxygen pressure ( $\text{PIO}_2$ ) at high altitude [25] is critical for the delivery of oxygen to tissue. The  $\text{VO}_2\text{max}$  performance parameter indicates the maximal oxidative metabolic capacity or oxygen supply integrating every step of transport and metabolic capacity of the body [26]. Reduced oxygen delivery at high altitude is responsible for  $\text{VO}_2\text{max}$  limitation [27].

A KD influences  $\text{VO}_2\text{max}$  by shifting mitochondrial metabolism capacity. Increasing fat rate oxidation requires greater oxygen consumption, thus leading to higher maximal oxygen supply for maintaining a given exercise load [2]. Some evidence suggests a positive effect of a KD on  $\text{VO}_2\text{max}$  [21, 28–31] but is contrasted by recent work of Burke et al. [21]. At present, these mixed findings are believed to be due to heterogeneity across studies and/or variability among athletes [32]. Nevertheless, this aspect was never investigated under hypoxic conditions. Despite the mixed effect on  $\text{VO}_2\text{max}$ , a KD could be a potential performance enhancer in hypoxia. In fact, optimising the fat oxidation rate could give access to the virtually endless fat store and reduce dependence on glycogen. This aspect is particularly important in long hypoxia training such as mountaineering. Furthermore, hypoxia is known to induce a reduction in CHOs

oxidation when CHOs are ingested before exercise, thus reinforcing the use of fat at high altitudes [33, 34]. This observation is supported by the subjective benefit of a high-fat diet in high altitude praised by the extreme high-altitude mountaineer Erhard Loretan (e.g., at Everest base camp in 1986).

According to this information, we hypothesized that a 4-week KD would have positive effects on  $\text{VO}_2\text{max}$  in healthy, recreational mountaineers during a maximal graded performance test under simulated hypoxic conditions. Various types of KD are described [3]. In our study, we focused on the isocaloric KD (ICKD) in which calories are in line with total energy expenditure.

## Methods

This pilot study was a single, blinded, randomised cross-over clinical trial. The study took place in Switzerland at the Clinique romande de réadaptation (Sion). The protocol was approved by CER-VD (Project-ID: 2020-00427).

### Study aim

This pilot study aimed to (1) assess the tolerance of a non-standardized 4-week ICKD in healthy, recreational mountaineers, (2) assess the possibility of evaluating participants' ICKD performance benefits under hypoxic conditions by a maximal graded exercise bike test and (3) gather data regarding the benefit of a 4-week ICKD on  $\text{VO}_2\text{max}$  during a maximal graded performance test under simulated hypoxic conditions. Furthermore, data concerning lactate threshold (LT) values ( $P_{\text{LT}}$ ,  $\text{HR}_{\text{LT}}$ ), peak values ( $P_{\text{peak}}$ ,  $\text{HR}_{\text{peak}}$ ), subjective Borg rating of perceived exertion (RPE) and oxygenation status (blood gases) were recorded.

### Participants

Eight recreational mountaineers were recruited to participate. Inclusion criteria were familiarity with altitude (>2500 m above sea level) and males/females 20–45 years old. Exclusion criteria were high training load (such as professional athletes) or new planned training and dietary restrictions. Participants were enrolled after giving their signed informed consent. Mountaineering level was reported as beginner for participants with no to little experience in mountaineering, medium for those who regularly experienced high altitudes, and experts who regularly mountaineered.

We did not calculate a sample size for this study because this was a pilot study to gather information about diet tolerance/acceptance, the feasibility of the testing procedure and preliminary data on the benefit of an ICKD diet for  $\text{VO}_2\text{max}$  in healthy persons.

### Study procedure

Individuals who gave signed informed consent were invited for a consultation during which a medical doctor explained the standardisation of the performance tests and the dietary protocol. In addition, the participant's ability to perform a maximal graded performance test was assessed with the physical activity aptitude questionnaire (Q-AAP) [35]. We assessed participants' ability for a ICKD and exposure to hypoxia by two other self-developed questionnaires using known contra-indication to KD [36], previously experienced exposure to hypoxia and predisposing factors to acute mountain sickness [37].

The participant was then asked to perform a maximal graded exercise bike test (performance test) to assess their baseline performance under normoxic conditions (T0N) and, 4 weeks later, under hypoxic conditions (T0H). This test was conducted under supervision by a sport scientist and a medical doctor. The medical doctor was also responsible for collecting an arterial blood sample after a 5-min rest post-exercise.

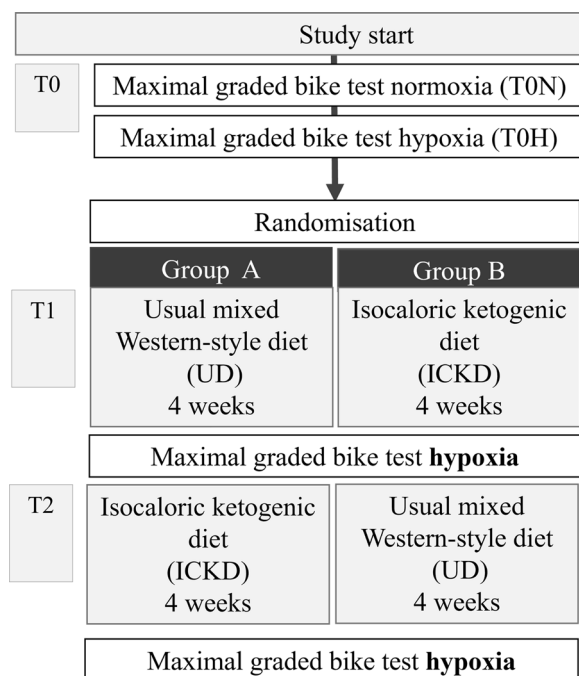
After this test, participants were randomly assigned to group A or group B with a block size of 4 by a collaborator who was not involved in the study protocol. The RALLOC function of Stata was used. Each participant received a with the group attribution, which allowed for blind the investigators. Group A began with a 4-week UD (T1) followed by a 4-week ICKD (T2), and group B began with a 4-week ICKD (T1) followed by a 4-week UD (T2).

Each 4-week diet period was terminated with a performance test under hypoxic conditions (same procedure as at baseline but under hypoxic conditions). We used a normobaric (940–980 hPa) hypoxic ( $\text{FIO}_2 = 12.7\text{--}12.9\%$ ) room simulating an altitude of ~4500 m. The study design is represented in Fig. 1.

### Maximal graded exercise bike test

The initial resistance was 60–90 W depending on training status and sex. The resistance was increased every 3 min by 30 W until exhaustion. Interruption conditions were a clear decrease in cycling frequency ( $< 70 \text{ min}^{-1}$ ) or a complete stop of cycling [38]. Oxygen respiratory flow ( $\text{VO}_2$ ), carbon dioxide respiratory flow ( $\text{VCO}_2$ ), heart rate (HR) and delivered power (P) were measured (Metalyzer 3B, Cortex) until the test's interruption. Maximal values are defined as peak values. In addition, capillary blood lactate (B-Lac) level was measured 30 s before the end of each increase in resistance. Finally, we used Borg RPE [39] at the end of the test to assess participant subjective perceived exertion of the physical work.

Hypoxia during the performance test was achieved in a simulated altitude facility (hypoxic room) with a hypoxic generator (ATS altitude, Sydney, Australia) by lowering



**Fig. 1** Study design

the fraction of inspired oxygen ( $FIO_2$ ), which simulates a very-high-altitude of 4500 m.

### Study intervention

#### Four-week ICKD

The ICKD definition was based on the works of Sansone et al. [2] and Trimboli et al. [3]. We defined ICKD as a daily CHOs ingestion  $<30\text{--}50\text{ g d}^{-1}$ , without any limitation in fat consumption. Participants self-selected their own diet based on a list of advised and forbidden foods developed to fit the definition of ICKD. There were no instructions to limit calories. Regular contact was maintained with all participants during the study with every time available to answer participants' dietary questions. The maximal graded bike test was planned after an adaptation period of 27 days.

