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RESEARCH ARTICLE

Exogenous ketosis does not alter oxygenation, oxygen uptake kinetics, or whole-body efficiency during submaximal exercise in early high-altitude acclimatization

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Abstract

Exogenous ketosis, induced via ketone monoester (KE) ingestion, has been shown to attenuate hypoxia-induced blood, muscle, and brain deoxygenation and augment oxygen uptake ($\dot{V}O_2$) under acute normobaric hypoxia. However, its effects on exercise responses during early acclimatization at terrestrial high-altitude remain unexplored. Thirty-four healthy, active adults completed four exercise sessions: one near sea level and then once per day during a 3 day altitude sojourn (3,375 m), with regular KE or placebo ingestion. Pulmonary gas exchange, minute ventilation, cardiac output, pulse oxygen saturation, skeletal muscle tissue saturation index (TSI), and brain TSI were measured during moderate- and heavy-intensity exercise. KE ingestion induced ketosis at the start of each exercise session (group × time interaction: $P < 0.001$). However, compared with placebo, KE resulted in a comparable (group × time interaction: $P = 0.501$) high-altitude-induced slowing of the primary phase time constant of $\dot{V}O_2$ kinetics during heavy-intensity exercise (time effect: $P < 0.001$). Moreover, both groups exhibited similar (all group × time interactions: $P > 0.123$) hypoxia-related decreases in gas exchange and increases in minute ventilation, accompanied by reductions in pulse oxygen saturation and brain TSI during both moderate- and heavy-intensity exercise across the 3 days (all time effects: $P < 0.015$). Notably, KE ingestion increased cardiac output during moderate-intensity exercise on the first altitude day (group × time interaction: $P = 0.042$). Whole-body energy efficiency was preserved across time at 3,375 m (time effect: $P = 0.060$) in both groups (group × time interaction: $P = 0.084$). These data indicate that intermittent exogenous ketosis does not attenuate altitude-induced alternations in $\dot{V}O_2$ kinetics or tissue oxygenation, nor improves whole-body efficiency, during moderate- or heavy-intensity exercise across 3 days at 3,375 m.

NEW & NOTEWORTHY This study demonstrates that intermittent exogenous ketosis does not alter the high-altitude slowing of the primary phase of $\dot{V}O_2$ kinetics during the transition to heavy-intensity exercise, nor does it change ventilatory, gas exchange, blood or tissue oxygenation responses, or whole-body efficiency across 3 days at 3,375 m. However, preexercise ketone monoester ingestion increased cardiac output during moderate-intensity exercise on arrival to 3,375 m and after 24 h, but this did not translate to broader physiological benefits.

hypobaric hypoxia; ketone bodies; ketone ester; sports performance

INTRODUCTION

Approximately 100 million people sojourn to high-altitude regions for either occupational or recreational purposes each year (1). Exercise at high-altitude is characterized by systemic hypoxia, eliciting a range of physiological adaptations (2) and diminishing exercise performance (3–7). At simulated high-altitude, elicited using normobaric hypoxia, pulmonary oxygen uptake ($\dot{V}O_2$) kinetics during the transition to both moderate- and heavy-intensity exercise are slowed compared with normoxia (8–11), which increases the oxygen deficit (9, 12). Furthermore, increased whole-body $\dot{V}O_2$ during exercise accentuates blood, skeletal muscle, and brain deoxygenation in hypoxia (3, 13), which are key contributors to exercise intolerance at altitude (14, 15).

Exogenous ketosis represents a nutritional strategy that could promote beneficial physiological adaptations during exercise at altitude (16). Oral administration of the ketone

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monoester (KE) (R)-3-hydroxybutyl (R)-3-hydroxybutyrate elevates blood β-hydroxybutyrate concentrations ([β-HB]) to ~1.5–6.5 mM (17). Such conditions have been shown to increase blood, skeletal muscle, and brain oxygenation, and to augment pulmonary $\dot{V}O_2$ at rest and during moderate-intensity exercise, under acute (≤15 h) simulated high altitude conditions (~2,500–6,096 m above sea level) (4, 6, 18–22). Furthermore, an increase in blood oxygen saturation at rest following KE administration protocol has been reported at terrestrial high-altitude (3,375 m) after ~48 h of exposure (23), likely due to accentuated hyperventilation secondary to ketoacidosis (4, 6, 7, 16, 18, 19, 23). In addition, exogenous ketosis has also been reported to elevate cardiac output at sea level, presumably via β-HB-mediated enhancement of myocardial contractility and/or vasodilation (24–26), suggesting that this nutritional state may improve oxygen delivery, and thus exercise tolerance, at high-altitude.

From a metabolic perspective, there is evidence to suggest that ketone bodies increase energetic efficiency relative to glucose (27–31) and are preferentially used by the brain under hypoxic conditions (32). Indeed, KE administration after an overnight fast has been shown to improve whole-body energy efficiency during incremental cycling exercise at sea level (33). Similarly, our recent findings suggest that exogenous ketosis combined with a standardized high-carbohydrate meal reduced oxygen extraction in skeletal muscle and the brain under acute simulated high-altitude conditions (≤4 h, ~1,000–4,000 m), reflecting enhanced efficiency in peripheral metabolically active tissue (6, 19). In contrast, exogenous ketosis increased pulmonary $\dot{V}O_2$ during moderate-intensity exercise under identical hypoxic conditions, suggesting reduced efficiency at the whole-body level (6). Consequently, the net effect of exogenous ketosis on local and whole-body energy efficiency under high-altitude conditions remains unclear.

A common feature of previous studies demonstrating the (beneficial) effects of intermittent exogenous ketosis is exposure of participants to acute, simulated high-altitude conditions in laboratory settings (i.e., acute normobaric hypoxia lasting ≤15 h). Although such experimental conditions allow for precise experimental control, we aim to extend these findings to more ecologically valid contexts—specifically, exercise during early acclimatization at terrestrial high-altitude (e.g., hypobaric hypoxia). Furthermore, despite similar inspired oxygen partial pressures, notable differences in physiological responses during submaximal exercise following exposure to normobaric versus hypobaric hypoxia have previously been reported (34, 35). Since barometric pressure per se may exert an independent effect (36), it is important to assess exogenous ketosis within the hypobaric hypoxic environments.

Accordingly, the aim of the present work was to investigate whether intermittent exogenous ketosis alters ventilatory, cardiovascular, muscular, and cerebral responses, as well as whole-body energy efficiency, during relative workload-matched, moderate- and heavy-intensity exercise across 3 days at 3,375 m above sea level. In line with existing evidence, we hypothesized that KE would *1*) attenuate altitude-induced blood, skeletal muscle, and brain oxygenation reductions via augmented ventilation and cardiac output, *2*) mitigate the altitude-induced slowing of the primary phase of $\dot{V}O_2$ kinetics during step transitions to moderate- and heavy-intensities, and *3*) reduce whole-body energy efficiency at altitude, given earlier KE-associated elevations in $\dot{V}O_2$ during submaximal exercise in normobaric hypoxia (6).

METHODS

Study Design

The present study used a randomized, double-blind, placebo-controlled, parallel-groups design. Following preliminary testing at ~295 m (Ljubljana, Slovenia), participants were stratified by peak oxygen uptake ($\dot{V}O_{2peak}$) and randomly allocated to intermittent exogenous ketosis (IEK; $n = 17$, 3 female) or placebo (PLA; $n = 17$, 3 female) group. Each participant then completed four exercise sessions: one at ~295 m (Ljubljana, Slovenia; barometric pressure, 735 ± 4 mmHg; ambient temperature, 26 ± 1°C; relative humidity, 52 ± 5%) without supplementation to establish a true baseline, and three approximately 6 wk later at 3,375 m (Rifugio Torino, Courmayeur, Italy; barometric pressure, 509 ± 7 mmHg; ambient temperature, 23 ± 2°C; relative humidity, 36 ± 6%). Throughout the high-altitude exposure, participants were supplemented with KE (IEK group) or placebo (PLA group) depending on the group assignment (see Fig. 1). Participants traveled by car (~7 h) and then by cable car (~20 min) to arrive at Rifugio Torino at approximately 14:00.

The exercise session at near sea level (SL) served as the control condition for both groups, and included first a series of repeated moderate-intensity exercise bouts, and then a heavy-intensity exercise bout after 15 ± 6 min rest. During the high-altitude sojourn, participants performed relative workload-matched, moderate-intensity exercise bouts immediately upon arrival on *day 0* (A, 1 ± 1 h postarrival at high altitude), 25 ± 1 h postarrival on *day 1* (D1), and 49 ± 1 h postarrival on *day 2* (D2). In addition, a relative workload-matched, heavy-intensity exercise bout was conducted at D2 (50 ± 1 h postarrival), initiated 8 ± 2 min after the preceding moderate-intensity exercise bout.

