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

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Abstract

Background: Ketogenic diet (KD) reduces carbohydrate (CHO) daily ingestion replacing majority of calories by fat. KD is of increasing interest among athletes for evidence about VO_2max increment. This is the principal performance limitation in high altitude. We so examine the tolerance of a 4-week isocaloric ketogenic diet (ICKD) under simulated hypoxia, the possibility of evaluating participant's ICKD performances benefit by a maximal graded exercise bike test in hypoxic condition and assess data on its effect on performance markers and arterial blood gases.

Methods: Using a randomised single blind cross-over model, 6 recreational mountaineers (24 to 44 years) completed a 4-week ICKD either followed or preceded by a 4-week habitual mixed western diet (HD). Performance parameters (VO_2max, lactate threshold (LT), peak power (P_{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 post 4-week HD and post 4-week ICKD under hypoxic condition.

Results: We analysed data of 6 participants. Hypoxia led to a decreased performance in all participants. ICKD diet decreased their PaO_2 by -14.5% and increased their VO_2max by +7.3% and P_{peak} by +4.7%.

Conclusion: All participants except one could complete the ICKD. VO_2max improved with ICKD under the hypoxia condition. ICKD is thus an interesting alternative to CHO dependency for endurance performances at high-altitude (1500-3500 m) including high-altitude training sessions and high-altitude races. Nevertheless, the PaO_2 decrement with ICKD remains a significant limitation of ICKD in very high- to extreme-altitude (>3500 m.). *Trial registration*: CER-VD, *2020-00427. Registered 18.08*.2020 - Prospectively registered

Background

High-fat / low- carbohydrate diet (or ketogenic diet (KD)) is an innovative strategy proposed to enhance endurance performances if exercise duration is long enough (e.g.>4h) and exercise intensity is low enough (50–60% VO_2max)(1). This strategy restricts daily carbohydrate consumption lower than 30–50 $gr.d^{-1}$, maintaining low to moderate quantities of proteins and so replacing the majority calories with fat(2, 3).

In a human evolutionary perspective (> 2mio. Years), fat played a dominant role in energy supply(4). However, the advent of agriculture shifted the major calories contributor from fat to carbohydrate (CHO) (5).

A century ago, modern science tried to determine the ideal human diet to optimize performance with several historical studies conducted between 1939–1967(6–8). The idea that only high CHO diet could optimize performance gained in credence. Until today, exercise and sport guidelines recommend a greater amount of CHO consumption (250–1200 $gr.d^{-1}$) than usual while exercising(9, 10).

However, in the early 1980s, a link between high fat diets and exercise capacity has been demonstrated. Phinney, S.D. et al. (1980)(11) showed an unimpaired performance in patient with KD(12). Since then, there is increasing evidence that body can adapt to use fat as primary fuel during submaximal exercise(13). Indeed, KD induces metabolic changes and increases the fat oxidation rate (from 0.4–0.6 $gr.min^{-1}$ to 1.2–1.3 $gr.min^{-1}$.) probably by affecting the mitochondrial respiratory chain(2, 14–16). Furthermore, peak fat oxidation rate occurs in intensity between 47–64% of maximal oxygen uptake (VO_2max)(1, 13). Gradually, the idea gained that CHO consumption may limit athlete's performances when competing for an extended time(1, 5, 17, 18). It was shown that a high-CHO diet is associated with higher post-exercise lactate accumulation (Carr. A.J, et al. 2018)(19). Other argued that the glycogen supply provided by CHO is limited compared to a virtually endless fat store (Harvey 2019)(18). High-fat diet on the contrary, leads to a biological ketosis in forcing the liver to produce ketone bodies (KB) by diverting acetyl-CoA(2). Studies postulates that KB probably affects positively slow-muscle fibers (type I) and negatively fast-muscle fibers (type II) which potentially can enhance endurance exercises (Sato 1995)(2). KB are also suggested to be more energy efficient than glucose (Cotter 2013(20); Harvey 2019(18)).

High altitude mountaineering is said to be invented in middle XVIII century by H.B. de Saussure. Originally limited to scientists and conquistadors, mountaineering as a sport really emerged much later. The first mount Everest ascent without oxygen in 1978 contributed to this aspect. Since then, plethora of studies has explored the major performance limitation at high altitude. Diminished inspiratory oxygen pressure (PIO_2) which increases in altitude(21) is critical for the oxygen tissue delivery and is responsible for the reduction of VO_2max(22).

There is some evidences that KD positively increase VO_2max in normoxic conditions(19, 23–26), but this aspect has never been explored in hypoxic condition. However, subjective benefit of high fat diet in high altitude was praised by the extreme high-altitude mountaineer *Erhard Loretan*, e.g. at Everest base camp in 1986. Furthermore, hypoxia is known to induce a diminution of CHO oxidation when it is ingested prior to exercise increasing the value of fat in altitude activities(27, 28).

Based on the aforementioned information, we hypothesized that a 4-week KD has positive effects on VO_2max 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 ketogenic diet (ICKD) where calories are in line with total energy expenditure.

Methods

This pilot study used a single blind randomised cross-over clinical pilot trial. The study took place in Switzerland at CRR (Clinique romande de réadaptation, Sion). The protocol has been approved by CER-VD (*Project-ID: 2020 – 00427*).

Study aim

This pilot study aimed to assess (a) the tolerance of a non-standardized 4-week isocaloric ketogenic diet (ICKD) in healthy, recreational mountaineers, (b) the possibility of evaluating participant's ICKD performances benefit in hypoxic condition by a maximal graded exercise bike test and (c) to get data as regard to the benefit of a 4-week ICKD on VO_2max during a maximal graded performance test under simulated hypoxic conditions. Further, data concerning lactate threshold (LT) values (P_{LT}, HR_{LT}), peak values (P_{peak}, HR_{peak}), subjective Borg rating of perceived exertion (RPE) and oxygenation status (blood gases) were recorded too.

Participants

8 recreational mountaineers were recruited to participate. Inclusion conditions were familiarity with altitude (> 2500 meter above sea level) and aged between 20 to 45 years. Participants were enrolled after having signed the informed consent.