#### Four-week UD

There were no limitations on food consumption. Participants were instructed to eat as close as possible to their usual diet.

Participants were instructed to track their 4-week ICKD and UD by using the analysis program MyFoodRepo® (EPFL, Switzerland), a user-friendly smartphone application. The database used by the application is based on Switzerland's foods and is in constant development. Food intake was manually reported on a daily basis by an investigator for diet monitoring. Participant adherence

to ICKD was checked by their daily CHOs intake. If daily CHOs intake was  $>50\text{ g}$  and if the  $\beta$ -hydroxybutyrate ( $\beta$ -OHB) level was  $<170\text{ }\mu\text{mol L}^{-1}$ , data for the participant were excluded from the statistical data analysis and the study.

### Blood analysis

An arterial blood sample was taken after a 5-min rest at the end of each performance test. Under hypoxic conditions, the participants remained in the hypoxic room for blood collection. The blood samples were analysed on an ABL800 FLEX blood gas analyzer (Radiometer, Denmark) within 10 min for partial arterial oxygen pressure ( $PaO_2$  [kPa]), partial arterial carbon dioxide pressure ( $PaCO_2$  [kPa], pH, and bicarbonate concentration ( $HCO_3^-$  [mmol  $L^{-1}$ ]) automatically calculated by using the Henderson–Hasselbalch equation.

Venous blood was sampled after each test. Venous blood was placed into a perchloric acid-tube and frozen at  $-80\text{ }^\circ\text{C}$ . All samples were analyzed within 3 months for  $\beta$ -OHB and acetoacetate (AcAc) with enzymatic analysis [40]. Reference values (percentile 2.5–97.5) provided by the laboratory (Lausanne university hospital, Switzerland) were for  $\beta$ -OHB,  $58\text{--}170\text{ }\mu\text{mol L}^{-1}$ , and AcAc,  $18\text{--}78\text{ }\mu\text{mol L}^{-1}$ .

### Statistical analysis

We used descriptive statistical analysis for (1) diet tolerance, (2) performance values under normoxic and hypoxic conditions and (3) performance values under a UD and ICKD. Performance test results under normoxic and hypoxic conditions are expressed as mean (SD). Because of limited sample size ( $n=6$ ), no confidence intervals or p-values were calculated.

To assess diet tolerance, we analysed the number of dropouts and reported side effects. We assessed diet tolerance by calculating median daily values for CHOs, fat and protein content and energy expenditure for all participants, then calculated median daily CHOs, fat, and protein consumption and energy expenditure for all participants. Further blood analysis of KBs including  $\beta$ -OHB and AcAc were assessed for diet tolerance.

Feasibility of maximal graded exercise was assessed by comparing the values under normoxia and hypoxia. These values were then expressed as percentage difference in “median” (“minimal values” to “maximal value”). We then checked whether these values agreed with previously reported performance decreases under acute hypoxia [41–43].

The effect of ICKD on performance is also expressed as percentage differences in median (range), calculated by comparing the values of performance parameters after the ICKD diet and the UD diet. For Group A, UD values

are T1. For Group B, UD values are T0H. VO<sub>2</sub>max performance parameters after ICKD (hypoxia) compared to UD (hypoxia) were the primary outcome. As a secondary outcome, performance parameters such as LT values (P<sub>LT</sub>, HR<sub>LT</sub>), peak values (P<sub>peak</sub>, HR<sub>peak</sub>), subjective values (Borg RPE) and oxygenation status (blood gas values) were analysed. LT determination was based on the D<sub>max</sub> model established in 1992 [44], which uses the maximal perpendicular distance from the line connecting the start with the endpoint of the lactate curve. We used the “modified D<sub>max</sub> threshold” (D<sub>mod</sub>), which is an updated D<sub>max</sub> model by Bishop et al. [45]. This model eliminates the effect of start intensity and maximal effort and determines the LT as the moment when a rapid change in the inclination of the blood lactate curve occurs. This situation matches the maximal lactate steady state reflecting the anaerobic threshold [46].

**Results**

**Diet tolerance**

At the beginning, 8 participants were enrolled (4 males). One participant dropped out after the second performance test because of a schedule mismatch rather than a regimen intolerance. In addition, the data of another participant were excluded from data analysis because of abnormally high daily CHOs intake (>50 g d<sup>-1</sup>) and low

β-OHB level (<170 μmol/L), which led to suspecting invalid data (Fig. 2).

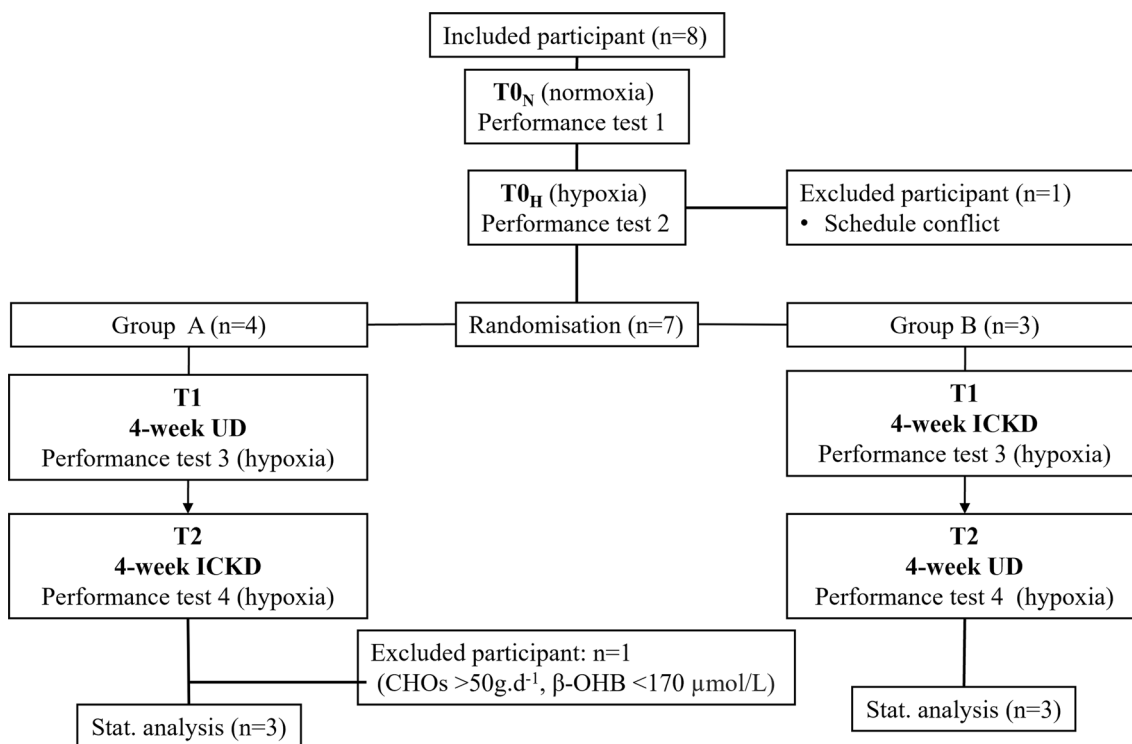
Participants were aged 24–44 years (median 29 years) and the median BMI was 22.8 kg m<sup>-2</sup>.

Frequently reported side effects were weight loss and gastrointestinal disorders. After ICKD, subjective exercise load perception by the RPE scale [39] were similar to reference values for two participants, increased for three participants and decreased for one participant. Nutrition features with the UD and ICKD are presented in Table 1.

**UD and ICKD follow-up**

The 4-week UD diet was characterized by a median CHOs intake of 197 g d<sup>-1</sup>. The median post-UD β-OHB level 44.0 μmol/L and AcAc level 22.5 μmol/L were within reference values. With the 4-week ICKD, the median CHOs intake was 40 g d<sup>-1</sup>. The median post-4-week ICKD β-OHB value 288.0 μmol/L and AcAc value 80.0 μmol/L were above reference values fixed by the laboratory.