Participants and Recruitment

The study received ethical approval from the National Committee for Medical Ethics at the Ministry of Health of the Republic of Slovenia (Approval No. 0120-524/2022/3) and from the Aosta Hospital Ethical Committee (06/05/2021.0038781.I). The trial was also preregistered at ClinicalTrials.gov (NCT06097754). A total of 34 participants were enrolled and successfully completed the study ($n = 17$/group, 28 males, 6 females). Eligibility criteria included: age (18–35 yr), body mass index (18.5–25.0 $kg \cdot m^{-2}$), physical activity status [minimum Tier 1 classification (37)], and permanent residence <1,000 m. Participants were excluded if they had any chronic diseases, were habitual smokers, regularly used medication or exogenous ketone supplements, adhered to a ketogenic diet, or underwent exposure to altitude (≥2,000 m) within 1 mo preceding each testing session. All participants provided written informed consent upon arrival for the preliminary testing visit. They were instructed to maintain their usual physical activity routines and dietary habits, without the use of nutritional supplements, throughout the entire

Table 1. *Baseline participant characteristics*

Characteristics	IEK (n = 17)	PLA (n = 17)
Age, yr	22 ± 2	23 ± 3
Body mass, kg	73.2 ± 10.2	70.0 ± 9.1
Height, m	1.79 ± 0.08	1.77 ± 0.08
BMI, kg·m^{-2}	22.6 ± 1.7	22.3 ± 1.9
Body fat, %	15 ± 4	15 ± 4
$\dot{V}O_{2peak}$, mL·kg^{-1}·min^{-1}	53.5 ± 7.0	52.6 ± 5.3
PPO, W	327 ± 64	320 ± 47
GET, %$\dot{V}O_{2peak}$	58 ± 3	58 ± 6
GET, W	166 ± 40	155 ± 20
RCP, %$\dot{V}O_{2peak}$	87 ± 4	86 ± 4
RCP, W	270 ± 58	254 ± 36

Data are means ± SD; IEK, n = 17; PLA, n = 17. BMI, body mass index; GET, gas exchange threshold; IEK, intermittent exogenous ketosis group; PLA, placebo group; PPO, peak power output; RCP, respiratory compensation point; $\dot{V}O_{2peak}$, peak oxygen uptake.

study period. The baseline characteristics of the participants in both groups are presented in Table 1.

Nutritional Intervention

Fig. 1 illustrates a schematic overview of the experimental protocol, detailing the KE dosing strategy and corresponding blood [β-HB] measurements in relation to high-altitude arrival and the timing of the high-altitude exercise sessions.

As this study was part of a larger international project scrutinizing the effects of intermittent exogenous ketosis during early acclimatization to high-altitude (7, 23), participants in the IEK group received repeated KE supplementation (*R*)-3-hydroxybutyl (*R*)-3-hydroxybutyrate (KetoneAid Inc., Falls Church, Virginia; ~7 kcal·g^{-1}). The KE drinks were administered in 25 g boluses 30 min before the onset of the constant workload exercise sessions (at ~0.5, ~24.5, and ~48.5 h following high-altitude exposure), as well as before resting measurements (~2.5, ~17.5, ~29.5, ~41.5, and ~43.5 h) (23), and each night 30 min before sleep (~7.5 and ~31.5 h). This supplementation protocol resulted in a cumulative KE dose of 250 g (3.54 ± 0.51 g·kg^{-1} body mass; ~1,750 kcal) over the first 49 h at high-altitude in the IEK group. At the same time points, participants in the PLA group received 25 g of an inert, noncaloric, taste-, and viscosity-matched placebo drink (3.65 ± 0.53 g·kg^{-1} body mass; 0 kcal), which consisted of 1 mM bitter sucrose octa-acetate (Sigma-Aldrich, Bornem, Belgium) dissolved in water. An additional 5% wt/vol sucralose (MyProtein, New York) and 1.0% vol/vol strawberry flavor drops (MyProtein, New York) were added to all supplements to soften the bitterness and to prevent the supplement taste from interfering with the development of acute mountain sickness-type symptoms or introducing general discomfort. Both supplements were administered in nontransparent 50 mL tubes, followed immediately by ingestion of a sugar- and caffeine-free beverage (the Coca-Cola Company, Atlanta, Georgia) to minimize potential visual or taste-based identification.

All supplement administration procedures and capillary blood [β-HB] measurements were conducted by an independent researcher not involved in other aspects of the study. Investigators collecting data remained blinded to group allocation. Participants were asked via an exit questionnaire to indicate which group they believed they had been assigned to and to rate their confidence on a scale ranging from 0% ("no idea at all") to 100% ("completely certain"). In both groups, 65% of participants (11 out of 17) correctly identified their group allocation, with similar confidence levels (IEK, 67 ± 15%; PLA, 66 ± 16%). In addition, gastrointestinal symptoms and their severity were assessed using a validated Likert-type questionnaire (38) upon morning awakening and before sleep in the night at sea level and high-altitude (8, 16, 32, and 40 h postarrival at 3,375 m). Six participants in the IEK group reported mild gastrointestinal discomfort (means ± SD:14 ± 6 out of a maximum of 88 points). No such symptoms were observed in the PLA group.

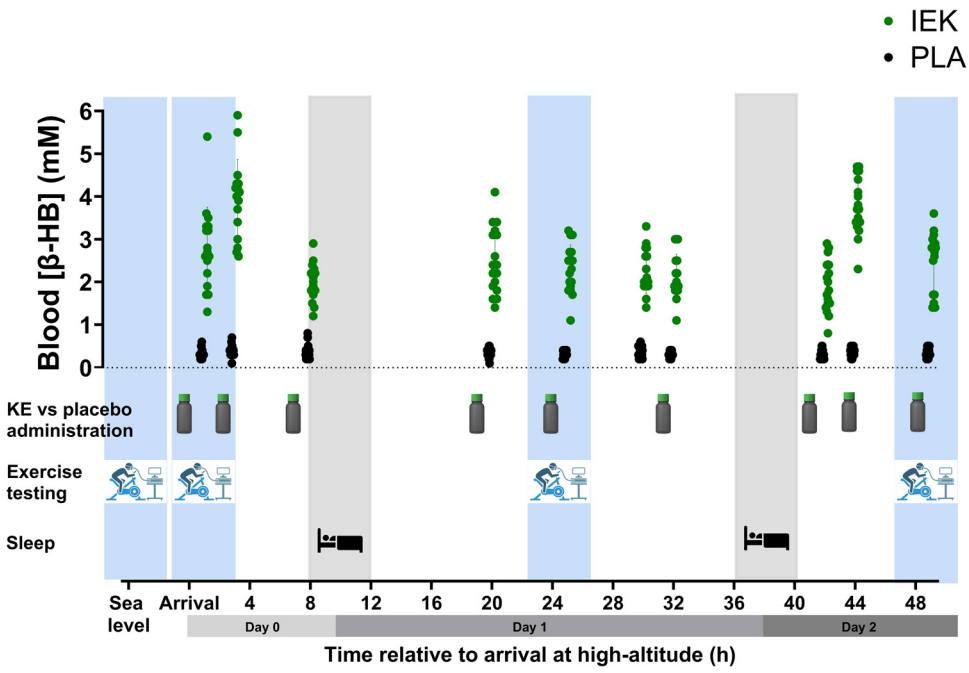

Figure 1. Schematic representation of the experimental protocol, illustrating capillary β-hydroxybutyrate ([β-HB]) concentrations across 3 days of high-altitude exposure in participants assigned to the intermittent exogenous ketosis (IEK, n = 17; green) and placebo (PLA, n = 17; black) groups. Data are presented as means ± SD. Capillary blood samples were consistently collected 30 min following supplement ingestion. Capillary [β-HB] measurements at 1, 25, and 49 h following arrival at high-altitude coincided with the onset of the respective high-altitude exercise sessions.

Preliminary Testing

At ~295 m, participants performed an incremental exercise test to exhaustion on an electromagnetically braked cycle ergometer (E100 bike ergometer; COSMED, Rome, Italy). After 3 min seated rest and a 2-min warm-up at 50 W, the workload increased continuously at 1 W·3 s^{-1} (= 20 W·min^{-1}). Participants were blinded to workload, but were instructed to maintain a cadence of 80–90 rpm and received strong verbal encouragement until exhaustion. Gas exchange data were recorded breath-by-breath using a calibrated metabolic cart (Quark CPET, COSMED, Rome, Italy). Peak power output (PPO) was defined as the highest workload achieved immediately before exercise termination, and $\dot{V}O_{2peak}$ was defined as the average $\dot{V}O_2$ measured over the final 20 s of the test. Gas exchange threshold (GET) and respiratory compensation point (RCP) were identified by three independent investigators following the procedures outlined by Keir et al. (39). The average of the two closest assessments was used for exercise prescription.

Exercise Intensity Prescription

The moderate-intensity exercise bouts corresponded to the power output at 80% of the $\dot{V}O_2$ at GET. The heavy-intensity exercise bouts were prescribed as the power output corresponding to the $\dot{V}O_2$ halfway between the $\dot{V}O_2$ at GET and RCP (40). Since high-altitude-induced hypoxia reduces $\dot{V}O_{2peak}$, the power output prescriptions were adjusted based on the equation proposed by MacInnis et al. (41). Specifically, the percentage decrease in $\dot{V}O_{2peak}$ at an altitude of 3,375 m was individually determined for each participant (range 14%–28%). These individualized reductions were then applied to the power output prescriptions for the high-altitude exercise bouts, theoretically resulting in similar relative intensities between conditions. An incremental exercise test to exhaustion was conducted on the final, fourth day of the high-altitude sojourn (7), enabling the retrospective quantification of the prescribed exercise intensities relative to $\dot{V}O_{2peak}$ under each environmental condition.