No sample size calculation was done for this study as we planned a pilot study to gather information about diet tolerance/acceptance, the feasibility of the testing procedure as well as to collect preliminary data about the benefit of an ICKD diet on VO_2max in healthy persons.

Study procedure

Once a person signed the informed consent, he was invited for a consultation during which a medical doctor explained him 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 using the physical activity aptitude questionary (Q-AAP)(29). We assessed participant's ability for ICKD and exposition to hypoxia by two other self-developed questionnaires using known contra-indication to KD(30), previously experienced exposition to hypoxia and predisposing factors to acute mountain sickness(31).

The participant was then asked to do a maximal graded exercise bike test (performance test) to assess his/her baseline performance under normoxic condition (T0N) and hypoxic condition (T0H). This test was conducted under supervision of a sport scientist and a medical doctor. The medical doctor was also responsible to collect an arterial blood sample after a rest of 5 minutes post-exercise.

After this test, participants were randomly assigned to group A or group B by a collaborator who was not involved in the study protocol. Each participant received a self-destinated letter with his group attribution which permitted to blind the investigators. Group A began with a 4-week HD (T1) followed by 4-week ICKD (T2) while group B began with a 4-week ICKD (T1) followed by 4-week HD (T2).

Each 4-week diet period was terminated with a performance test under hypoxic condition (same procedure as at baseline but under hypoxic condition) The study design is represented in Fig. 1.

Maximal graded exercise bike tests

The initial charge was 60–90 W depending on training status and sex. The resistance was incremented every three minutes by 30W until the participants exhaustion. Interruption condition were a clear decrease of cycling frequency (< 70.min^{-1}) or stop of cycling(32). Oxygen respiratory flow (VO_2), carbon dioxide respiratory flow (VCO_2), hearth rate (HR) and delivered power (P) were measured (*Metalyzer 3B, Cortex*) until test interruption. Maximal values are defined as peak values. In addition, capillary blood lactate (B-Lac) was measured thirty seconds before the end of each incrementation. Finally, we used a Borg RPE(33) at the end of the test to assess participant subjective perceived exertion of the physical work.

Hypoxia during performance test was achieved in a simulated altitude facility (hypoxic room) with hypoxic generator (*ATS altitude, Sydney Australia*) by lowering the fraction of inspired oxygen (FIO_2). This simulating a very high-altitude of 4500 m.

Study intervention

The 4-week isocaloric ketogenic diet (ICKD)

ICKD definition was based on works of Sansone (2018)(2) and Trimboli (2020)(3). We defined ICKD as a daily CHO ingestion less than 30–50 gr.d^{-1}, without fats limitation. Participant self-selected their own diet based on a list of advised and forbidden foods developed to fit the definition of ICKD. There were no calories restriction instruction. A regular contact was maintained with all the participants during the study with every time availability to answer dietary participant's questions.

The 4-week self habitual mixed western diet (HD)

There were no food limitations. Participant were instructed to fit as much as possible to their usual diet.

Participants were instructed to track their 4-week ICKD and HD 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.

Blood analysis

An arterial blood sample was taken after a rest of 5 minutes at the end of each performance test. Under hypoxic condition the participants remained into the hypoxic room for the blood collection. The blood samples were analysed on an ABL800 FLEX blood gas analyzer (Radiometer, Denmark) within 10 minutes 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})) was automatically calculated using the Henderson-Hasselbalch equation.

Venous blood was also sampled after each test. The venous blood was put into a perchloric acid-tube and then frozen at -80°C. All samples were analyzed within 3 months for β-OHB (β-hydroxybutyrate) and AcAc (acetoacetate) with enzymatic analysis (Wiliamson, 1974(34)). Reference values (percentile 2.5–

97.5) provided by the laboratory (CHUV, Switzerland) were β-OHB: 58–170µmol.L^{-1} and AcAc: 18–78µmol.L^{-1}.

Statistical analysis

We used a descriptive statistical analysis for (a) diet tolerance, (b) performance values under normoxic and hypoxic condition and (c) performance values under HD and ICKD. Performance test results under normoxic and hypoxic condition were expressed as mean (± standard deviation). Because of limited sample size (n = 6) no confidence intervals nor p-value were calculated.

To assess diet tolerance, we analysed the number of dropouts and reported side effects. Diet tolerance was further assessed by daily CHO, fat, proteins abundance, energy expenditure, and blood analysis on KB including β-OHB and AcAc. We calculated daily median values for CHO, fat, proteins and energy expenditure of each six participant. Based on that, we calculated median daily CHO, fat, protein consumption and energy expenditure for all participants. Participant adherence to ICKD was checked by their daily CHO intake. If the daily CHO intake was more than 50gr and if β-OHB was < 170µmol.L^{-1} the participant was excluded from statistical data analysis and dropped out.

Feasibility of maximal graded exercise was assessed by comparing the values under normoxia with those under hypoxia. These values were then expressed as percentage difference in “median” (“minimal values” to “maximal value”). The authors checked then if these values are superposable to previously reported performance drops under acute hypoxia(35–37).

The effect of ICKD on performance is also expressed in percentage difference in “median” (“minimal values” to “maximal value”). This was calculated by comparing the values of performance parameter after the ICKD diet and the values of performance parameter after the HD diet. For Group A, HD values are T1. For Group B HD values are T0H. VO_2max performance parameter after ICKD (hypoxia) compared to HD (hypoxia) was used as primary outcome. For secondary outcome, performance parameters like lactate threshold (LT) values (P_{LT}, HR_{LT}), peak values (P_{peak}, HR_{peak}), subjective values (Borg RPE) and oxygenation status (blood gases) were analysed. LT determination was based on D_{max}-model established in 1992(38) which used the maximal perpendicular distance from the line connecting the start with the endpoint of the lactate curve. We used “*modified D_{max} threshold*” (D_{mod}) which is an updated D_{max}-model by Bishop et al.(39). It eliminates the influence of start intensity and maximal effort. Such it determines the LT as the moment when a rapid change in the inclination of the blood lactate curve occurs. This matches with the maximal lactate steady state reflecting the anaerobic threshold(40).