One participant showed excess CHOs daily intake and too low β-OHB blood level. His median post-4-week UD CHOs intake was 259 g d<sup>-1</sup> and 4-week ICKD intake 67 g d<sup>-1</sup>. The β-OHB/AcAc blood content was 41.0/23.0 and 152.0/56.0 mmol L<sup>-1</sup>. This participant was not included in the statistical analysis.



**Fig. 2** Flow of participants in the study. ICKD: isocaloric ketogenic diet; UD: usual mixed Western-style diet; CHOs: carbohydrates; β-OHB: β-hydroxybutyrate level

**Table 1** Nutrition features of participants with a usual mixed Western-style diet (UD) and isocaloric ketogenic diet (ICKD)

	UD			ICKD		
	Median	Min	Max	Median	Min	Max
CHO <sub>s</sub> (g d <sup>-1</sup> )	197	152	321	40	21	49
Protein (g d <sup>-1</sup> )	82	51	122	97	51	169
Fat (g d <sup>-1</sup> )	93	63	140	143	43	164
Energy (Kj d <sup>-1</sup> )	7774	6366	12,603	8496	4475	9841
β-OHB (μmol/L)	44.0	41.0	65.0	288.0	190.0	462.0
AcAc (μmol/L)	22.5	6.7	33.0	80.0	59.0	132.0

Recorded data for UD and ICKD diet characteristics with median (range) showing adherence to the ICKD diet. Reference values (percentile 2.5–97.5) provided by the laboratory (CHUV, Switzerland) are for β-OHB, 58–170 μmol L<sup>-1</sup>, and for AcAc, 18–78 μmol L<sup>-1</sup>. CHO<sub>s</sub> carbohydrates, β-OHB β-hydroxybutyrate, AcAc acetoacetate

**Table 2** Effect of hypoxia alone on performance values

	Normoxia Mean (SD)	Effect of hypoxia (%)		
		Median	Min	Max
VO <sub>2</sub> max (ml kg <sup>-1</sup> min <sup>-1</sup> )	44.6 (5.8)	-27.1	-36.5	-20.3
P <sub>LT</sub> (W)	203 (64)	-28.6	-34.6	-17.9
P <sub>peak</sub> (W)	266 (65)	-22.4	-30.8	-12.8
HR <sub>LT</sub> (beat min <sup>-1</sup> )	156 (23)	2.0	-7.1	17.6
HR <sub>peak</sub> (beat min <sup>-1</sup> )	183 (17)	-5.4	-15.0	-1.9
B-Lac <sub>peak</sub> (mmol L <sup>-1</sup> )	10.7 (2.2)	-0.8	-28	16.1
PaO <sub>2</sub> (kPa)	17.8 (2.2)	-50.9	-71.1	-12.2
pH	7.24 (0.06)	0.15	-0.59	2.22
PaCO <sub>2</sub> (kPa)	3.8 (0.2)	-9.6	-19.5	5.9
HCO <sub>3</sub> <sup>-</sup> (mmol L <sup>-1</sup> )	11.9 (2.1)	0.0	-0.2	0.1

Maximal graded exercise test values under normoxic conditions for baseline were compared with performance values under hypoxic conditions

Normoxia baseline values (TON) are compared with hypoxia values (T0H) assessing the effect of hypoxia. VO<sub>2</sub>max maximal oxygen uptake, LT lactate threshold, P power, HR heart rate, B-Lac blood lactate, PaO<sub>2</sub> partial oxygen arterial pressure, PaCO<sub>2</sub> partial carbon dioxide arterial pressure

### Feasibility of the maximal graded exercise bike test under hypoxia

We used expected and previously characterised performance decreases under hypoxia [41–43] to evaluate the feasibility of the performance test and trustworthiness of the recorded values. We found no adverse events related to the combination of a 4-week ICKD, hypoxia exposure and maximal graded exercise bike test.

### Effect of hypoxia

The results of the performance test under normoxic conditions at baseline are presented in Table 2. The measured effect of hypoxia is expressed as the median difference with normoxic values in percentages. Median performance values decreased for VO<sub>2</sub>max (-27.1%), P<sub>LT</sub> (-28.6%) and P<sub>peak</sub> (-22.4%) under hypoxic conditions. Arterial blood samples showed a reduction in median PaO<sub>2</sub> by -50.9%. Median values for pH, PaCO<sub>2</sub> and HCO<sub>3</sub><sup>-</sup> all remained unaffected.

**Table 3** Effect of ICKD under hypoxic conditions on performance values

	Hypoxia Mean (SD)	Effect of ICKD (%)		
		Median	Min	Max
VO <sub>2</sub> max (ml kg <sup>-1</sup> min <sup>-1</sup> )	31.6 (3.4)	7.3	-16.8	25.5
P <sub>LT</sub> (W)	147 (47)	0.7	-21.5	46.6
P <sub>peak</sub> (W)	205 (48)	4.7	-7.1	11.1
HR <sub>LT</sub> (beat min <sup>-1</sup> )	160 (22)	7.5	-5.4	23.8
HR <sub>peak</sub> (beat min <sup>-1</sup> )	171 (15)	3.6	-2.6	15.2
B-Lac <sub>peak</sub> (mmol L <sup>-1</sup> )	10.3 (3.0)	-8.8	-40.9	17.1
PaO <sub>2</sub> (kPa)	9.0 (3.4)	-14.5	-32.1	-11.5
pH	7.28 (0.96)	0.28	0.08	1.62
PaCO <sub>2</sub> (kPa)	3.5 (0.4)	2.1	-23.3	11.8
HCO <sub>3</sub> <sup>-</sup> (mmol L <sup>-1</sup> )	12.0 (3.1)	-0.1	-0.3	0.1

Hypoxic (T0H) performance values were used for baseline and were compared with performance values from a maximal graded exercise test performed after a 4-week ICKD under hypoxic conditions

ICKD isocaloric ketogenic diet, UD usual mixed Western diet, VO<sub>2</sub>max maximal oxygen uptake, LT lactate threshold, P power, HR heart rate, B-Lac blood lactate, PaO<sub>2</sub> partial oxygen arterial pressure, PaCO<sub>2</sub> partial carbon dioxide arterial pressure

### ICKD effect on performance

Performance test results under hypoxic conditions at baseline are in Table 3. Keeping the cross-over design, hypoxic baseline values (UD) are at T1 for Group A and T0H for group B. The effect of ICKD on performance test values was assessed by comparing parameter values at T1 with T2 (Group A) and T0H with T1 (Group B). A return to the normal situation could be assessed only in group B by comparing the performance values of T0H and T2.

### Effect of ICKD

Median performance values increased for VO<sub>2</sub>max (+7.3%), P<sub>peak</sub> (4.7%), HR<sub>peak</sub> (+3.6%) and P<sub>LT</sub> (+0.7%) but with large interindividual variability (Table 3).

Median  $bLa_{base}$  and  $bLa_{peak}$  values decreased by  $-21.0\%$  and  $-8.8\%$ . Median  $PaO_2$  decreased  $-14.5\%$ . Values for other parameters, pH,  $PCO_2$  and  $HCO_3$ , could be considered stable.

In Group B, the cross-over design allowed for assessing a return to the normal situation when switching again from a 4-week ICKD to a 4-week UD. So we compared T0H and T2 values for the three participants in group B, which should theoretically be the same values. We expressed results as a percentage difference between T0H and T2. Of note, only median  $PaO_2$  ( $+1.4\%$ ) returned to the initial value. We did not observe a return to initial values for median  $VO_{2max}$  ( $+18.1\%$ ),  $P_{peak}$  ( $-8.3\%$ ), or PLT ( $+3.3\%$ ).