Constant-Workload Exercise Protocols

Exercise bouts in the moderate-intensity domain consisted of a 3 min rest period, followed by 2 min of unloaded cycling at 0 W, and then 3 × 6 min intervals of cycling at the prescribed constant workload, each interspersed with 6 min of unloaded cycling. Exercise bouts in the heavy-intensity domain began with a 3 min rest period, followed by 2 min of cycling at 0 W, and then a single 8 min bout at the prescribed constant workload. At the end of each exercise bout, participants reported their ratings of perceived exertion using a standard 6–20 Borg scale (42).

Data Sampling

Throughout the exercise sessions, $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$), tidal volume (V_T), respiratory frequency (R_f), end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$), and pulse oxygen saturation (Sp_{O_2}) were recorded breath-by-breath using a calibrated metabolic cart (Quark CPET, COSMED, Rome, Italy). A noninvasive transthoracic impedance cardiography system (PhysioFlow Enduro; Manatec Biomedical, Paris, France) measured heart rate (HR) and stroke volume (SV) at a frequency of 1 Hz, allowing for the determination of cardiac output ($\dot{Q}$). A near-infrared spectroscopy (NIRS) device was used to assess oxygenation in the brain and skeletal muscle (PortaLite, Artinis Medical Systems, Elst, the Netherlands). Following standard skin preparation protocols (43), the brain NIRS sensor was positioned over the left prefrontal cortex, whereas the muscle NIRS sensor was placed on the *vastus lateralis* muscle of the right leg. The placement was standardized across all sessions by the same experimenter, with devices secured using transparent double-sided tape and elastic bandages to minimize movement artifacts and prevent signal contamination from ambient light. The NIRS device measures relative changes in the concentrations of oxygenated ($\Delta[O_2Hb + Mb]$) and deoxygenated hemoglobin/myoglobin ($\Delta[HHb + Mb]$) at tissue depths of ~15, ~17.5, and ~20 mm, using light absorption at wavelengths of 760 and 850 nm. These measurements enabled the quantification of the absolute tissue saturation index (TSI; ratio between $\Delta[O_2Hb + Mb]$ and $\Delta[O_2Hb + Mb] + \Delta[HHb + Mb] \times 100$) in both cerebral (brain TSI) and skeletal muscle tissues (muscle TSI). Due to logistical constraints, NIRS measurements were only performed during exercise sessions conducted at SL, D1, and D2.

Data Processing

R packages *readxl*, *dplyr*, *signal*, *whippr*, and *minpack.lm* (v.4.4.2, R Core Team, Vienna, Austria) were used for data processing. Breath-by-breath data were initially processed by identifying and removing outliers, defined as datapoints falling outside the 95% prediction interval of an exponential fit. The filtered data were subsequently interpolated to a sampling frequency of 1 Hz. Muscle and brain oxygenation signals were recorded at 50 Hz and exported at 10 Hz. Further data processing involved smoothing using a 10th-order low-pass zero-phase Butterworth filter with a 0.8 Hz cut-off frequency. The filtered data were then downsampled to 1 Hz and temporally aligned with the ventilatory, gas exchange, and cardiac output measurements. All interpolated data from the three transitions during moderate-intensity bouts were ensemble averaged to generate the final dataset, thereby minimizing signal noise and enhancing the underlying physiological response patterns.

The $\dot{V}O_2$ kinetics during a step transition from a baseline intensity (0 W) to a relative workload-matched, moderate-, or heavy-intensity exercise bout was analyzed using a mono- or biexponential model, respectively, using a computerized nonlinear regression method (44). For moderate-intensity exercise bouts, key model parameters of interest included the amplitude of the primary response ($Amp\dot{V}O_2$), defined as the difference between baseline and steady-state $\dot{V}O_2$ values, and the time constant ($\tau\dot{V}O_2$) of the primary phase, which represents the time required to reach 63% of $Amp\dot{V}O_2$. For heavy-intensity exercise bouts, an additional time constant and amplitude of the slow component ($\tau_2\dot{V}O_2$ and $Amp_2\dot{V}O_2$) were incorporated into the model. $Amp_2\dot{V}O_2$ was defined as a $\dot{V}O_2$ rise above the predicted steady-state, whereas $\tau_2\dot{V}O_2$ represented the temporal rate of this increase.

End-exercise steady-state values during relative workload-matched, moderate- and heavy-intensity exercise bouts were subsequently defined as 60 s averages (arithmetic mean)

calculated 30 s before termination of the given exercise. This range was used to avoid the spline interpolation artifact often induced by the final few breaths in the metabolic cart raw data traces. In addition, resting Sp_{O_2} values were defined as 60 s mean of the processed data recorded before the initiation of each exercise testing session.

Net efficiency during the moderate-intensity cycling exercise was calculated as $\{[W \cdot (E - E_{rest})^{-1}] \times 100\}$, where W represents mechanical power, and $(E - E_{rest})$ denotes the metabolic power above resting level previously described (45, 46).

Sample Size Estimation

An a priori sample size estimation was performed using G*Power (v.3.1.9.7, Heinrich Heine University Duesseldorf, Duesseldorf, Germany). In line with previous work from our research group (6) in which high-altitude-induced physiological impairments were mitigated following exogenous KE versus placebo administration, the outcome measure to which the present sample size was statistically powered was determined to be Sp_{O_2} during submaximal exercise (the smallest effect indicated, $\eta_p^2 = 0.21$). To detect the resulting moderate effect size ($d = 0.52$), and to account for a between group × within time interaction (ANOVA: Repeated measures, between factors), a minimum of 26 participants (13/group) would be required ($\alpha = 0.05$, $1 - \beta = 0.80$, number of groups: 2, number of measurements: 2, and correlation among repeated measurements: 0.5). As previously described, all exercise sessions were successfully completed by 17 participants in each group. Nevertheless, certain exercise bouts and specific outcome variables were excluded from analysis due to suboptimal signal quality or technical malfunctions. As a result, the final analyses included data from at least 14 participants/group across all comparisons.

Statistical Analysis

All statistical analyses were performed using GraphPad Prism v.10.4.1 (GraphPad Software, La Jolla, CA). Data normality was assessed using the Shapiro–Wilk test. Retrospective analyses of the prescribed exercise intensities were performed using two-tailed independent Student's t tests. Differences between the IEK and PLA groups over time for relative workload-matched, moderate-intensity exercise were evaluated using separate mixed-effects models, with group (IEK and PLA) and time (SL, A, D1, and D2) as fixed effects and participant ID as a random effect. When a significant main effect of time or a group × time interaction was detected, post hoc comparisons were conducted using Šidák's correction, and reported P values primarily refer to these post hoc analyses; otherwise, P values for the main effects are reported. Similarly, differences between IEK and PLA groups across environmental conditions for relative workload-matched, heavy-intensity exercise were assessed using separate mixed-effects models incorporating two-level factors for group and condition (sea level and high-altitude) as fixed effects and participant ID as a random effect. Significant main effect of condition or group × condition interactions were examined and adjusted using Šidák's post hoc procedure. Data are presented as means ± SD unless otherwise stated. Statistical significance was defined as $P < 0.05$. Effect sizes were interpreted according to conventional thresholds: trivial (0.0–0.2), small (0.2–0.5), medium (0.5–0.8), and large (>0.8) (47).

RESULTS

Exercise Intensity Prescription

Table 2 provides an overview of the prescribed power outputs for the IEK and PLA groups, together with the corresponding exercise-intensity data obtained during the constant-workload exercise bouts performed at sea level and high-altitude. $\dot{V}O_2$ values derived from steady-state exercise bouts under both conditions were retrospectively compared with $\dot{V}O_{2peak}$ values obtained from incremental exercise tests conducted during preliminary testing at sea level and on the final day of high-altitude sojourn (7). Across both sea level and high-altitude, the prescribed moderate- and heavy-intensity workloads elicited comparable relative intensities between the IEK and PLA groups (sea level: $P > 0.473$; high altitude: $P > 0.915$). Overall, exercise intensities did not differ between altitudes (condition effect: $P > 0.572$), irrespective of group allocation (group × condition interaction: $P > 0.242$). Furthermore, the estimated $\dot{V}O_{2peak}$ values at high-altitude did not differ from the directly measured $\dot{V}O_{2peak}$ under the same environmental condition (estimated vs. measured $\dot{V}O_{2peak}$: 3.12 ± 0.49 vs. 3.13 ± 0.54; $P = 0.833$) regardless of group (IEK vs. PLA: $P = 0.640$).