Results

Diet Tolerance

At the beginning 8 participants were enrolled the study. One participant dropped out after the second performance test, but this was due to a schedule mismatch rather than a regimen intolerance. In addition,

the data of another participant were excluded from data analysis because of abnormal high daily CHO ingestion (> 50gr.d^{-1}) and low β-OHB (< 170µmol/L) which led to suspect invalid data (Fig. 2).

Frequently reported side effects were weight loss and gastro-intestinal disorder. Subjective exercise load perception by RPE(33) scale after ICKD scale were: similar to reference values for two participant, increased for three participants and decreased for one participants... HD and ICKD characteristics are presented in Table 1.

HD and ICKD follow-up: Participant's 4-week HD diet was characterized by median ingested CHO: 197 gr.d^{-1}. Median post HD β-OHB: 44.0µmol/L and AcAc: 22.5 µmol/L were within reference values. The dietary characteristics of the 4-week ICKD showed median ingested CHO: 40 gr.d^{-1}. Median post-4-week ICKD β-OHB: 288.0 µmol/L and AcAc: 80.0 µmol/L were without reference values fixed by the laboratory.

Recorded data showed an excess in CHO daily intake and too low β-OHB blood concentration for one participant. His 4-week HD were characterized by median CHO: 259 gr.d^{-1} And his4-week ICKD were by median CHO: 67 gr.d^{-1}β-OHB / AcAc blood concentration were at 41.0 / 23.0 mmol.L^{-1} for HD and 152.0 / 56.0 mmol.L^{-1} under ICKD. This participant was not included in statistical analysis.

Table 1
Participant HD and ICKD characterization

	HD			**ICKD**		
	Median	Extremes		Median	Extremes	
CHO *(gr.d^{-1})*	197	152	321	40	21	49
Proteins *(gr.d^{-1})*	82	51	122	97	51	169
Fat *(gr.d^{-1})*	93	63	140	143	43	164
Energy *(Kj.d^{-1})*	7774	6366	12603	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

Table 1: Recorded data for HD and ICKD diet characteristics with median, smallest, and largest values showing adherence to ICKD diet. **β-OHB** and AcAc blood concentration are also showed. Reference values (percentile 2.5–97.5) provided by the laboratory (CHUV, Switzerland) are for β-OHB: 58–170µmol.L^{-1} and for AcAc: 18–78µmol.L^{-1}.

Feasibility of the maximal graded exercise bike test under hypoxia

We used expected and previously characterised performance decrease under hypoxia(35–37) for evaluating feasibility of the performance test and trustworthiness of the recorded values. There were no adverse events related to the combination of 4-week ICKD, hypoxia exposure and maximal graded exercises bike test.

Effect of hypoxia: We used a normobaric (940–980 hPa) hypoxic (FIO_2 = 12.7–12.9%) room simulating an altitude of ~ 4500m. The results of the performance test under normoxic conditions at baseline are presented in Table 2 as mean (± SD). Measured effect of hypoxia are expressed as the median difference with normoxic values in percent. Performance values for VO_2max: -27.1%, P_{LT}: -28.6% and P_{peak}: -22.4% clearly decreased under hypoxic conditions. Arterial blood samples showed a reduction of PaO_2 by -50.9% while pH, PaCO2 and HCO3- all remained unaffected. Smallest and largest differences are also indicated

Table 2
Differences in percentage (%) between T0N and T0H assessing effect of hypoxia.

	Normoxia		**Effect of hypoxia (%)**		
	Mean (± SD)		**Median**	**Extemes**	
VO_2max *($ml.kg^{-1}.min^{-1}$)*	44.6 (5.8)	*(%)*	*-27.1*	*-36.5*	*-20.3*
P_{LT} *(W)*	203 (64)	*(%)*	*-28.6*	*-34.6*	*-17.9*
P_{peak} *(W)*	266 (65)	*(%)*	*-22.4*	*-30.8*	*-12.8*
HR_{LT} *($beat.min^{-1}$)*	156 (23)	*(%)*	*2.0*	*-7.1*	*17.6*
HR_{peak} *($beat.min^{-1}$)*	183 (17)	*(%)*	*-5.4*	*-15.0*	*-1.9*
B-Lac_{peak} *($mmol.L^{-1}$)*	10.7(2.2)	*(%)*	*-0.8*	*-28*	*16.1*
PaO_2 *(kPa)*	17.8 (2.2)	*(%)*	*-50.9*	*-71.1*	*-12.2*
pH	7.24 (0.06)	*(%)*	*0.15*	*-0.59*	*2.22*
$PaCO_2$ *(kPa)*	3.8 (0.2)	*(%)*	*-9.6*	*-19.5*	*5.9*
HCO_3^- *($mmol.L^{-1}$)*	11.9 (2.1)	*(%)*	*0.0*	*-0.2*	*0.1*

Table 2: *VO_2max*: maximal oxygen uptake; *LT*: lactate threshold; *P*: power; *HR*: hearth rate; *B-Lac*; blood lactate; PaO_2: Partial oxygen arterial pressure; *$PaCO_2$*: Partial carbon dioxide arterial pressure.

Hypoxia induced a clear decrease in VO_2max, P_{LT} and P_{peak} performance parameter recorded. PaO_2 also clearly decrease with hypoxia exposure.

ICKD effect on performance

Performance test results under hypoxic condition at baseline are presented as mean (± SD) in Table 3. Keeping the cross-over design, hypoxic baseline values (HD) are at T1 for Group A and T0H for group B. Effect of ICKD on performance tests values was assessed by comparing parameter values T1 with T2 (Group A) and T0H with T1 (Group B).. This is presented as median percentage differences and extremes (Table 3). Return to normal situation could be assessed only in group B by comparing performance values of T0H and T2.

Effect of ICKD: Performance values for VO_2max: +7.3%; P_{peak}: 4.7%; HR_{peak}: +3.6% and P_{LT}: +0.7% increased but with a large interindividual variability. bLa_{base} and bLa_{peak} decreased by respectively − 21.0% and − 8.8%. Arterial sample showed a clear PaO_2 decrease of -14.5%. Other parameter pH and PCO_2 and HCO_3can be considered as stable.

In Group B, the cross-over design allowed to assess the return to normal situation when switching again from a 4-week ICKD to a 4-week HD. We so compared T0H and T2 for the three participants in group B which should be theoretically the same value. We expressed it in percentage of difference between T0H and T2. Interestingly only PaO2: 1.4% returned to initial value. We did not observe a return to initial values for VO_2max: 18.1%, Ppeak − 8.3%, and PLT:3.3%.