### Individual values

Individual performance and blood gas parameters at baseline (T0N) after UD and after ICKD are in Table 4. The 6 participants could be separated as showing a positive effect of ICKD or not (Table 5). Four participants showed an increase in  $VO_{2max}$  and  $P_{peak}$ .  $P_{LT}$  was used for further dividing participants. Figure 3 shows B-Lac and HR curves after UD or ICKD, as well as at T0N for every participant. Nr. 6 (Id 6) and Nr. 8 (Id 8) showed improvement in endurance and peak performance parameters. Nr. 1 (Id 1) and Nr. 2 (Id 2) showed improvement in peak performance parameter. Nr. 3 (Id 3) and Nr. 4 (Id 4) showed little to no response or a clear worsening of the performance parameter. One participant (no. 2) showed a particularly large decrease in  $HR_{peak}$  ( $-14.9\%$ ) with hypoxia exposure. ICKD clearly allowed for a return to normality for  $HR_{peak}$  values ( $+13.1\%$ ) as also confirmed by the cross-over analysis ( $-14.2\%$ ).

### Discussion

This novel study assessed the tolerance of an ICKD and the feasibility of a bike performance test under hypoxic conditions and gathered preliminary data on the effect of shifting from a UD to an ICKD on  $VO_{2max}$  under simulated very-high-altitude conditions. We used a maximal graded exercise bike test to assess endurance parameters and post-exercise arterial blood samples to assess oxygenation and pH status. We hypothesized that reduced CHOs intake would increase  $VO_{2max}$  performance values under hypoxia. To our knowledge, these aspects were never investigated before. We analysed data for all 6 participants. Mean  $VO_{2max}$  in the normoxic condition was  $44.6 \text{ ml kg}^{-1} \text{ min}^{-1}$ . Hypoxia led to decreased performance in all participants. With the ICKD diet, median values for  $PaO_2$  decreased by  $-14.5\%$  and  $VO_{2max}$  by  $+7.3\%$  and  $P_{peak}$  by  $+4.7\%$ .

### Diet tolerance

All participants except one could complete the ICKD. The recorded CHOs values for this participant were beyond the limitation and therefore the data were excluded from analysis. This situation emphasizes the need for a strict diet follow-up and blood KB analysis. Another participant dropped out because of a personal schedule mismatch, which underlines the importance of high motivation and collaboration between researchers and participants in particular because of the high number of maximal graded exercise bike tests with standardized time between the tests. Overall, only minor adverse events such gastrointestinal complaints at the beginning of the diet or weight loss were reported, but none of the participants had to stop the ICKD.

The median energy intake for UD and ICKD were below the typical energy requirements [47], so participants were in negative energy balance.

Moreover, we identified two major difficulties for participants in following the ICKD. First, high exercise load training was difficult during the first weeks of the ICKD diet. Indeed, we found a subjective performance drop at the beginning of the new diet because of ICKD adaptation [48]. Second, participants also reported a subjective social impact during the ICKD.

### Evaluating the ICKD benefits on performance under hypoxic conditions

We evaluated ICKD-induced performance benefits under hypoxic conditions by using a maximal graded exercise bike test. The observed decrease in median values for the performance parameters  $VO_{2max}$ ,  $P_{LT}$ ,  $P_{peak}$  and  $PaO_2$  when exposed to hypoxia strengthen the reliability of results and the feasibility of our protocol.

### Effect of hypoxia

For every participant, hypoxia induced a clear decrease in median  $VO_{2max}$  by  $13 \text{ ml kg}^{-1} \text{ min}^{-1}$  ( $-27.01\%$ ),  $P_{peak}$  by  $60 \text{ W}$  ( $-22.4\%$ ), and  $PaO_2$  by  $8.8 \text{ kPa}$  ( $-50.9\%$ ) (Table 2). This was expected because the primary limitation for  $VO_{2max}$  under hypoxic conditions is oxygen tissue availability [49]. Indeed, significant decreases in  $VO_{2max}$  were previously reported with acute exposure to hypoxia [41–43]. This situation results from decrease in barometric pressure with increasing altitude. Therefore  $PIO_2$  and, consequently, oxygen transport decrease [41, 50]. A research compilation by Robergs and Robert [51] reported a mean decrease of  $8.7\%$  per 1000 m in  $VO_{2max}$ . Nevertheless, an average value cannot be expressed because of high inter-individual variation in the reduction in  $VO_{2max}$  depending on sea level  $VO_{2max}$ , sex, sea level LT and lean body mass [27]. This observation may explain

**Table 4** Values for individual participants comparing performance after a UD and after an ICKD

	Test	Nr. 1	Nr. 2	Nr. 3	Nr. 4	Nr. 6	Nr. 8
Sex		F	M	M	M	F	F
Age (years)		29	27	44	24	29	28
BMI (kg m <sup>-2</sup> )		22.3	23.2	24.6	23.4	21.3	19.9
Mountaineering level		Medium	Medium	Medium	Expert	Medium	Expert
VO <sub>2</sub> max (ml kg <sup>-1</sup> min <sup>-1</sup> )	T0N	36.8	48.8	46.2	50.7	38.0	47.2
	UD	26.6	31.0	29.5	42.8	28.5	32.3
	ICKD	28.8	38.9	24.5	38.4	33.6	34.4
P <sub>LT</sub> (W)	T0N	114	261	266	224	136	215
	UD	81	186	182	159	89	103
	ICKD	79	146	168	165	124	151
P <sub>peak</sub> (W)	T0N	180	310	340	300	195	270
	UD	140	240	194	210	123	190
	ICKD	150	250	186	195	140	200
HR <sub>LT</sub> (beat min <sup>-1</sup> )	T0N	163	175	136	174	119	170
	UD	163	186	129	173	140	147
	ICKD	166	176	140	184	159	182
HR <sub>peak</sub> (beat min <sup>-1</sup> )	T0N	194	194	162	197	162	191
	UD	186	165	152	190	159	184
	ICKD	190	190	148	193	167	194
bLa <sub>peak</sub> (mmol L <sup>-1</sup> )	T0N	9.2	13.6	11.8	11.8	7.5	10.1
	UD	8.2	13.1	9.3	12.5	5.4	10.7
	ICKD	9.6	10.7	5.5	11.7	5.5	9.5
RPE	T0N	10	17	17	17	11	17
	UD	11	20	15	16	13	18
	ICKD	15	20	15	17	15	16
PaO <sub>2</sub> (kPa)	T0N	18	13.6	19	25.5	14	16.9
	UD	15.8	7.0	7.7	11.7	8.1	8.4
	ICKD	7.7	6.0	6.8	7.9	6.0	7.2
pH	T0N	7.22	7.14	7.26	7.26	7.34	7.24
	UD	7.21	7.21	7.42	7.20	7.38	7.28
	ICKD	7.25	7.33	7.42	7.22	7.45	7.29
PaCO <sub>2</sub> (kPa)	T0N	3.6	3.9	3.7	3.5	4.0	4.0
	UD	2.9	3.4	3.2	3.7	3.8	3.7
	ICKD	3.0	3.8	3.5	2.9	3.9	3.1
HCO <sub>3</sub> <sup>-</sup> (mmol L <sup>-1</sup> )	T0N	10.8	9.5	12	11.3	15.6	12.3
	UD	8.4	10	15	10.5	16.5	12.4
	ICKD	9.4	14.7	16.8	8.5	20.2	10.9

Only VO<sub>2</sub>max, P<sub>LT</sub> and P<sub>peak</sub> values are shown for baseline T0N

T0N baseline test under normoxia, UD values after usual mixed Western-style diet under hypoxia, ICKD isocaloric ketogenic diet under hypoxia, VO<sub>2</sub>max maximal oxygen uptake, LT lactate threshold, P power, HR heart rate, bLa peak lactate, RPE Borg rating of perceived exertion, PaO<sub>2</sub> partial oxygen arterial pressure, PaCO<sub>2</sub> partial carbon dioxide arterial pressure, Nr. subject number

the large range in VO<sub>2</sub>max decrease (−36.5 to −20.3%) in our study. Furthermore, we found no significant difference in arterial blood pH, PaCO<sub>2</sub> and HCO<sub>3</sub>.