Blood β-HB Concentrations

KE administered 30 min preexercise at high-altitude consistently induced ketosis in the IEK group, with blood [β-HB] of ~2.5 mM (range: 1.1–5.4 mM, group effect: $P < 0.001$, $\eta_p^2 = 0.91$). More specifically, blood [β-HB] in the IEK group was

Table 2. *Prescribed power outputs and corresponding exercise-intensity data during constant-workload exercise bouts at sea level and high-altitude*

Exercise Intensity	Altitude	Group	Power Output (W)	% $\dot{V}O_{2peak}$ (%)	% PPO (%)
Moderate-intensity	Sea level 295 m	IEK	123 ± 32	55 ± 6	39 ± 5
		PLA	114 ± 17	52 ± 6	36 ± 5
	High-altitude 3,375 m	IEK	90 ± 20	54 ± 8	34 ± 6
		PLA	84 ± 15	54 ± 9	32 ± 6
Heavy-intensity	Sea level 295 m	IEK	218 ± 48	81 ± 7	69 ± 5
		PLA	204 ± 27	78 ± 7	65 ± 6
	High-altitude 3,375 m	IEK	167 ± 29	81 ± 7	64 ± 18
		PLA	157 ± 21	80 ± 11	62 ± 13

Data are means ± SD; IEK, $n = 17$; PLA, $n = 17$. IEK, intermittent exogenous ketosis group; PLA, placebo group; PPO, peak power output; $\dot{V}O_{2peak}$, peak oxygen uptake.

2.8 ± 1.0 mM (A, 1 ± 1 h postarrival at high-altitude), 2.3 ± 0.6 mM (D1, 25 ± 1 h postarrival at high-altitude), and 2.5 ± 0.7 mM (D2, 49 ± 1 h postarrival at high-altitude). In contrast, blood [β-HB] in the PLA group remained below 0.5 mM at all time points (IEK vs. PLA; A: $P < 0.001$, $d = 3.6$; D1: $P < 0.001$, $d = 4.9$; D2: $P < 0.001$, $d = 4.4$; see Fig. 1).

Relative Workload-Matched, Moderate-Intensity Exercise

$\dot{V}O_2$ kinetics.

The IEK and PLA groups' changes in $\dot{V}O_2$ kinetics during the step transition from a baseline intensity (0 W) to a moderate-intensity workload at sea level and across 3 days of high-altitude sojourn, are presented in Fig. 2. $\tau\dot{V}O_2$ displayed neither a group × time interaction ($P = 0.682$), nor overall main effects of group ($P = 0.857$) or time ($P = 0.143$). In contrast, a main effect of time was observed for $Amp\dot{V}O_2$ ($P < 0.001$, $\eta_p^2 = 0.77$), indicating a large overall decrease from SL to A ($P < 0.001$, $d = 1.65$) in both groups (group × time interaction: $P = 0.181$). This reduction relative to SL persisted throughout time at high-altitude in both groups (SL vs. D1 or D2: $P < 0.001$, average $d = 1.61$), with only trivial changes between A and D2 ($P > 0.258$).

Ventilation, gas exchange, and perceived exertion.

End-exercise steady-state ventilation and gas exchange, along with perceived exertion at sea level and high-altitude time points in both experimental groups, are presented in Fig. 3. For $\dot{V}O_2$ a main effect of time was observed ($P < 0.001$, $\eta_p^2 = 0.68$), indicating an overall large decrease from SL to A ($P < 0.001$, $d = 1.55$) in both groups (group × time interaction: $P = 0.182$). Relative to SL, this large reduction remained evident on both D1 and D2 (SL vs. D1 or D2: $P < 0.001$, average $d = 1.11$), with only trivial changes observed between consecutive high-altitude time points (A vs. D1, D1 vs. D2: $P > 0.167$). A group × time interaction was observed for $\dot{V}CO_2$ ($P = 0.016$, $\eta_p^2 = 0.10$); however, post hoc analyses revealed no between-group differences at any time point (all $P > 0.513$). A main effect of time ($P < 0.001$, $\eta_p^2 = 0.74$), however, indicated a large overall decrease in $\dot{V}CO_2$ from SL to A ($P < 0.001$, $d = 1.32$), with a persistent reduction relative to SL observed over the subsequent 2 days at high-altitude (SL vs. D1 or D2: $P < 0.001$, average $d = 1.18$). A main effect of time was observed for $\dot{V}E$ ($P < 0.001$, $\eta_p^2 = 0.49$), indicating no overall change from SL to A ($P = 0.189$), followed by a progressive increase from A to D1 ($P < 0.001$, $d = 0.79$) and D1 to D2 ($P = 0.005$, $d = 0.27$) in both groups (group × time interaction: $P = 0.518$). Overall, R_f remained unchanged from SL to A ($P > 0.999$), yet increased from A to D1 ($P < 0.045$, $d = 0.51$), and remained elevated relative to SL throughout the reminder of acclimatization period in both groups (SL vs. D1 or D2: $P < 0.007$; main effect of time: $P < 0.001$, $\eta_p^2 = 0.27$; main effect of group: $P = 0.147$, $\eta_p^2 = 0.10$). No differences in V_T were observed in any main- or interaction-effect comparisons (all $P > 0.194$). $P_{ET}CO_2$ markedly decreased from SL to A ($P < 0.001$, $d = 2.13$), without subsequent further changes across high-altitude time points (A vs. D1, D1 vs. D2: $P > 0.395$) in both groups (time effect: $P < 0.001$, $\eta_p^2 = 0.68$; group × time interaction: $P = 0.123$, $\eta_p^2 = 0.07$). For RPE, a main effect of time was observed ($P = 0.004$, $\eta_p^2 = 0.11$), indicating a reduction from SL to A ($P = 0.018$, $d = 0.41$). Values remained unchanged relative to SL at D1 ($P = 0.588$) but were reduced again at D2 ($P = 0.036$, $d = 0.46$) in both groups (group × time interaction: $P = 0.436$).

Cardiac output.

Fig. 4 depicts the end-exercise steady-state cardiac output responses at SL and across 3 days at 3,375 m in the IEK and PLA groups. Regarding SV, a group × time interaction ($P = 0.025$, $\eta_p^2 = 0.10$) was observed; however, post hoc analyses revealed no between-group differences at any time point (IEK vs. PLA; SL: $P = 0.999$; A: $P = 0.222$; D1: $P = 0.094$; D2: $P = 0.716$). Overall, HR was maintained from SL to A ($P > 0.978$), before exhibiting a moderate increase from A to D1 ($P < 0.001$, $d = 0.54$), resulting in sustained elevation relative to SL across D1 and D2 (SL vs. D1 or D2: $P < 0.001$, average $d = 0.76$) in both groups (time effect: $P < 0.001$, $\eta_p^2 = 0.48$; group × time interaction: $P = 0.840$). For $\dot{Q}$ a group × time interaction was detected ($P = 0.042$, $\eta_p^2 = 0.09$), indicating higher exercising $\dot{Q}$ in the IEK versus PLA group at both A ($P = 0.013$, $d = 1.19$) and D1 ($P = 0.023$, $d = 1.05$). Furthermore, within-group, between-time comparisons

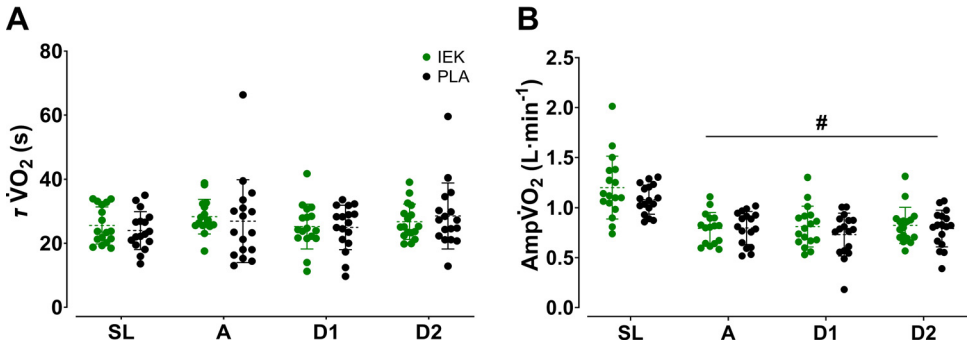

Figure 2. Time constant ($\tau\dot{V}O_2$, *A*) and amplitude ($Amp\dot{V}O_2$, *B*), of the primary phase during a step transition from a baseline intensity (0 W) to a relative workload-matched, moderate-intensity exercise at sea level (SL), upon arrival (1 ± 1 h postarrival) at high-altitude (A), and 25 ± 1 h (D1), and 49 ± 1 h postarrival (D2) in the IEK (green, $n = 17$) and PLA (black, $n = 17$) groups. Data are presented as individual values (dots) together with group means (dashed horizontal lines) ± SD (whiskers). Statistical inferences were obtained using linear mixed-effects models with time (SL, A, D1, and D2) and group (IEK and PLA) specified as fixed factors, and participant-level random intercepts to account for within-subject repeated measurements. Significant main effects of time were further investigated using post hoc pairwise comparisons with Šidak adjusted *P* values. #$P < 0.05$ main effect of time (SL vs. A, D1, and D2). IEK, intermittent exogenous ketosis; PLA, placebo group.