Individual values

Individual performance and blood gas parameters at baseline (TO_N), after HD and after ICKD are listed in Table 4. This allowed to classify six participants in either ICKD-responder or ICKD-non-responder groups (Table 5). Four participants were ICKD-responders showing an increase in VO_2max and P_{peak}. P_{LT} is used for further sub-division of ICKD-responder depending on its modulation. Figure 3 shows B-Lac and HR curves after HD or ICKD, as well as at TO_N for participants Nr 6 and 8. These are considered as ICKD-responder on VO_2max and peak parameters. We noticed for one participant (Nr. 2) a particular large decrease in HR_{peak} (-14.9%) with hypoxia exposition. Interestingly, ICKD clearly allowed a return to normality for HR_{peak} values (+ 13.1%) confirmed by the cross-over analysis (-14.2%) which illustrated the effect of the ICKD for ICKD-responders.

Table 3
Difference in percentage (%) between ICKD and HD for assessing effect of ICKD intervention.

	Hypoxia		Effect of ICKD compared to HD (in %)		
	Mean (± SD)		Median	Extremes	
VO_2max *(ml.kg⁻¹.min⁻¹)*	*31.6 (3.4)*	*(%)*	*7.3*	*-16.8*	*25.5*
P_{LT} *(W)*	*147 (47)*	*(%)*	*0.7*	*-21.5*	*46.6*
P_{peak} *(W)*	*205 (48)*	*(%)*	*4.7*	*-7.1*	*11.1*
HR_{LT} *(beat.min⁻¹)*	*160 (22)*	*(%)*	*7.5*	*-5.4*	*23.8*
HR_{peak} *(beat.min⁻¹)*	*171 (15)*	*(%)*	*3.6*	*-2.6*	*15.2*
$B\text{-}Lac_{peak}$ *(mmol.L⁻¹)*	*10.3 (3.0)*	*(%)*	*-8.8*	*-40.9*	*17.1*
PaO_2 *(kPa)*	*9.0 (3.4)*	*(%)*	*-14.5*	*-32.1*	*-11.5*
pH	*7.28 (0.96)*	*(%)*	*0.28*	*0.08*	*1.62*
$PaCO_2$ *(kPa)*	*3.5 (0.4)*	*(%)*	*2.1*	*-23.3*	*11.8*
HCO_3^- *(mmol.L⁻¹)*	*12.0 (3.1)*	*(%)*	*-0.1*	*-0.3*	*0.1*

Table 3 : *ICKD*: isocaloric ketogenic diet; *HD*: Habitual mixed Western diet, *VO_2max*: maximal oxygen uptake; *LT*: lactate threshold; *P*: power; *HR*: hearth rate; *B-Lac*; blood lactate, *PaO_2*: Partial oxygen arterial pressure; *$PaCO_2$*: Partial carbon dioxide arterial pressure

Table 4
Individual values comparing performances after a HD and after an ICKD. Only VO_2max, P_{LT} and P_{peak} values are shown for baseline T0N.

	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 ($kg.m^{-2}$)		*22.3*	*23.2*	*24.6*	*23.4*	*21.3*	*19.9*
VO_2max ($ml.kg^{-1}.min^{-1}$)	*T0N*	*36.8*	*48.8*	*46.2*	*50.7*	*38.0*	*47.2*
	HD	*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_{LT} (W)	*T0N*	*114*	*261*	*266*	*224*	*136*	*215*
	HD	*81*	*186*	*182*	*159*	*89*	*103*
	ICKD	*79*	*146*	*168*	*165*	*124*	*151*
P_{peak} (W)	*T0N*	*180*	*310*	*340*	*300*	*195*	*270*
	HD	*140*	*240*	*194*	*210*	*123*	*190*
	ICKD	*150*	*250*	*186*	*195*	*140*	*200*
HR_{LT} ($beat.min^{-1}$)	*T0N*	*163*	*175*	*136*	*174*	*119*	*170*
	HD	*163*	*186*	*129*	*173*	*140*	*147*
	ICKD	*166*	*176*	*140*	*184*	*159*	*182*
HR_{peak} ($beat.min^{-1}$)	*T0N*	*194*	*194*	*162*	*197*	*162*	*191*
	HD	*186*	*165*	*152*	*190*	*159*	*184*
	ICKD	*190*	*190*	*148*	*193*	*167*	*194*
bLa_{peak} ($mmol.L^{-1}$)	*T0N*	*9.2*	*13.6*	*11.8*	*11.8*	*7.5*	*10.1*
	HD	*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*
	HD	*11*	*20*	*15*	*16*	*13*	*18*
	ICKD	*15*	*20*	*15*	*17*	*15*	*16*

	Test	*Nr. 1*	*Nr. 2*	*Nr. 3*	*Nr. 4*	*Nr. 6*	*Nr. 8*
PaO_2	*T0N*	*18*	*13.6*	*19*	*25.5*	*14*	*16.9*
(kPa)	*HD*	*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*
	HD	*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*
$PaCO_2$	*T0N*	*3.6*	*3.9*	*3.7*	*3.5*	*4.0*	*4.0*
(kPa)	*HD*	*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_3^-	*T0N*	*10.8*	*9.5*	*12*	*11.3*	*15.6*	*12.3*
($mmol.L^{-1}$)	*HD*	*8.4*	*10*	*15*	*10.5*	*16.5*	*12.4*
	ICKD	*9.4*	*14.7*	*16.8*	*8.5*	*20.2*	*10.9*

Table 4: *T0N*: Baseline test under normoxia; *HD*: Values after Habitual mixed Western diet under hypoxia; *ICKD*: Values after a isocaloric ketogenic diet under hypoxia; *VO_2max*: maximal oxygen uptake; *LT*: lactate threshold; *P*: power; *HR*: hearth rate; *bLa;* blood lactate;; *PaO_2*: Partial oxygen arterial pressure; *$PaCO_2$*: Partial carbon dioxide arterial pressure; *Nr.*: Subject number.