#### Recorded data

##### Effect of ICKD on maximal graded exercise test

Improved median VO<sub>2</sub>max (+7.3%) and P<sub>peak</sub> (+4.7%) with a 4-week ICKD under hypoxic conditions in 4 of 6

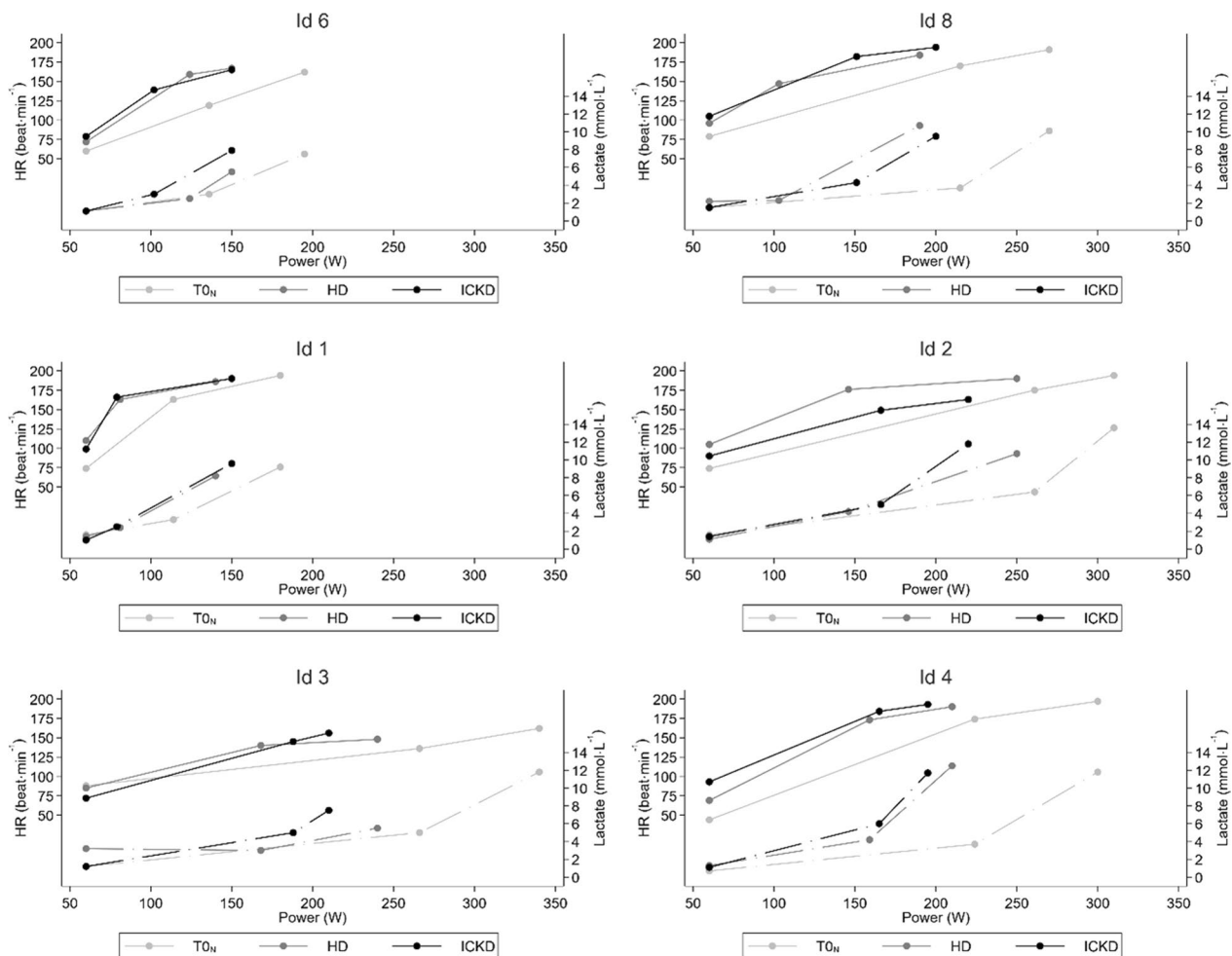
participants (Tables 3, 4) do not allow for concluding on the effects of the KD. We found no performance marker systematically affected by ICKD. This recorded improvement was similarly reported in part under normoxia [21, 32]. VO<sub>2</sub>max reflects the cardiorespiratory fitness [52] and is considered a gold standard for measuring aerobic metabolism [53]. A greater VO<sub>2</sub>max indicates greater endurance capacity. Actual known factors affecting



**Table 5** Effect of ICKD on performance parameters

Type	Nr	VO <sub>2</sub> max	P <sub>LT</sub> and HR <sub>LT</sub>	P <sub>peak</sub>	Remark
Positive effect of ICKD	6;8	↑	↑	↑	ICKD conferred improvement regarding endurance and peak performance parameters
	1;2	↑	↓	↑	ICKD had positive effects despite a decrease in LT parameter values. Indeed, P <sub>peak</sub> and VO <sub>2</sub> max confirmed a benefit
Negative effect of ICKD	4	↓	↑	↓	ICKD conferred little to no response. UD and ICKD values for performance tests can be considered equal
Non-assessable	3	↓	↓	↓	Clear worsening of test performance

ICKD isocaloric ketogenic diet, UD usual mixed Western-style diet, VO<sub>2</sub>max maximal oxygen uptake (ml min<sup>-1</sup> kg<sup>-1</sup>), P<sub>LT</sub> power at lactate threshold (W), P<sub>peak</sub> peak power (W), HR<sub>LT</sub> heart rate at lactate threshold (beat min<sup>-1</sup>), Nr. subject number



**Fig. 3** Effect of ICKD on performance test. ICKD B-Lac and HR curves were drawn for T0N, UD, and ICKD. The first point represents the values at the beginning of the test. The second point is the value at lactate threshold and the third point is the maximal or peak value. ID: participant number

VO<sub>2</sub>max are age, sex, genetics, body composition, state of training and mode of exercise [54].

The KD has been newly identified as a potential positive factor for VO<sub>2</sub>max [28, 30, 31] by shifting mitochondrial metabolism [17, 19]. These studies were summarized by Bailey et al. [32]. The authors

suggested that several factors such as genetics, trainability and or chronic substrate utilization may be affected by KD, which thus might increase VO<sub>2</sub>max. The positive effect of the ICKD on VO<sub>2</sub>max under hypoxic conditions we observed strengthens the idea

that a high-fat diet might be beneficial for endurance exercise under acute hypoxia exposure.

In addition, other performance LT values were improved in two participants considered ICKD responders (Table 5). As shown in Fig. 3, B-Lac kinetics were lower with the ICKD than UD. Points for LT and maximal value shifted to the right (right curve-shifting). HR kinetics were higher with the ICKD than UD. Points for LT and maximal values were at higher power (left curve-shifting). LTs are performance indicators strongly correlated with endurance performance [46]. They represent the aerobic-anaerobic transition because lactate kinetics are highly related to the metabolic rate and less to oxygen availability [46]. A higher workload to a given blood lactate concentration can be interpreted as improved endurance capacity [55]. Previous studies have reported a shift in the B-Lac curve to higher workloads under KD conditions [56]. This phenomenon is still not fully understood but may be due to an association with decreased glycolysis rate or limited lactate efflux from muscle due to reduced blood buffering capacity [28, 56]. Furthermore, depleted glycogen stores (due to an ICKD, for example) is a known factor leading to lower blood lactate concentration at the same work rate [57].