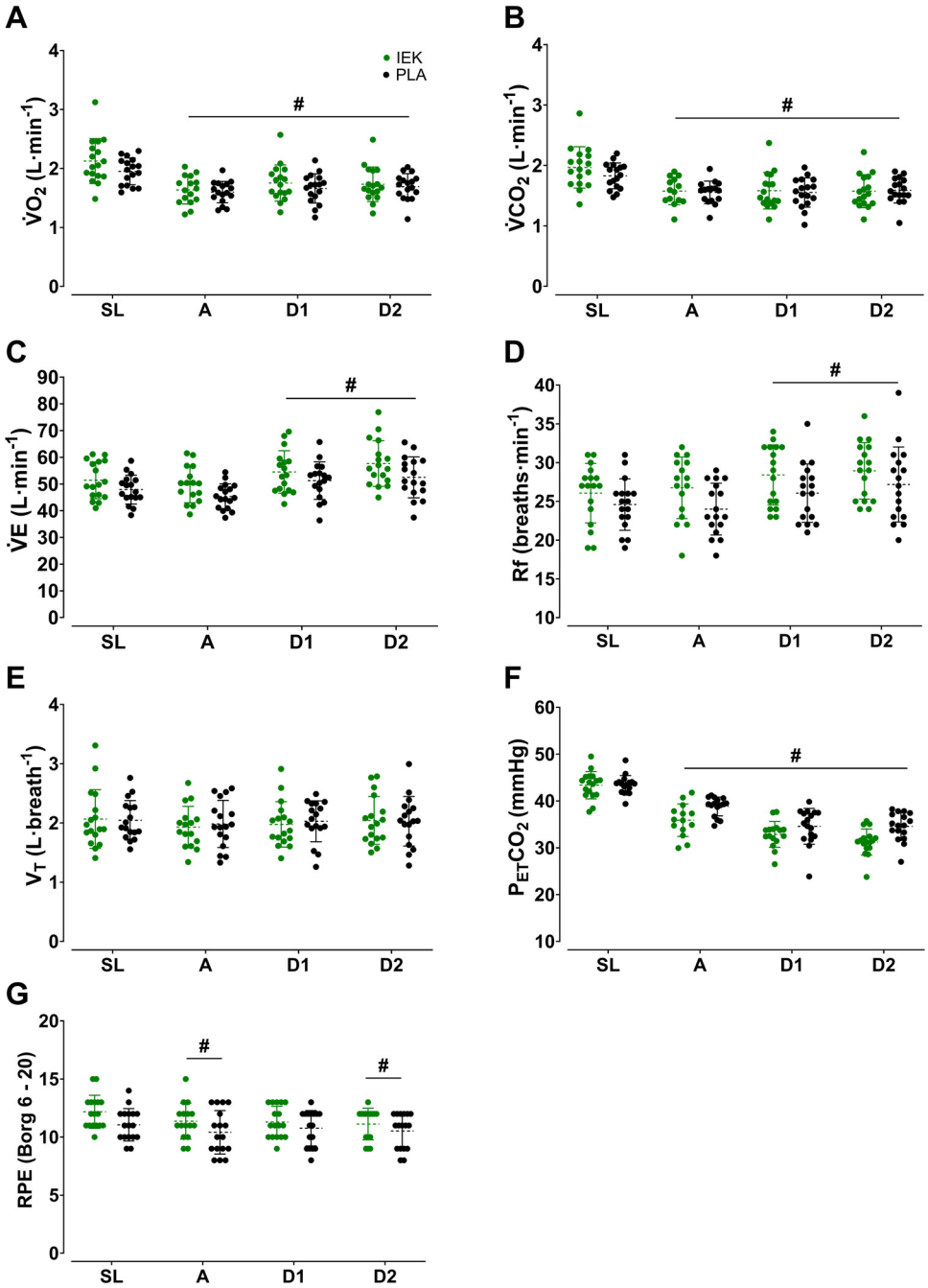

Figure 3. Oxygen uptake ($\dot{V}O_2$; *A*), carbon dioxide production ($\dot{V}CO_2$; *B*), pulmonary ventilation ($\dot{V}E$; *C*), respiratory frequency (R_f; *D*), tidal volume (V_T; *E*), end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$; *F*), and rating of perceived exertion (RPE; *G*) during the steady state at the end of the moderate-intensity bouts in the IEK (green, $n = 17$) and PLA (black, $n = 17$) groups. All data are presented as individual values (dots) together with group means (dashed horizontal lines) ± SD (whiskers). Differences between the IEK and PLA groups over time were evaluated using separate mixed-effects models, with group (IEK and PLA) and time (SL, A, D1, and D2) as fixed effects and participant ID as a random effect. Significant main effects of time or a group × time interactions were explored using post hoc comparisons with Šidák-adjusted *P* values. #$P < 0.05$ main effect of time (SL vs. A, D1, and D2). A, 1±1 h postarrival at high-altitude; D1, 25±1 h postarrival; D2, 49±1 h postarrival; IEK, intermittent exogenous ketosis; PLA, placebo group; SL, sea level.

indicated that $\dot{Q}$ decreased from D1 to D2 in the IEK group ($P = 0.036$), whereas it remained consistent in the PLA group ($P = 0.981$).

Blood, skeletal muscle, and brain oxygenation.

Fig. 5 depicts capillary, skeletal muscle, and brain oxygenation during the steady-state at the end of the moderate-intensity bouts. A main effect of time was observed for Sp_{O_2} ($P < 0.001$, $\eta_p^2 = 0.87$), indicating an overall large decrease from SL to A ($P < 0.001$, $d = 4.40$), which persisted through D1 (SL vs. D1: $P = 0.862$). A small overall increase was then observed from D1 to D2 ($P = 0.015$, $d = 0.43$), yet Sp_{O_2} still remained lowered relative to SL (SL vs. D2: $P < 0.001$) in both groups (group × time interaction: $P = 0.302$, $\eta_p^2 = 0.02$). Muscle TSI during steady-state exercise displayed neither a group × time interaction ($P = 0.602$) nor overall main effects of group ($P = 0.414$) or time ($P = 0.136$). Finally, a main effect of time was evident for Brain TSI ($P < 0.001$, $\eta_p^2 = 0.40$), characterized by a large decrease from SL to D1 ($P < 0.001$, $d = 1.38$), followed by a sustained reduction relative to SL at D2 (SL vs. D1 or D2: $P < 0.001$, average $d = 1.38$) in both groups (group × time interaction: $P = 0.585$).

Resting Sp_{O_2} (IEK group: 99±1% at SL, 93±2% at A, 94±3% at D1, 95±2% at D2; PLA group: 99±1% at SL, 92±3% at A, 93±3% at D1, 93±3% at D2) showed no significant group × time interaction ($P = 0.204$) or main effect of group