Table 5
ICKD-responder vs ICKD non-responder

Type	*Nr.*	*VO_2max*	*P_{LT} & HR_{LT}*	*P_{peak}*	*Remark*
ICKD responder	6;8	↑	↑	↑	ICKD shows improvement *regarding endurance and peak performance parameters.*
	1;2	↑	↓	↑	ICKD showed positive effects despite dropped in LT parameters. *Indeed, P_{peak} and VO_2max confirmed a benefit.*
ICKD Non-responder	4	↓	↑	↓	ICKD showed little to no response. *HD- and ICKD performance test can be considered as superposable.*
Non-assessable	*3*	↓	↓	↓	*Clear worsening of test performance.*

Table 5: *ICKD*: isocaloric ketogenic diet; VO_2max: maximal oxygen uptake ($ml.min^{-1}.kg^{-1}$); P_{LT}: power at lactate threshold (W); P_{peak}: Peak power (W); HR_{LT}: hearth rate at lactate threshold ($beat.min^{-1}$), Nr. : Participant's number

Figure 3

Performance test of ICKD-responders, ICKD Non-responder / non assessable. Nr. 6 (Id 6) and Nr. 8 (Id 8) showed improvement on endurance and peak performance parameter. 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.

Discussion

This novel study assessed the tolerance of an ICKD, the feasibility of a bike performance test under hypoxic condition and gathered preliminary data on effects of shifting from a HD to an ICKD on VO_2max under a simulated very high-altitude condition. We used maximal graded exercise bike tests for assessing endurance parameters and post-exercise arterial blood samples for assessing oxygenation and pH status. We hypothesized that a reduced CHO intake would increase VO_2max performance parameters under hypoxia. To our knowledge, these aspects were never investigated before.

Diet tolerance

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

With a median intake for HD and ICKD were below typical energy requirement(41) so participants were in negative energy balance.

Moreover, we identified two major difficulties for participants to follow the ICKD. First, high exercises load training turned out to be difficult during the first weeks of an ICKD diet.. Indeed, there was a subjective performance drop at the beginning of the new diet because of ICKD adaptation(42). Second, participants also reported a social impact during the ICKD.

Evaluating participant's ICKD performances benefit in hypoxic condition

We evaluated ICKD-induced performance benefit in hypoxic condition by using a maximal graded exercises bike test. The observed decrease of 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

Hypoxia induced for every participant a clear decrease in VO_2max by 13 $ml.kg^{-1}.min^{-1}$ (-27.01%), P_{peak} by 60W (-22.4%), and PaO_2 by 8.8 KpA(-50.9%) (Table 2). This was expected as the primary limitation for VO_2max under hypoxic conditions is oxygen tissue availability(43). Indeed, significant drop of VO_2max were previously reported with acute exposition to hypoxia(35–37). This results from the dropping of the barometric pressure with increasing altitude. Therefore PIO_2 and consequently oxygen transport decrease(35, 44). A research compilation by Robergs and Robert (1997) reported an average decrement of VO_2max by 8.7% per 1000m(45). Nevertheless, it is not appropriate to express an average value as there is a highly inter-individual variation in the reduction of VO2max depending on sea level VO_2max, gender, sea level LT and lean body mass(22). This may explain the large range of VO_2max drop (-36.5% to -20.3%) in our study. Furthermore, we noticed no significant difference in arterial blood pH, PaCO2 and HCO3.

Recorded data

Effect of ICKD on performance parameters

VO_2max (+ 7.3%) and P_{peak} (+ 4.7%) improvement with a 4-week ICKD under hypoxic condition in 4 out of 6 participants (Tables 3 and 4) do not allowed conclusion on the effects of KD. We noticed no performance marker which is systematically affected by ICKD. This recorded improvement has been similarly partially reported in normoxia(17, 25). VO_2max reflects the cardiorespiratory fitness(46) and is considered as a gold standard for measuring aerobic metabolism(47). A greater VO_2max indicates greater endurance capacity. Actual known factors influencing VO_2max are age, gender, heredity, body composition, state of training and mode of exercise(48).

KD has been newly identified as a potential positive factor for VO_2max(19, 23, 25, 26) by shifting mitochondrial metabolism(5, 17). These studies were summarized by Bailey et al. (2020)(17). They suggest that several factors such as genetic variation, trainability and or chronic substrate utilization may be influenced by KD, which consequently might increase VO_2max. The positive effect of ICKD on VO_2max under hypoxic condition observed in our study strengthened the idea that a high-fat ingestion might be beneficial for an endurance exercise under an acute hypoxia exposition.

In addition, further performance LT parameters were improved in two participants considered as ICKD-responder (Table 5). As showed in Fig. 3, B-Lac kinetic is lower with ICKD. Points for LT and maximal value are shifted to the right (right curve-shifting). HR kinetic is higher with ICKD. Points for LT and maximal values are at higher power (left curve shifting). LTs are performance indicators which strongly

correlate with endurance performances (40). It represents aerobic-anaerobic transition because lactate kinetic is highly related to the metabolic rate and less to oxygen availability(40). A higher workload to a given blood lactate concentration can be interpreted as an improved endurance capacity(49). Previous studies have reported a shift in B-Lac curve to higher workloads under KD condition(50). This phenomenon is still not fully understood but a relationship with a decreased glycolysis rate or limited lactate efflux from muscle due to reduced blood buffering capacity is hypothesized(23, 50). Further, depleted glycogen stores (due to e.g. ICKD) is a known factor leading to lower lactate blood concentration at the same work rate(51).

In this context and considering key performance parameters (VO_2max, P_{LT}, HR_{LT} and P_{peak}), we profiled the 6 participants either as ICKD responders or ICKD non-responders. ICKD responders showed a right-shifting in B-Lac kinetics (Fig. 3) which can be interpreted as a better performance test(49). Peak values (P_{peak} and VO_2max) also demonstrated a better performance. HR-curve left shifting showed a higher HR work range with ICKD. For ICKD non-responders, the intervention showed little to no effect, and ICKD- and HD-tests were superimposable. The variations were probably mostly due to the physical condition of the participants on that day. One participant clearly worsened his global ICKD-performance at every time point without clear explanation. Several factors could be a reason including bad day shape, or influence of ICKD on age-related VO_2max-factors like decline in maximal hearth rate, stroke volume, fat-free mass and arterio-veinous oxygen differences(52).