In this context and considering key performance parameters ( $VO_{2max}$ ,  $P_{LT}$ ,  $HR_{LT}$  and  $P_{peak}$ ), we separated the 6 participants into two groups: a group showing a positive effect of the ICKD and a group showing no benefits or even negative effects of the ICKD. The group with a positive effect of the ICKD showed a right-shift in B-Lac kinetics (Fig. 3) which can be interpreted as better performance [55]. Peak values ( $P_{peak}$  and  $VO_{2max}$ ) also demonstrated better performance. A left-shifting HR curve showed a higher HR work range with the ICKD. For the second group, the intervention had little to no effect, and ICKD and UD tests were considered equal. One participant showed clearly worsened global ICKD performance at every time point, with no clear explanation. Several factors that could explain this performance decrease include a “bad shape day” or the influence of the ICKD on age-related  $VO_{2max}$  factors such as a decline in maximal heart rate, stroke volume, fat-free mass and arteriovenous oxygen differences [58].

#### **Effect of ICKD on blood gas parameters**

With the ICKD, post-exercise  $PaO_2$  decreased in all participants (median – 14.5%), a response confirmed in the cross-over group B when returning to the UD (+ 14.5%). A physiological approach can explain the ICKD-related hypoxemia.  $PaO_2$  is determined by alveolar  $PO_2$  ( $PAO_2$ ), ventilation, diffusion capacity of the lung and perfusion

by the heart.  $PAO_2$  depends on the respiratory gas-exchange ratio (RER). RER is the ratio between  $CO_2$  pulmonary output ( $\dot{V}CO_2$ ) and  $O_2$  uptake ( $\dot{V}O_2$ ) expressed as  $RER = \frac{\dot{V}CO_2}{\dot{V}O_2}$ , which can be included in the alveolar air equation  $PAO_2 = PIO_2 - (\frac{PaCO_2}{RER})$ . RER depends on the steady state (e.g., resting state) for the food metabolized [59]. An ICKD increases fat oxidation and lowers RER (~0.7), and consequently  $PAO_2$  and  $PaO_2$  decrease [59]. Furthermore, the maximal graded test result is not a steady state, and RER varies with exercise. Within a few minutes into recovery, RER decreases to <0.7 as ventilation declines and the  $CO_2$  store re-increases [60]. Decreased ventilation could also affect  $PaO_2$ , as observed in respiratory failure, a well-known process in diabetic ketoacidosis. Ketosis generates a respiratory response in the form of hyperpnea [61], which leads to respiratory muscle fatigue (known as Kussmaul respiration) [62]. An ICKD could lead to a mismatch of the lung maintaining  $PaO_2$  by a form of respiratory muscle fatigue due to KBs.

Alternative explanations for the effect of heart perfusion on  $PaO_2$  are not relevant. Although KBs can influence heart flow, they increase rather than decrease the hydraulic efficiency of the heart [18]. The higher heart flow rate leads to an increase in pulmonary venous blood admission. Finally, CHOs are known to increase  $PaO_2$  at high altitude by increasing the relative production of carbon dioxide and increasing the drive for ventilation [63].

Consistent with a previous study by Hansen et al. [60], ICKD worsened the hypoxemia in our simulated very-high to extreme altitude (>3500 m). This is a relevant limitation of using the ICKD above a very-high-altitude [50, 64], whereas at high-altitude (1500–3500 m),  $PaO_2$  is significantly diminished but with only minor impairments in oxygen transport ( $SaO_2 > 90\%$ ) [50]. Therefore, an ICKD could be used for this altitude.

Arterial blood sampling also showed non-significant effects of the ICKD on pH (+0.278%) post-exercise, which is below analytical precision. Increased pH could be expected because KBs are acids known to induce ketoacidosis [65, 66]. Nevertheless, Carr et al. contrasted these earlier beliefs by describing the minimal effects of KD on acid base status in elite athletes [30]. They also reported no statistical blood pH differences between high CHOs versus high fat content pre- and post-exercise. Blood pH stability may be due to increased exercise-induced ventilation rate and so would increase the pH.

In conclusion, our preliminary data showed a benefit of ICKD on performance parameters. We found a positive increase in  $VO_{2max}$  (primary outcome) and LT performance parameters (secondary outcome). ICKD intervention decreased  $PaO_2$ , which is consistent with previous

findings [60] and may limit the use of an ICKD in very-high-altitude sports.

### Further research

Further characterisation of the ICKD benefits at high-altitude (1500–3500 m) is needed. Despite ICKD-induced hypoxemia, this may not impair oxygen delivery at this altitude. Furthermore, diet modifications (CHOs vs. fat) could be an interesting path for improving acclimation or performance at high-altitude and preventing acute mountain sickness. PaO<sub>2</sub> analysis during the whole effort would be needed for a complete assessment of the effect of an ICKD on blood gas values. The cross-over design of the study is pertinent to assess the effectiveness of an ICKD.

The previous experience of participants with KD-like diets seems to be an effective supplementary inclusion criterion for diet tolerance. Moreover, whether subjective perception of KD tolerance matches performance improvements would be interesting and might help predict whether a person would show a positive effect of ICKD or not. This would be possible with a simple assessment by a questionnaire without a maximal graded performance test.

### Strengths and limitations

Our study assessed for the first time the effect of KD implementation in simulated very-high-altitude performance test. We used a maximal graded exercise bike test with a primary outcome of the effect on VO<sub>2</sub>max. However, with a sample of 6 participants, we focused on individual values, profiling, and trends. The negative energy balance observed without recorded data on body mass at the end of KD limits concluding on its effect. In addition, our design also limits the blood gas kinetics view during the performance test. Moreover, our findings were obtained in acute simulated hypoxia, which limits practical implications for the real-life high-altitude condition.

### Conclusions

The present protocol shows the feasibility of evaluating the benefits of an ICKD on recreational athlete performance by a maximal graded exercise test under hypoxia conditions. Our study successfully combined ICKD, hypoxia and maximal graded exercise, which shows the feasibility of the present protocol. The pilot data showed improved VO<sub>2</sub>max with the ICKD under hypoxia in 4 participants. Nevertheless, this study does not allow to make any final conclusions about the benefit of ICKD. KD remains an interesting alternative to CHOs dependency for endurance performance. This regimen may be interesting for endurance exercises at high-altitude (1500–3500 m) [67] with only minor

impairment in arterial oxygen transport [50]. It could concern typical high-altitude exercises such as high-altitude training [67], high-altitude races [68], trail-running, mountaineering and ski-touring [69].

### Abbreviations

AcAc	Acetoacetate
β-OHB	Beta-hydroxybutyrate
B-Lac	Blood lactate
CER-VD	Commission d'éthique et recherche du canton de Vaud
CHO	Carbohydrate
CRR	Clinique romande de réadaptation
D <sub>max</sub>	Methods for calculating lactate threshold by Bishop et al. [45]
Dmod	Modified D <sub>max</sub> threshold
FIO <sub>2</sub>	Fraction of inspired oxygen
UD	Self usual mixed Western-style diet
HR	Heart rate
KD	Ketogenic diet
ICKD	Isocaloric ketogenic diet
KB	Ketobodies
LT	Lactate threshold
P	Power
PaCO <sub>2</sub>	Partial arterial carbodioxide pressure
PaO <sub>2</sub>	Partial arterial oxygen pressure
PIO <sub>2</sub>	Inspiratory oxygen pressure
Q-AAP	Physical activity aptitude questionnaire
RPE	Rating of perceived exertion
SEMS	Sport and Exercise Medicine Switzerland
VO <sub>2</sub> max	Maximal oxygen uptake

### Acknowledgements

The completion of this study was possible by collaboration between the Clinique romande de readaptation (CRR), University hospital of Geneva (UNIGE), Valais-Wallis School of Health Sciences (HES-SO), Digital epidemiology lab, EPFL, Central institute of hospital (HVS), the laboratory of Lausanne university hospital (CHUV) and the Swiss Olympics medical center of the CRR. We would like to thank the *Groupe d'intervention medical en Montagne* (GRIMM), the Sport & Exercise Medicine Switzerland (SEMS) and Follomi Sports (SA) for the support.

