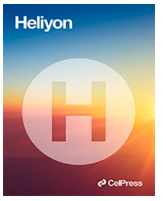
Heliyon 10 (2024) e23159

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



The importance of personalization in high altitude protocols for hematologic and metabolic benefits in sports: A multi-dimensional N-of-1 case study

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ARTICLE INFO

Keywords:
High altitude
Altitude tent
Performance
Hematologic measures
Case study
Hemoglobin
Hematocrit
Gut microbiome
Metabolic benefits
Hypoxic training
Heart rate variability

ABSTRACT

The hematologic and metabolic benefits of high altitude exposure have been extensively studied in athletes due to their promising performance enhancing effects. However, despite the increased research and development of various high altitude protocols for achieving peak performance, the reproducibility of the results at the individual level remains sparse. To systematically address this limitation and establish a more effective method to achieve consistent results at the individual level, we conducted a multi-dimensional study of one elite endurance athlete in two Phases. In Phase 1, we applied the standard protocol of LHTH (Live-High-Train-High) using a commercially available, at-home, normobaric, high altitude simulation tent under the SHTL (Sleep-High-Train-Low) model. Then, we developed the athlete's personalized protocol for peak hematologic parameters during their off-season. This protocol determined the exact total high altitude exposure time required to achieve peak hematologic parameters, which in the case of this athlete, amounted to 45 nights with approximately 8hrs per night. In Phase 2, we replicated the Phase 1 protocol during the athlete's in-season and observed the same or even higher hematologic and metabolic benefits compared to Phase 1. During both phases, we collected thousands of multi-dimensional data points to ensure that the athlete's lifestyle and environmental factors remained stable, and to increase the likelihood that physiological changes resulted primarily from the high altitude exposure. The data trends in both Phases validated that, for this athlete, hematologic measures such as red blood cell count, hematocrit, and hemoglobin, as well as electrolyte content, body weight and gut microbiome composition improved to their personal best values after a total of approximately 15 days of high altitude exposure (45 nights with roughly 8hrs per night totaling 360hrs or 15days). These improvements did not occur after the 21 days recommended by the LHTH protocol highlighting the significance of personalization in high altitude protocols that are designed for peak performance parameters. Therefore, to maximize the benefits in hematologic and other metabolic values and thus increase muscle oxygen supply and peak aerobic capacity through high altitude exposure, each athlete may require a unique total duration of high altitude exposure tailored to their individual physiology. This duration must be determined by their specific response in hematologic peaking. Therefore, initially establishing a personalized protocol for an athlete by determining their required total duration of high altitude exposure for peak hematologic values during their off-season and applying this protocol during

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https://doi.org/10.1016/j.heliyon.2023.e23159
Received 3 October 2023; Received in revised form 27 November 2023; Accepted 28 November 2023
Available online 5 December 2023

their in-season phase may lead to more successful and reproducible benefits compared to following a generalized protocol alone.

1. Introduction

The improvement of athletic performance following intermittent or continuous exposure to high altitudes has been the subject of study for over two decades, using various methodologies. However, despite the plethora of research and efforts to develop high altitude protocols for performance enhancement, the application of the results at the individual level remains controversial [1,2].

Research suggests that exposure to high altitudes (≥8,000ft or 2,500 m above sea level) can lead to improvements in important hematologic parameters related to red blood cell volume, oxygen transport capacity and aerobic performance [3,4]. High altitude exposure may also influence the sympathovagal balance of the autonomic nervous system [5,6] and may improve body composition by reducing body weight and fat while increasing muscle mass [7,8]. Although these findings are significant within the context of specific studies, they have seen limited follow-up experiments and limited applicability at the individual level. This may be attributed to the highly personalized physiological responses and adaptation times in high altitude environments, and other confounding factors and limitations [9].

Some of these factors include limitations in study design regarding specific altitudes or specific durations of exposure. For instance, some studies exclusively investigate one type of high altitude environment such as only hypobaric hypoxia (natural) or only normobaric hypoxia (artificial via a chamber or a tent) [10]. Other studies may explore different models and protocols but often do not include control groups or validation experiments. Additionally, other factors that may decrease the robustness of existing studies include a limited number of participating athletes or not accounting for potential confounding parameters like different backgrounds, physiologies, lifestyle habits, or gender [11,12]. More importantly, significant variability in results may arise from individual responses to specific high altitudes. As a result, these factors can make it challenging to successfully replicate study protocols across all athletes, even within the same discipline and the same training schedule [13,14].