Effect of ICKD on blood gases

ICKD showed post-exercise PaO_2 decrease in all participants (-14.5%), a response confirmed in cross-over group B when returning to HD (+ 14.5%). A physiological approach allows explaining 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. It is well described that PAO_2 depends on the respiratory gas-exchange ratio (RER). RER is the ratio between CO_2 pulmonary output () and O_2 uptake () expressed as. This can be drawn to the alveolar air equation. RER depends in the steady state (like by resting) on the food metabolized(53). ICKD increases fat oxidation, lowers RER (~ 0.7) and consequently PAO_2 and PaO_2 decrease(53). Furthermore, maximal graded test is not a steady state and RER varies with exercises. Within a few minutes into recovery RER fall below 0.7 as ventilation declines and the CO_2 store re-increases(54). Decreased ventilation could also influence PaO_2. This is observed in respiratory failure, a well-known process in diabetic ketoacidosis. Ketosis is generating a respiratory response in form of hyperpnea(55). This leads to respiratory muscles fatigue (known as Kussmaul respiration)(56). ICKD could lead to a mismatch of the lung maintaining PaO_2 by a form of respiratory muscle fatigue due to KB.

Alternative explanation concerning influence of heart perfusion on PaO_2 is not relevant. Although, KB can influence heart flow, it increases the hydraulic efficiency of the heart rather than decreasing it(16). The higher heart flow rate leads to an increase in pulmonary venous blood admission. Finally, CHO are known

to increase PaO_2 at high-altitude by increasing the relative production of carbon dioxide so increasing the drive for ventilation(57).

Consistent with a previous study made by Hansen et al (1967)(54), ICKD worsened the hypoxemia in our simulated very high-to extreme altitude (> 3500 m.). This is a relevant limitation of using ICKD diets above a very high-altitude(44, 58), whereas at high-altitude (1500–3500 m.), PaO_2 is significantly diminished but with only minor impairments in oxygen transport (SaO_2 > 90%)(44). ICKD could therefore be used for this altitude.

Arterial blood sampling also showed a nonsignificant effects on the pH (+ 0.278%) post-exercise that is below analytical precision... It could be expected a increased pH asKB are acids known to induce ketoacidosis(59, 60). Nevertheless, Carr et al. (2018) contrasted these earlier beliefs by describing minimal effects of KD on acid base status in elite athletes(19). They also reported no statistical blood pH differences between high CHO vs high fat in pre- and post-exercises.. Blood pH stability is possibly due to higher exercise induced ventilation rate and so would increase the pH.

In conclusion our preliminary data showed a benefit of ICKD on performance parameters. A positive increment on VO_2max (primary outcome) and further LT performance parameter (secondary outcome) could be recorded. ICKD intervention decreased however PaO_2, a observation which is consistent with previous studies(54) and may limit ICKD application in very high altitude.

Further research

Further characterisation of ICKD benefits in high-altitude (1500-3500m.) is needed. Although there is an ICKD-induced hypoxemia, this may not impair oxygen delivery at this altitude. Furthermore, diet modifications (CHO vs. fat) could be an interesting path for improving acclimation or performances at high altitude and preventing acute mountain sickness. PaO_2 analysis during the whole effort would be needed for a complete assessment of influence of ICKD on blood gases. The cross-over design of the study is pertinent to assess effectiveness of ICKD.

Previous experience of participants with KD-like diet seems to be an effective supplementary inclusion criterion for diet tolerance. Moreover, it would also be interesting to assess if subjective perception of KD tolerance is matching with performance improvements and might help to predict whether a person is a responder or non responder. This would be possible with a simple assessment through a questionnaire without realizing 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 on VO_2max. 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 the conclusion on his effect. In addition, our design also limits the blood gases kinetic view during de

performance test. Moreover, our findings were obtained in acute simulated hypoxia limiting the practical implication for real-life high-altitude condition.

Conclusion

The present protocol shows the feasibility of evaluating recreational athlete performance benefits after ICKD by a maximal graded exercise test under hypoxia condition. Our study was successfully performed in combining ICKD, hypoxia and maximal graded exercise. This shows the feasibility of the present protocol. Although pilot data showed improved VO_2max with ICKD under hypoxia in 4 participants, this do not allowed conclusion about ICKD in this study. KD stay an interesting alternative to CHO dependency for endurance performances. This regime may be particularly interesting for endurance exercises in high-altitude (1500–3500 m.)(61) where only minor impairment exists in arterial oxygen transport(44). This could concern typical high altitude exercises like high-altitude trainings(61), high-altitude races(62), trail-running, mountaineering and ski-touring(63).

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_{max}	Methods for calculating lactate threshold by Bishop et al. (1992)
Dmod	Modified D_{max} threshold
FiO2	Fraction of inspired oxygen
HD	Self habitual mixed western diet
HR	Hearth rate
KD	Ketogenic diet
ICKD	Isocaloric ketogenic diet
KB	Ketobodies
LT	Lactate threshold
P	Power
$PaCO_2$	Partial arterial carbodioxide pressure
PaO_2	Partial arterial oxygen pressure
PiO_2	Inspiratory oxygen pressure
Q-AAP	Physical activity aptitude questionary
RPE	Rating of percieved exertion
SEMS	Sport & Exercices Medicine Switzerland
VO_2max	Maximal oxygen uptake

Declarations

Ethics approval: Approval was obtained from ethics committee of CER-VD. Trial registration *2020-00427. Registered 18.08.*2020 - Prospectively

registered, https://www.kofam.ch/de/studienportal/studie/52560/. The procedure used in this study adhere to the tenets of the declaration of Helsinki.

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

Consent to participate: Informed consent was obtained from all individual participants in the study.

Availability of data and material: 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

Competing interest: The authors have no relevant financial or non-financial interest to disclose. Authors M. De Riedmatten and N. Chiarello are affiliated to the GRIMM who gives partial funding

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Authors' contribution: N. C. Participated in designing the methods, conceived and planned the experiment, carried out the experiment, contributed to the interpretation of the results and took the lead in writing the manuscript. *L.A.* Participated in designing the methods an to shape the research, helped with planning the experiment, contributed to the interpretation of the results, supervised the whole process of this study and provided critical feedback of the manuscript. *M.F.R.* Discussed the design of the study and the relevance of controls, contributed to the interpretation and presentation of data. *P.V.* Participated in designing the methods, helped with planning the experiment, contributed to the statistical analysis and interpretation of the results, and provided critical feedback of the manuscript. A. R and M. D. provided technical support for 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.