### Author contributions

NC Participated in designing the methods, conceived and planned the experiment, carried out the experiments, contributed to the interpretation of the results and took the lead in writing the manuscript. LA Participated in designing the methods and to shape the research, helped with planning the experiments, contributed to the interpretation of the results, supervised the whole process of this study and provided critical feedback of the manuscript. MFR Discussed the design of the study and the relevance of controls, contributed to the interpretation and presentation of data. PV Participated in designing the methods, helped with planning the experiments, contributed to the statistical analysis and interpretation of the results, and provided critical feedback for the manuscript. AR and MD Provided technical support for the maximal graded bike test and contributed to interpretations of the results. All authors have read the manuscript, provided critical feedback, and approved the final version.

### Funding

This study was funded by collaboration between the Clinique romande de réadaptation, Sion, Switzerland (CRR), the University Hospitals of Geneva (HUG, department of Medicine) and the Valais-Wallis School of Health Sciences (HES-SO). Partial financial support was received from the Mountain medical intervention group (GRIMM) and Follomi Sports SA.

### Availability of data and materials

The data that support the finding of this study are available on request from the corresponding author (N.C.). The data are not publicly available due to legal restriction of the rehabilitation clinic where the data were assessed.

## Declarations

### Ethics approval and consent to participate

Approval was obtained from ethics committee of CER-VD. Trial Nr. 2020-00427. Registered 18.08.2020—Prospectively registered. Clinical trial registration NCT05603689 (Clinicaltrials.gov). The procedure used in this study adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from all individual participants in the study.

### Consent for publication

The authors affirm that human research participants provided informed consent for publication of their data.

### Competing interests

The authors have no relevant financial or non-financial interest to disclose. M. De Riedmatten and N. Chiarello are affiliated with Groupe d'intervention medical en Montagne (GRIMM), which gave partial funding.

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Received: 16 March 2022 Accepted: 13 March 2023

Published online: 20 March 2023

## References

- Costa RJS, Hoffman MD, Stellingwerf T. Considerations for ultra-endurance activities: part 1-nutrition. *Res Sports Med*. 2019;27(2):166–81.
- Sansone M, Sansone A, Borriore P, Romanelli F, DiLuigi L, Sgrò P. Effects of ketone bodies on endurance exercise. *Curr Sports Med Rep*. 2018;17(12):444–53.
- Trimboli P, Castellana M, Bellido D, Casanueva FF. Confusion in the nomenclature of ketogenic diets blurs evidence. *Rev Endocr Metab Disord*. 2020. <https://doi.org/10.1007/s11154-020-09546-9>.
- Westman EC, Mavropoulos J, Yancy WS, Volek JS. A review of low-carbohydrate ketogenic diets. *Curr Atheroscler Rep*. 2003;5(6):476–83.
- Volek JS, Noakes T, Phinney SD. Rethinking fat as a fuel for endurance exercise. *Eur J Sport Sci*. 2015;15(1):13–20.
- Christensen EH, Hansen O III. Arbeitsfähigkeit und Ernährung I. *Skand Arch Physiol*. 1939;81(1):160–71.
- Bergström J, Hultman E. Muscle glycogen synthesis after exercise: an enhancing factor localized to the muscle cells in man. *Nature*. 1966;210(5033):309–10.
- Bergström J, et al. Diet, muscle glycogen and physical performance. *Acta Physiol Scand*. 2021. <https://doi.org/10.1111/j.1748-1716.1967.tb03720.x>.
- Helge JW. A high carbohydrate diet remains the evidence based choice for elite athletes to optimise performance. *J Physiol*. 2017;595(9):2775.
- Phinney SD, Horton ES, Sims EAH, Hanson JS, Danforth E, Lagrange BM. Capacity for moderate exercise in obese subjects after adaptation to a hypocaloric, ketogenic diet. *J Clin Invest*. 1980;66(5):1152–61.
- Ross AC, Caballero BH, Cousins RJ, Tucker KL, Ziegler TR. *Modern nutrition in health and disease*. Eleventh edn. Wolters Kluwer Health Adis (ESP); 2012. <https://jhu.pure.elsevier.com/en/publications/modern-nutrition-in-health-and-disease-eleventh-edition>.
- Achten J, Jeukendrup AE. Optimizing fat oxidation through exercise and diet. *Nutrition*. 2004;20(7–8):716–27.
- Prins PJ, Noakes TD, Welton GL, Haley SJ, Esbenschade NJ, Atwell AD, et al. High rates of fat oxidation induced by a low-carbohydrate, high-fat diet, do not impair 5-km running performance in competitive recreational athletes. *J Sports Sci Med*. 2019;18(4):738–50.
- Hu XF, Kenny TA, Chan HM. Inuit country food diet pattern is associated with lower risk of coronary heart disease. *J Acad Nutr Diet*. 2018;118(7):1237–1248.e1.
- Harvey KL, Holcomb LE, Kolwicz SC. Ketogenic diets and exercise performance. *Nutrients*. 2019;11(10):2296.
- Venables MC, Achten J, Jeukendrup AE. Determinants of fat oxidation during exercise in healthy men and women: a cross-sectional study. *J Appl Physiol*. 2005;98(1):160–7.
- Volek JS, Freidenreich DJ, Saenz C, Kunces LJ, Creighton BC, Bartley JM, et al. Metabolic characteristics of keto-adapted ultra-endurance runners. *Metabolism*. 2016;65(3):100–10.
- Sato K, Kashiwaya Y, Keon CA, Tsuchiya N, King MT, Radda GK, et al. Insulin, ketone bodies, and mitochondrial energy transduction. *FASEB J*. 1995;9(8):651–8.
- Anderson KA, Hirschey MD. Mitochondrial protein acetylation regulates metabolism. *Essays Biochem*. 2012;52:23–35.
- Cotter DG, Schugar RC, Crawford PA. Ketone body metabolism and cardiovascular disease. *Am J Physiol Heart Circ Physiol*. 2013;304(8):H1060–10766.
- Burke LM, Ross ML, Garvican-Lewis LA, Welvaert M, Heikura IA, Forbes SG, et al. Low carbohydrate, high fat diet impairs exercise economy and negates the performance benefit from intensified training in elite race walkers. *J Physiol (Lond)*. 2017;595(9):2785–807.
- Kreider RB, Wilborn CD, Taylor L, Campbell B, Almada AL, Collins R, et al. ISSN exercise & sport nutrition review: research & recommendations. *J Int Soc Sports Nutr*. 2010;7:7.
- Michalczyk M, Czuba M, Zydek G, Zając A, Langfort J. Dietary recommendations for cyclists during altitude training. *Nutrients*. 2016;8(6):377.
- Burke LM, Cox GR, Cummings NK, Desbrow B. Guidelines for daily carbohydrate intake. *Sports Med*. 2001;31(4):267–99.
- West JB, Luks AM, Schoene RB, Milledge JS. 15. Nutrition, metabolism and intestinal function. In: *High altitude medicine and physiology*. 5 edn. Wagner PD. New ideas on limitations to VO<sub>2</sub>max. *Exerc Sport Sci Rev*. 2000;28(1):10–4.
- Robergs RA, Quintana R, Lee Parker D, Frankel CC. Multiple variables explain the variability in the decrement in VO<sub>2</sub>max during acute hypobaric hypoxia. *Med Sci Sports Exerc*. 1998;30(6):869–79.
- Zając A, Poprzecki S, Maszczyk A, Czuba M, Michalczyk M, Zydek G. The effects of a ketogenic diet on exercise metabolism and physical performance in off-road cyclists. *Nutrients*. 2014;6(7):2493–508.
- Langfort J, Pilis W, Zarzeczny R, Nazar K, Kaciuba-Uściłko H. Effect of low-carbohydrate-ketogenic diet on metabolic and hormonal responses to graded exercise in men. *J Physiol Pharmacol*. 1996;47(2):361–71.
- Carr AJ, Sharma AP, Ross ML, Welvaert M, Slater GJ, Burke LM. Chronic ketogenic low carbohydrate high fat diet has minimal effects on acid-base status in elite athletes. *Nutrients*. 2018;10(2):236.
- Heatherly AJ, Killen LG, Smith AF, Waldman HS, Seltmann CL, Hollingsworth A, et al. Effects of Ad libitum low-carbohydrate high-fat dieting in middle-age male runners. *Med Sci Sports Exerc*. 2018;50(3):570–9.
- Bailey CP, Hennessy E. A review of the ketogenic diet for endurance athletes: performance enhancer or placebo effect? *J Int Soc Sports Nutr*. 2020;17(1):33.
- Margolis LM, Wilson MA, Whitney CC, Carrigan CT, Murphy NE, Radcliffe PN, et al. Acute hypoxia reduces exogenous glucose oxidation, glucose turnover, and metabolic clearance rate during steady-state aerobic exercise. *Metabolism*. 2020;103:154030.
- Young AJ, Berryman CE, Kenefick RW, Derosier AN, Margolis LM, Wilson MA, et al. Altitude acclimatization alleviates the hypoxia-induced suppression of exogenous glucose oxidation during steady-state aerobic exercise. *Front Physiol*. 2018. <https://doi.org/10.3389/fphys.2018.00830/full>.
- Warburton DE, Jamnik VK, Bredin SS, McKenzie DC, Stone J, et al. Evidence-based risk assessment and recommendations for physical activity clearance: an introduction. *Appl Physiol Nutr Metab*. 2011. <https://doi.org/10.1139/h11-060>.
- Stafstrom CE, Rho JM, editors. *Epilepsy and the ketogenic diet*. Totowa: Humana Press; 2004. p. 352.
- Lovis A, Duplain H, Nicod L, Scherrer U, Sartori C. Maladies liées à l'altitude et consultation de médecine de montagne. *Forum Med Suisse*. 2012;12(41):783–9.