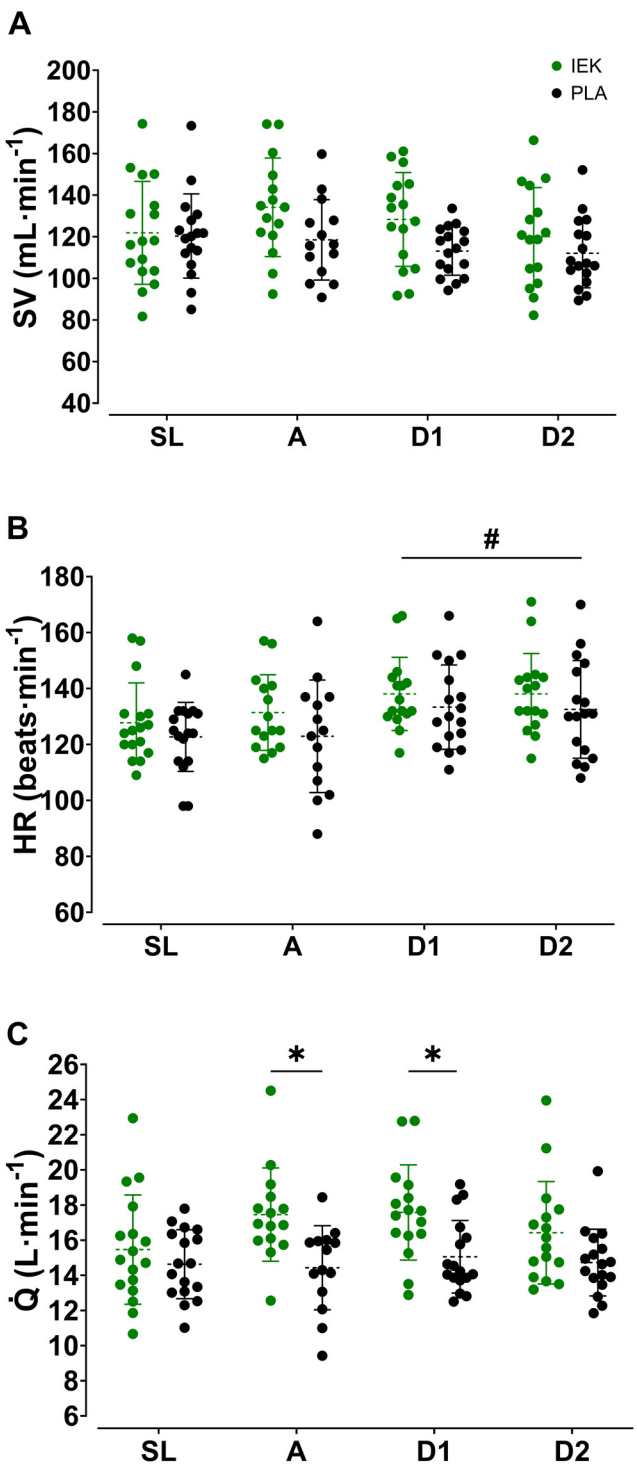

Figure 4. Stroke volume (SV; *A*), heart rate (HR; *B*), and cardiac output ($\dot{Q}$; *C*) during the steady-state at the end of the moderate-intensity bouts in the IEK (green, $n = 17$) and PLA (black, $n = 17$) groups. All data are presented as individual values (dots) together with group means (dashed horizontal lines) ± SD (whiskers). Differences between the IEK and PLA groups over time were evaluated using separate mixed-effects models, with group (IEK and PLA) and time (SL, A, D1, and D2) as fixed effects and participant ID as a random effect. Significant main effects of time or a group × time interactions were explored using post hoc comparisons with Šidák-adjusted *P* values. #$P < 0.05$ main effect of time (SL vs. A, D1, and D2), *$P < 0.05$ for IEK vs. PLA. A, 1±1 h postarrival at high-altitude; D1, 25±1 h postarrival; D2, 49±1 h postarrival; IEK, intermittent exogenous ketosis; PLA, placebo group; SL, sea level.

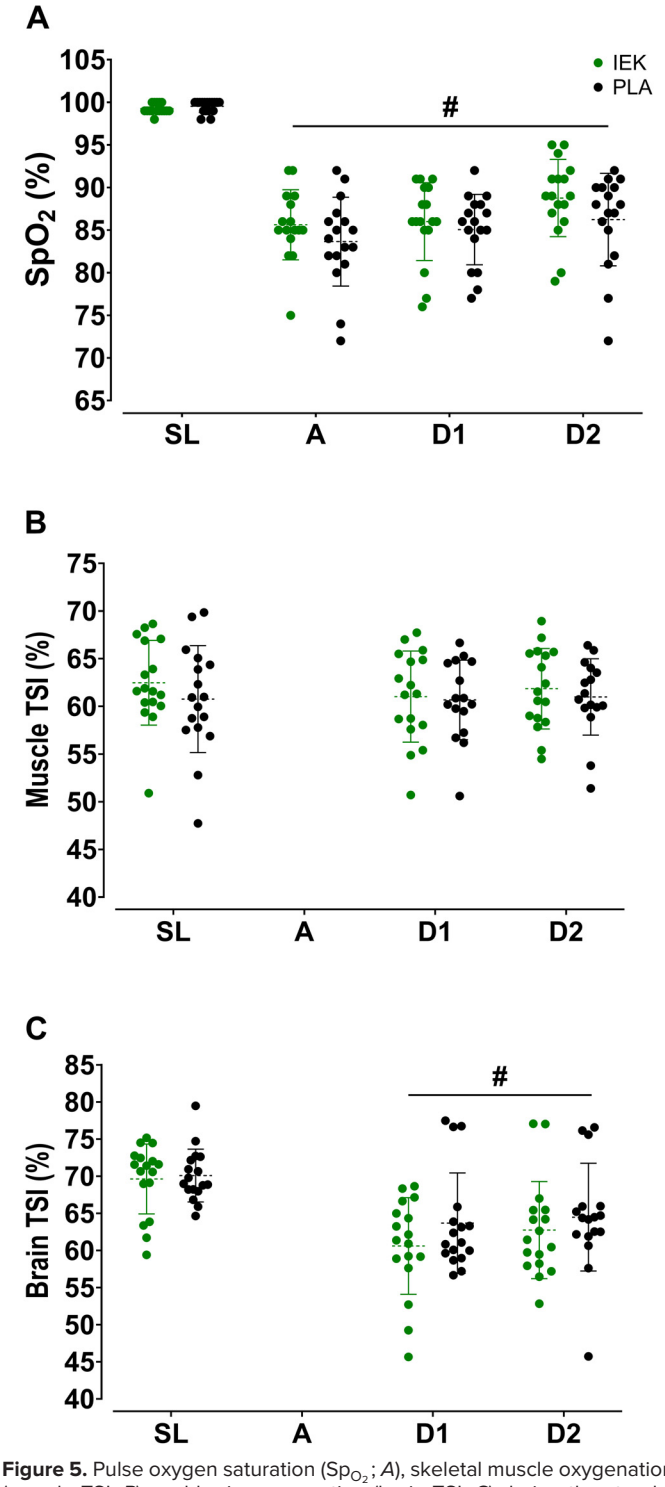

Figure 5. Pulse oxygen saturation (Sp_{O_2}; *A*), skeletal muscle oxygenation (muscle TSI; *B*), and brain oxygenation (brain TSI; *C*) during the steady-state at the end of the moderate-intensity bouts in the IEK (green, $n = 17$) and PLA (black, $n = 17$) groups. All data are presented as individual values (dots) together with group means (dashed horizontal lines) ± SD (whiskers). Differences between the IEK and PLA groups over time were evaluated using separate mixed-effects models, with group (IEK and PLA) and time (SL, A, D1, and D2) as fixed effects and participant ID as a random effect. Significant main effects of time were explored using post hoc comparisons with Šidák-adjusted *P* values. #$P < 0.05$ main effect of time (SL vs. A, D1, and D2). A, 1±1 h postarrival at high-altitude; D1, 25±1 h postarrival; D2, 49±1 h postarrival; IEK, intermittent exogenous ketosis; PLA, placebo group; SL, sea level.

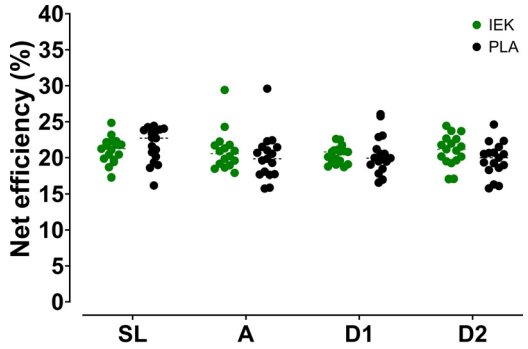

Figure 6. Net efficiency during steady-state, moderate-intensity exercise in the IEK (green, $n = 17$) and PLA (black, $n = 17$) groups. All data are presented as individual values (dots) together with group means (dashed horizontal lines) ± SD (whiskers). Differences between the IEK and PLA groups over time were evaluated using separate mixed-effects models, with group (IEK and PLA) and time (SL, A, D1, and D2) as fixed effects and participant ID as a random effect. A, 1±1 h postarrival at high-altitude; D1, 25±1 h postarrival; D2, 49±1 h postarrival; IEK, intermittent exogenous ketosis; PLA, placebo group; SL, sea level.

($P = 0.317$). A significant main effect of time was observed ($P < 0.001$, $\eta_p^2 = 0.77$), reflecting an overall large decrease from SL to A ($P < 0.001$, $d = 3.59$), which persisted on both D1 and D2 across both groups ($P < 0.001$, average $d = 2.90$), with only trivial changes between A and D2 ($P > 0.233$).

Whole-body energy efficiency.

Fig. 6 illustrates changes in net efficiency during relative workload-matched, moderate-intensity exercise at SL, A, D1, and D2 in both the IEK and PLA groups. Net efficiency displayed neither a group × time interaction ($P = 0.084$), nor overall main effects of group ($P = 0.556$) or time ($P = 0.060$).

Relative Workload-Matched, Heavy-Intensity Exercise

Descriptive and inferential statistical outcomes for the comparison of relative workload-matched, heavy-intensity exercise at sea level and 50±1 h postarrival at high-altitude in the IEK and PLA groups are outlined in Table 3. Overall, high-altitude prolonged $\tau\dot{V}O_2$ ($P < 0.001$, $d = 0.64$) and decreased $Amp\dot{V}O_2$ ($P < 0.001$, $d = 1.50$) during the transition from baseline intensity (0 W) to heavy-intensity exercise. However, neither $\tau_2\dot{V}O_2$ ($P = 0.450$) nor $Amp_2\dot{V}O_2$ ($P = 0.151$) differed between high-altitude and sea level in either group. A main effect of condition was observed for $\dot{V}O_2$ at the end of the heavy-intensity bout ($P < 0.001$), indicating an overall large ($d = 1.36$) decrease from sea level to high-altitude. $\dot{V}CO_2$ demonstrated a group × condition interaction effect ($P < 0.001$); however, post hoc analysis revealed no differences between groups at sea level ($P = 0.087$) or at high-altitude ($P = 0.999$). In addition, a main effect of condition for $\dot{V}CO_2$ indicated a large overall reduction from sea level to high-altitude in both groups ($P < 0.001$, $d = 1.34$). $\dot{V}E$ was higher at high-altitude ($P < 0.001$, $d = 0.91$), primarily due to an increase in R_f ($P < 0.001$, $d = 0.66$), whereas V_T remained unchanged ($P = 0.921$). $P_{ET}CO_2$ was in turn lower at high-altitude ($P < 0.001$, $d = 2.88$). Both SV ($P = 0.058$) and HR ($P = 0.784$) were maintained at high-altitude. However, $\dot{Q}$ exhibited an overall increase under high-altitude conditions ($P = 0.045$, $d = 0.41$). Both Sp_{O_2} ($P < 0.001$, $d = 2.68$) and brain TSI ($P = 0.015$, $d = 0.62$) were reduced at high-altitude in both groups. In contrast, muscle TSI was preserved, showing no change at high-altitude ($P = 0.143$). RPE was maintained