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Figures

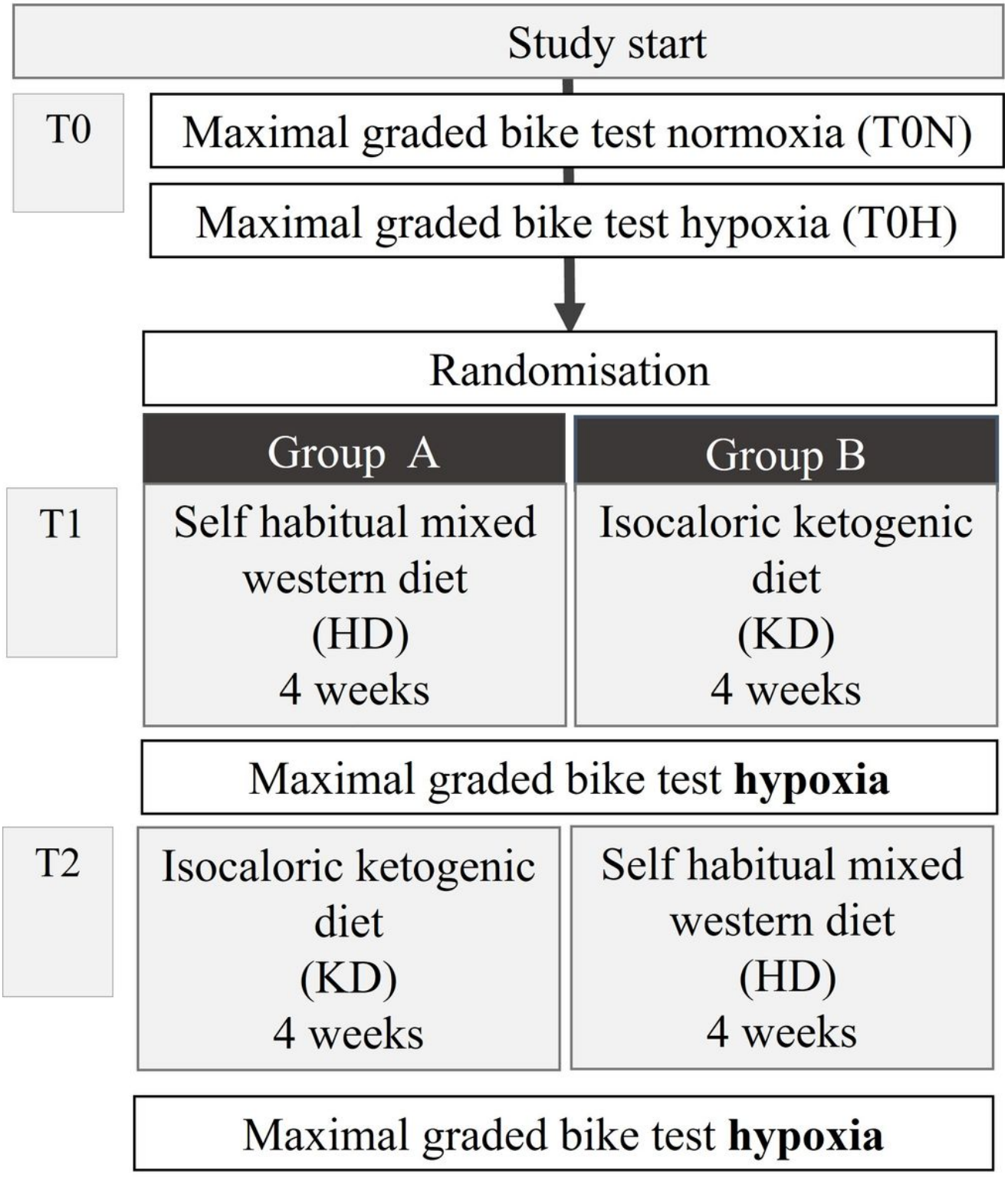


Figure 1

Study design

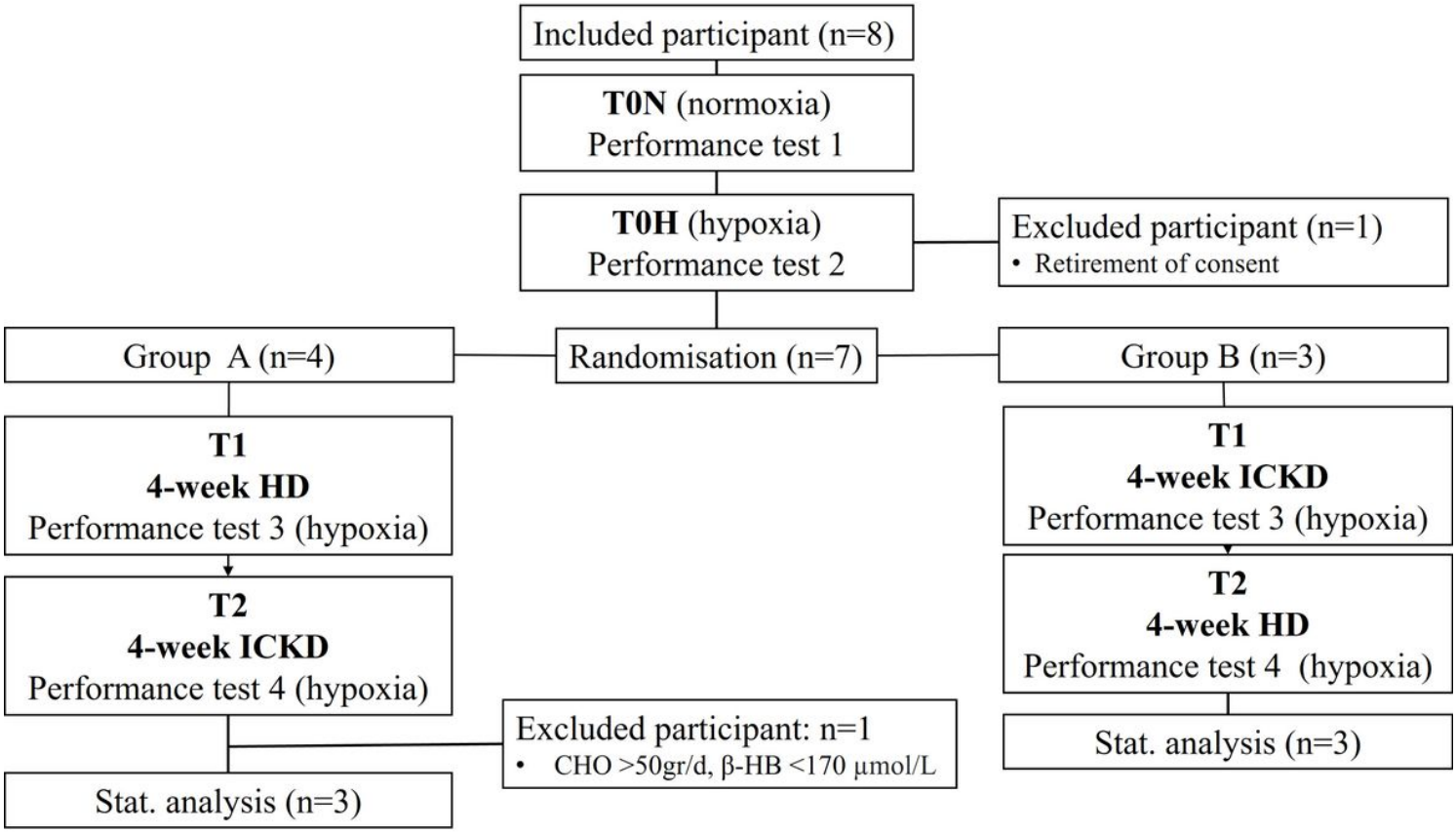


Figure 2

Flow chart. ICKD: isocaloric ketogenic diet; HD: Habitual mixed Western diet