38. Dr Micah Gross, Office fédéral du sport OFSPO Haute école fédérale de sport de Macolin HEFSM Département Sport de performance. Manuel de diagnostic de performance. 2015. [https://www.swissolympic.ch/dam/jcr:6ea9b202-857b-4561-81de-bbc799b6b690/Diagnostic\\_de\\_performance\\_manual\\_160201\\_FR.pdf](https://www.swissolympic.ch/dam/jcr:6ea9b202-857b-4561-81de-bbc799b6b690/Diagnostic_de_performance_manual_160201_FR.pdf).
39. Williams N. The Borg rating of perceived exertion (RPE) scale. *Occup Med.* 2017;67(5):404–5.
40. Williamson DH, Mellanby J. D-(–)-3-Hydroxybutyrate. In: Bergmeyer HU, editor. *Methods of enzymatic analysis*. 2nd ed. Cambridge: Academic Press; 1974. p. 1836–9.
41. Lawler J, Powers SK, Thompson D. Linear relationship between  $\text{VO}_2\text{max}$  and  $\text{VO}_2\text{max}$  decrement during exposure to acute hypoxia. *J Appl Physiol.* 1988;64(4):1486–92.
42. Cymerman A, Reeves JT, Sutton JR, Rock PB, Groves BM, Malconian MK, et al. Operation Everest II: maximal oxygen uptake at extreme altitude. *J Appl Physiol.* 1989;66(5):2446–3253.
43. Dill DB, Adams WC. Maximal oxygen uptake at sea level and at 3,090-m altitude in high school champion runners. *J Appl Physiol.* 1971;30(6):854–9.
44. Cheng B, Kuipers H, Snyder AC, Keizer HA, Jeukendrup A, Hesselink M. A new approach for the determination of ventilatory and lactate thresholds. *Int J Sports Med.* 1992;13(7):518–22.
45. Bishop D, Jenkins DG, Mackinnon LT. The relationship between plasma lactate parameters,  $\text{Wpeak}$  and 1-h cycling performance in women. *Med Sci Sports Exerc.* 1998;30(8):1270–5.
46. Faude O, Kindermann W, Meyer T. Lactate threshold concepts: how valid are they? *Sports Med.* 2009;39(6):469–90.
47. Allowances NRC (US) S on the TE of the RD. Energy. Recommended Dietary Allowances: 10th Edition. National Academies Press (US); 1989 [cité 10 mars 2022]. <https://www.ncbi.nlm.nih.gov/books/NBK234938/>.
48. Phinney SD. Ketogenic diets and physical performance. *Nutr Metab (Lond).* 2004;1(1):2.
49. Dempsey JA, Wagner PD. Exercise-induced arterial hypoxemia. *J Appl Physiol.* 1999;87(6):1997–2006.
50. Paralikar SJ, Paralikar JH. High-altitude medicine. *Indian J Occup Environ Med.* 2010;14(1):6–12.
51. Robergs RA, Roberts S. *Exercise physiology: exercise, performance, and clinical applications*. St. Louis: Mosby; 1997.
52. Akalan C, Kravitz L, Robergs RR.  $\text{VO}_2\text{max}$ : essentials of the most widely used test in exercise physiology. *ACSM's Health Fitness J.* 2004;8(3):5–9.
53. Morton RH, Billat V. Maximal endurance time at  $\text{VO}_2\text{max}$ . 9.
54. Wagner PD. A theoretical analysis of factors determining  $\text{VO}_2\text{max}$  at sea level and altitude. *Respir Physiol.* 1996;106(3):329–43.
55. Yoshida T, Udo M, Chida M, Ichioka M, Makiguchi K, Yamaguchi T. Specificity of physiological adaptation to endurance training in distance runners and competitive walkers. *Eur J Appl Physiol.* 1990;61(3):197–201.
56. Helge JW. Long-term fat diet adaptation effects on performance, training capacity, and fat utilization. *Med Sci Sports Exerc.* 2002;34(9):1499–504.
57. McLellan TM, Gass GC. The relationship between the ventilation and lactate thresholds following normal, low and high carbohydrate diets. *Eur J Appl Physiol Occup Physiol.* 1989;58(6):568–76.
58. Rogers MA, Hagberg JM, Martin WH, Ehsani AA, Holloszy JO. Decline in  $\text{VO}_2\text{max}$  with aging in master athletes and sedentary men. *J Appl Physiol.* 1985;68(5):2195–9.
59. Bergman BC, Brooks GA. Respiratory gas-exchange ratios during graded exercise in fed and fasted trained and untrained men. *J Appl Physiol.* 1999;86(2):479–87.
60. Hansen JE, Hartley LH, Hogan RP. Arterial oxygen increase by high-carbohydrate diet at altitude. *J Appl Physiol.* 1972;33(4):441–5.
61. Gallo de Moraes A, Surani S. Effects of diabetic ketoacidosis in the respiratory system. *World J Diabetes.* 2019;10(1):16–22.
62. Pierce NF, Fedson DS, Brigham KL, Mitra RC, Sack RB, Mondal A. The ventilatory response to acute base deficit in humans. Time course during development and correction of metabolic acidosis. *Ann Intern Med.* 1970;72(5):633–40.
63. Lawless NP, Dillard TA, Torrington KG, Davis HQ, Kamimori G. Improvement in hypoxemia at 4600 meters of simulated altitude with carbohydrate ingestion. *Aviat Space Environ Med.* 1999;70(9):874–8.
64. West JB. High-altitude medicine. *Am J Respir Crit Care Med.* 2012;186(12):1229–37.
65. Kitabchi AE, Wall BM. Diabetic ketoacidosis. *Med Clin N Am.* 1995;79(1):9–37.
66. Greenhaff PL, Gleeson M, Maughan RJ. The effects of diet on muscle pH and metabolism during high intensity exercise. *Eur J Appl Physiol.* 1988;57(5):531–9.
67. Berglund B. High-altitude training. *Sports Med.* 1992;14(5):289–303.
68. Praz C, Léger B, Kayser B. Energy expenditure of extreme competitive mountaineering skiing. *Eur J Appl Physiol.* 2014;114(10):2201–11.
69. Praz C, Fasel B, Vuistiner P, Aminian K, Kayser B. Optimal slopes and speeds in uphill ski mountaineering: a laboratory study. *Eur J Appl Physiol.* 2016;116(5):1011–9.

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