Table 3. *Descriptive (means ± SD) and inferential (P value) statistical results for various physiological parameters during exercise intensity transition and steady-state exercise at a relative workload-matched, heavy-intensity exercise at sea level and 50±1 h postarrival at high-altitude (3,375 m), in the IEK and PLA groups*

Variables	IEK Group		PLA Group		Group	Condition	Group × Condition
	Sea Level	High-Altitude	Sea Level	High-Altitude			
$\tau\dot{V}O_2$, s	24±6	29±6	24±5	27±8	0.615	**<0.001**	0.501
$Amp\dot{V}O_2$, L·min^{-1}	1.96±0.51	1.43±0.23	1.91±0.34	1.39±0.25	0.674	**<0.001**	0.951
$\tau_2\dot{V}O_2$, s	176±100	116±86	138±86	158±136	0.931	0.450	0.129
$Amp_2\dot{V}O_2$, L·min^{-1}	0.38±0.18	0.29±0.19	0.29±0.13	0.31±0.19	0.507	0.151	0.084
$\dot{V}O_2$, L·min^{-1}	3.16±0.58	2.53±0.38	2.93±0.35	2.43±0.25	0.229	**<0.001**	0.123
$\dot{V}CO_2$, L·min^{-1}	3.24±0.61	2.51±0.40	2.94±0.32	2.51±0.30	0.287	**<0.001**	**<0.001**
$\dot{V}E$, L·min^{-1}	85.9±13.9	96.8±14.1	77.5±8.6	92.3±17.4	0.121	**<0.001**	0.441
R_f, breaths/min	32±6	36±7	29±6	34±7	0.303	**<0.001**	0.675
V_T, L·breath^{-1}	2.8±0.7	2.8±0.6	2.7±0.5	2.6±0.5	0.815	0.921	0.705
$P_{ET}CO_2$, mmHg	43±4	30±4	43±4	32±4	0.456	**<0.001**	0.292
SV, mL·min^{-1}	125±25	133±27	121±21	129±25	0.568	0.058	0.967
HR, beats/min	171±12	171±11	161±21	160±24	0.089	0.784	0.801
$\dot{Q}$, L·min^{-1}	21±4	22±4	19±2	21±4	0.069	**0.045**	0.751
Sp_{O_2}, %	97±5	84±5	96±6	83±4	0.584	**<0.001**	0.688
Muscle TSI, %	56±6	54±6	55±8	52±14	0.515	0.143	0.844
Brain TSI, %	64±8	57±8	64±6	62±9	0.289	**0.015**	0.282
RPE, 6–20	16±1	16±1	15±1	15±2	>0.999	>0.999	0.231

Power output prescribed as 50% of the difference between GET and RCP, as determined from an incremental exercise test performed at sea level. For the high-altitude trial, this workload was appropriately adjusted (by 14%–28%) using a correction factor (see *Methods*). Mixed-effects models specified for each outcome measure, with group and condition defined as fixed effects, and a random effect accounting for interindividual variability. Statistically significant P values (<0.05) for main and/or interaction effects are highlighted in bold. Interaction effect(s) were further investigated using Šidak's post hoc testing procedure. IEK, $n = 17$; PLA, $n = 17$. Amp, amplitude; HR, heart rate; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide; $\dot{Q}$, cardiac output; R_f, respiratory frequency; RPE, rating of perceived exertion; Sp_{O_2}, pulse oxygen saturation; SV, stroke volume; TSI, tissue saturation index; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, pulmonary ventilation; $\dot{V}O_2$, oxygen uptake; VT, tidal volume; τ, time constant.

at high-altitude ($P > 0.999$). The high-altitude-induced changes in all of the aforementioned variables occurred independently of KE versus placebo supplementation, as indicated by the absence of group × condition interaction effects (all $P > 0.084$).

DISCUSSION

We sought to investigate whether intermittent exogenous ketosis modifies ventilatory, cardiovascular, muscular, and cerebral responses to relative workload-matched, moderate- and heavy-intensity exercise across 3 days at 3,375 m. Preexercise KE administration effectively induced ketosis at the onset of each exercise session, but did not affect $\dot{V}O_2$ kinetics in response to moderate- or heavy-intensity exercise transitions. Furthermore, KE ingestion did not mitigate the high-altitude-induced reductions in exercising blood, muscle, or brain oxygenation, having negligibly affected pulmonary ventilation. In addition, KE had no discernible effect on whole-body energy efficiency, but increased cardiac output during moderate-intensity exercise at both arrival and after ∼24 h at 3,375 m.

$\dot{V}O_2$ Kinetics

Previous studies have indicated that transitions to moderate- and heavy-intensity exercise under acute normobaric hypoxia (simulating altitudes of ∼2,000–5,200 m) are associated with a slowing and amplitude reduction of the primary phase and/or slow component of pulmonary $\dot{V}O_2$ kinetics (8–11). Such slower $\dot{V}O_2$ kinetics are considered to impair exercise performance (48) and capacity (49), and have been primarily attributed to reduced oxygen delivery to skeletal muscle (8, 10, 49). KE administration has been shown to augment whole-body $\dot{V}O_2$ during intermittent cycling exercise under progressively increasing normobaric hypoxia (∼1,000–3,000 m) (6); however, a subsequent study did not replicate such an effect during submaximal exercise following 3 h of exposure to normobaric hypoxia (∼4,000 m) (4). Notably, these responses were consistently accompanied by KE-induced hyperventilation and concomitant elevations in blood pO_2 and Sp_{O_2} (4, 6, 16, 18, 19); the former presumably representing a key regulatory factor governing the drive of oxidative metabolism across the exercise-intensity transition (49). In addition, exogenous ketosis has been associated with increased cardiac output (50) and muscle blood flow (51) in normoxia. Collectively, these observations led to the hypothesis that KE ingestion might enhance oxygen delivery to active musculature under hypoxic conditions and, consequently, accelerate $\dot{V}O_2$ kinetics during exercise-intensity transitions. Inccontrast, our findings showed that KE ingestion neither modified $\dot{V}O_2$ kinetics during the transition to moderate-intensity exercise nor mitigated their slowing during the transition to heavy-intensity exercise across the 3 day sojourn at 3,375 m. This outcome is most likely underlined by comparable oxygen availability throughout the oxygen transport cascade (resting and/or exercising Sp_{O_2} and muscle TSI), reflecting a similar hypoxic ventilatory response in both the IEK and PLA groups. The divergence in oxygen availability and subsequent rate of utilization compared with previous studies remains unclear and warrants further investigation. Nevertheless, we propose that these differences may be related to the specific diurnal KE administration strategy used in the present study, characterized by longer between-dosing intervals [1–7 vs. 0.5–1.5 h (4, 6, 19)], which may have attenuated the impact of KE ingestion on metabolic (keto-)acidosis and its compensatory increase in $\dot{V}E$. Furthermore, previous observations of enhanced oxygen diffusion, reduced oxygen cost of breathing (52) and reduced cardiac output (35) in hypobaric versus normobaric hypoxia may also underlie the pulmonary $\dot{V}O_2$ findings observed with intermittent exogenous ketosis during exercise at terrestrial high-altitude.

Blood Oxygen Saturation

Given the growing body of evidence suggesting that exogenous ketosis can attenuate hypoxia-induced reductions in blood oxygen saturation at rest and during moderate-intensity exercise under acute (≤15 h) simulated high-altitude conditions (∼2,500–6,096 m above sea level; 4, 6, 18–22), as well as at rest following ∼48 h of exposure to terrestrial high-altitude (3,375 m) (23), we initially hypothesized that this KE-induced effect would also manifest as increased exercise Sp_{O_2} during moderate- and/or heavy-intensity exercise throughout early high-altitude acclimatization. Consistent with our previous observations in a cohort of healthy, physically active men at rest and during moderate- and/or heavy-intensity exercise in the same geographical location (13), Sp_{O_2} exhibited a large decrease from SL to A, followed by a progressive increase from A to D2 of high-altitude exposure. However, the Sp_{O_2} responses during both moderate- and heavy-intensity exercise, as well as at rest before exercise testing sessions remained unaffected by KE administration at any time point during high-altitude exposure in the current study. This contradicts some of the previous work from our group (4, 6, 18, 19, 23) and others (20–22, 53) in normobaric hypoxia, showing that acute exogenous ketosis increases Sp_{O_2}. This discrepancy may again be attributable to the nature of the hypoxic exposure in our study, as exposure to hypobaric versus normobaric hypoxia (∼4,000 m) has been shown to elevate Sp_{O_2} during submaximal exercise by ∼2% through a $\dot{V}E$-independent mechanism (34); e.g., enhanced oxygen diffusivity, reduced work of breathing and airway resistance induced by hypobaria per se. Moreover, it is plausible that the ventilatory and oxygenation effects of intermittent exogenous ketosis during exercise across three days at high-altitude (especially at D1 and D2) were attenuated by the ventilatory acclimatization process itself (2, 5, 13). Indeed, in our study, $\dot{V}E$ during exercise increased by ∼7%–16%, resulting in ∼1.1%–3.5% enhancement in Sp_{O_2} throughout ∼49 h (at D2) of high-altitude exposure relative to arrival (at A). This increase is, in fact, comparable with (or greater than) the acute hyperventilatory response during exercise elicited by KE intake alone, which has been shown to enhance $\dot{V}E$ by ∼4%–12% and subsequently improve Sp_{O_2} by ∼1.5%–4.2% during exercise under acute, simulated high-altitude conditions (4, 6, 20). Alternatively, KE ingestion has been reported to attenuate reductions in Sp_{O_2} only under certain (simulated) high-altitude conditions, with our recent findings (4) suggesting this effect is potentially influenced