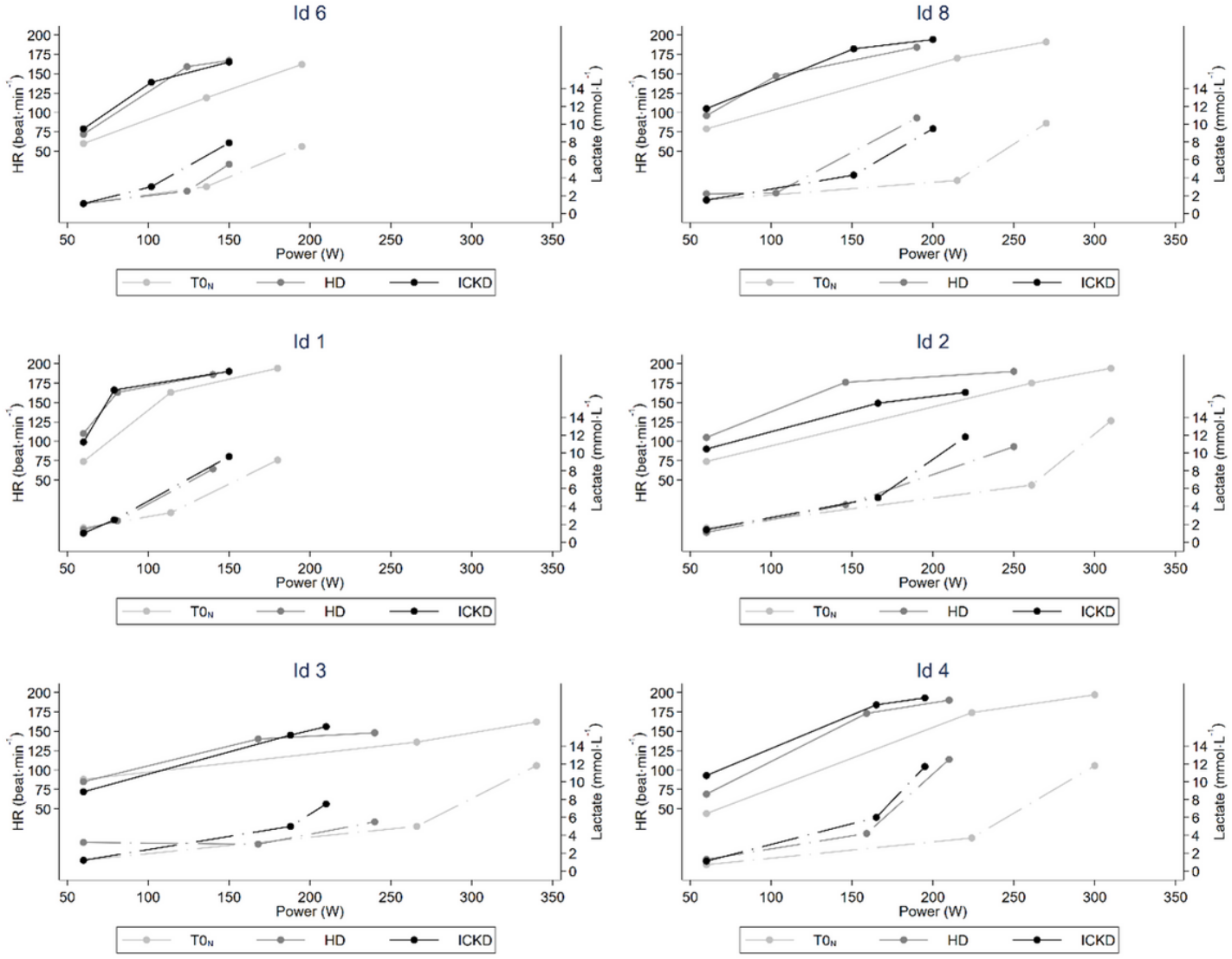


Figure 3

For comparison ICKD B-Lac and HR curves were drawn for T0N, HD, ICKD and . First point plugged represents values at the beginning of the test. Second point plugged is the values at LT and third point plugged is the maximal or peak value