by the severity of blood oxygen desaturation (KE ingestion attenuated the Sp_{O_2} decline when values declined below ~85%). Indeed, upon arrival and throughout early acclimatization, Sp_{O_2} values at rest and during exercise on average ranged from ~83% to 95% in both groups. This range corresponds to the plateau region on the right-hand side of the sigmoidal oxyhemoglobin dissociation curve, where a potential KE-induced increase in blood pO_2 will barely affect Sp_{O_2} (54). This interpretation is consistent with our observations during maximal exercise, ~1.5 h postexposure to simulated altitude (~4,000 m) (4). Therefore, it can be speculated that the hypoxic and/or exercise-stimulus induced by our experimental design was insufficient to elicit the previously observed exogenous ketosis-induced improvements in blood oxygenation.

Skeletal Muscle and Brain Oxygenation

In contrast to earlier studies (8, 19), KE also did not alter muscle or brain TSI during exercise in hypoxia. Although the underlying mechanisms responsible for the observed discrepancies remain to be elucidated in the future, the divergent findings may again be partly explained by differences in KE administration protocols [~3.42 $g \cdot kg^{-1}$ body mass over 49 h vs. ~3.21 $g \cdot kg^{-1}$ body mass over 29 h (4, 19)] and/or the hypobaric versus normobaric hypoxic conditions applied, potentially producing distinct (dose response) effects on blood acid-base balance and gasses tensions (55, 56). Furthermore, as observed for Sp_{O_2}, acclimatization processes may have attenuated the effects of KE ingestion at the time of assessment [~2.4% improvement in brain TSI from D1 to D2 vs. ~2.5%–3.0% improvement after acute KE exposure (4, 19)].

Cardiac Output

Interestingly, KE ingestion increased $\dot{Q}$ during moderate-intensity exercise performed upon acute exposure (at A) and 1 day postarrival at 3,375 m (at D1). This aligns with earlier data in healthy adults (24, 25) and individuals with type 2 diabetes and/or heart failure with preserved ejection fraction (25, 26, 50), which consistently indicated increased $\dot{Q}$ at rest (24–26) and during moderate-intensity exercise (50) with exogenous ketosis under sea level conditions. Although the underlying mechanisms are not fully understood, KE-induced increases in $\dot{Q}$ may could been attributed to enhanced SV, potentially mediated by increased myocardial contractility and/or reduced systemic vascular resistance (24, 26) secondary to β-HB-induced improvements in sarcomere shortening (57) and vasodilation (51, 58). Alternatively, elevations in $\dot{Q}$ may arise from increased HR due to augmented sympathetic nervous system activation following KE ingestion (18, 19, 24, 25, 59, 60) observed at rest and during exercise both at sea level (24, 25, 59, 60) and during acute simulated high-altitude exposure (≤15 h, ≤4,000 m) (18, 19). We believe that the increase in $\dot{Q}$ at A and D1 observed in our study was likely driven by increases in SV (group × time interaction: $P = 0.025$, IEK vs. PLA: $P = 0.222$ at A and $P = 0.094$ at D1), as HR remained similar between groups at high-altitude. However, given that our study was not statistically powered to detect differences in SV, the sample size may have been insufficient to reach statistical significance. In support of this interpretation, our previous work indicated that KE ingestion can suppress diuresis at both sea level and high-altitude (6, 59, 61), which may enhance plasma volume preservation (62) and help increase SV (63) during exercise in the early high-altitude acclimatization period. Nevertheless, whether this KE-induced mechanism exerts beneficial or detrimental effects on cardiovascular adaptation during prolonged hypoxia warrants further investigation, given that hemoconcentration represents one of the key adaptive responses during early acclimatization (2).

Whole-Body Energy Efficiency

Improved energetic efficiency has been proposed as a potential benefit of exogenous ketosis (30, 64, 65), and one which may, in turn, confer an ergogenic benefit during exercise (29). Indeed, an acute elevation of blood [β-HB] via KE administration improved whole-body efficiency during incremental cycling (33) and running (65) exercise at sea level, an effect primarily driven by minor reductions in $\dot{V}O_2$ at matched workloads (33, 65). Furthermore, our recent findings suggested that KE ingestion reduced peripheral skeletal muscle and cerebral oxygen extraction at rest and during exercise under acute simulated high-altitude conditions (6, 19). In contrast, an increased pulmonary $\dot{V}O_2$ during moderate-intensity exercise (at 90% of the lactate threshold) was observed in our earlier study under progressively increasing normobaric hypoxia, implying reduced whole-body energy efficiency with exogenous ketosis at high-altitude (6). Consequently, the impact of exogenous ketosis on whole-body energy efficiency during exposures to high-altitudes remains equivocal. In the present study, whole-body energy efficiency (assessed via net efficiency calculation) remained consistent across high-altitude time points, irrespective of KE versus placebo supplementation. Furthermore, in both groups, both $\dot{V}O_2$ and $\dot{V}CO_2$ markedly decreased (in parallel with reductions in absolute workloads) from SL to A, and then stabilized at these reduced values on D1 and D2. Our findings, therefore, do not support the proposed KE-induced ergogenic benefits for whole-body energy efficiency during exercise throughout early high-altitude acclimatization. These findings are further compounded by ongoing debate over whether increased energetic efficiency, observed in rodent models (66), is reproducible in vivo in humans, given the competition for oxidative substrates (67). In fact, ketone bodies make only a modest contribution to skeletal muscle energy metabolism upon exogenous exposure (68, 69) and accounting for ~2.5%–4.5% of total energy expenditure during low- (25% W_{max}) to heavy-intensity (75% W_{max}) exercise (33). Moreover, although increasing ketone supply to the heart elevates ATP production, it does not improve cardiac efficiency (25, 70). Therefore, it remains questionable whether a modest increase in the contribution of ketone bodies to whole-body energy provision during exercise at high-altitude would have any meaningful impact on energy efficiency, thereby underscoring the need for further research specifically designed to examine such interactions.

Methodological Considerations and Limitations

Methodological constraints inherent to conducting applied research in a high-altitude field setting need to be taken into consideration when interpreting the present findings. Due to

logistical and personnel limitations during the altitude phase, it was not feasible to implement strict dietary standardization or continuous monitoring of participants' nutritional intake. Moreover, participants were not tested in a fasted state nor following controlled preexercise meals, which may have introduced variability in substrate availability and, consequently, in KE-induced physiological responses (71). Nevertheless, all individuals received one to three meals per day that were comparable in composition and served at relatively predictable times according to the mountain hut schedule. Participants were also instructed to maintain their usual eating habits and to refrain from using nutritional supplements for 2 mo before and throughout the study period. A further consideration relates to characteristics of the study sample. Although recruitment was open to all biological sexes, only six participants (18%) were women, and no control of menstrual cycle phase was implemented. Although this limits the degree to which the results can be generalized, recent evidence indicates that menstrual cycle phase exerts minimal influence on the specific physiological responses at high-altitude (72, 73). Nevertheless, future studies aimed at exploring potential sex-specific interactions between exogenous ketosis and hypoxic exposure remain warranted.

Conclusions

The present results suggest that intermittent exogenous ketosis neither alters $\dot{V}O_2$ kinetics during transitions to moderate- or heavy-intensity exercise, nor affects ventilatory, gas exchange, blood or tissue oxygenation responses, or whole-body energy efficiency, across 3 consecutive days at 3,375 m. Preexercise KE ingestion did, however, increase cardiac output during moderate-intensity exercise upon acute exposure and 1 day postarrival at high-altitude. As such, KE supplementation before exercise does not confer additional physiological advantages during early acclimatization at high terrestrial altitude.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available in the Repository of the University of Ljubljana, https://repozitorij.uni-lj.si/IzpisGradiva.php?id=173583&lang=eng.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.T., G.P.M., C.P., and T.D. conceived and designed research; D.T., M.S., and B.J.N. performed experiments; D.T. analyzed data; D.T. interpreted results of experiments; D.T. prepared figures; D.T. drafted manuscript; D.T. and T.D. edited and revised manuscript; D.T., M.S., B.J.N., G.P.M., C.P., and T.D. approved final version of manuscript.

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