However, despite these challenges, the LHTH model has been systematically studied and widely applied in research of elite sports [1,15]. The protocol of this model is structured around a 3-week or 21-day cycle of living and training at high altitude to achieve peak aerobic capacity. Upon return to sea-level, a 10-day unstable phase is observed [1]. The competition dates for peak aerobic capacity would most likely occur either within the first few days of the unstable phase or after the unstable phase [1].

In this study, we applied the LHTH protocol under the SHTL model in an elite endurance athlete by conducting a multi-dimensional, high-throughput N-of-1 case study in two phases. In Phase 1, the main experiment, we determined the exact duration of high altitude exposure to achieve peak hematologic parameters. In Phase2, we replicated the Phase 1 protocol duration and validated the findings of Phase 1. During both phases, the study was performed using a commercially available, at-home, normobaric high altitude simulation tent and exposure to 11,000ft for a nightly average of approximately 8hrs of sleep. The total high altitude exposure included 4 nights of

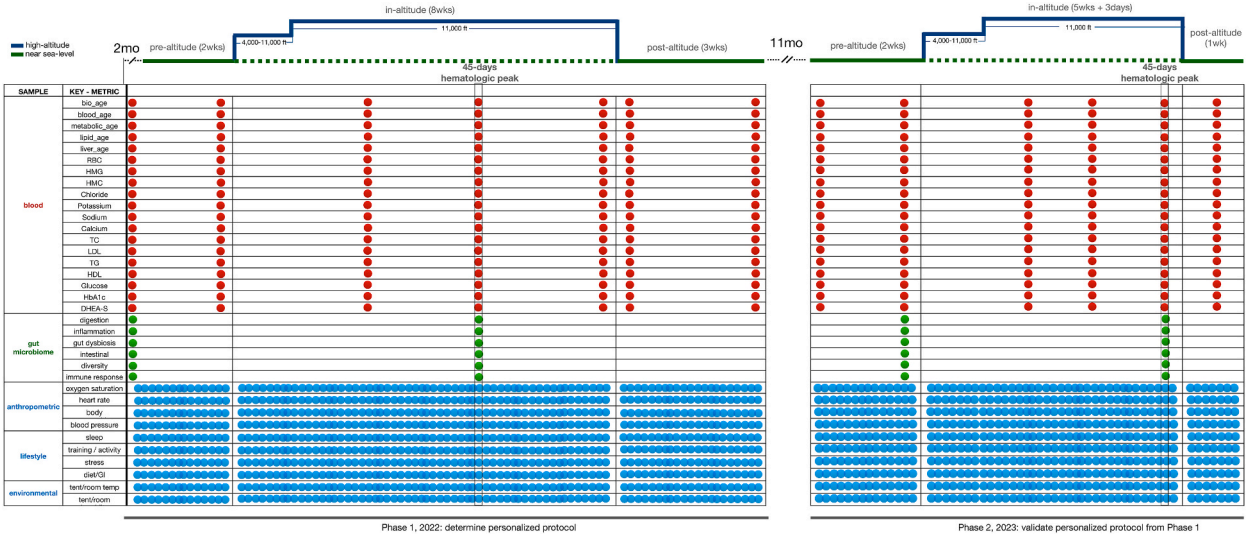

Fig. 1. Timeline and summary of data collected for both phases of the SHTL (Sleep High Train Low) model in this study. Red dots represent blood tests for each day (7 blood tests for Phase 1 and 6 blood tests for Phase 2); green dots represent fecal microbiome tests for each day (2 tests for Phase 1 and 2 tests for Phase 2 – one before and one after 45 days in the high altitude tent); blue dots represent daily measurements of various anthropometric, lifestyle and environmental metrics throughout each experiment. Squared is the time point when the 45-day hematologic peak was observed (in Phase 1) and then again repeated (in Phase 2). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

acclimatization accruing a 56-night of high altitude exposure in Phase 1, and a 45-night in Phase 2. Over 5000 data points were collected for the 91-day main experiment in Phase 1 and over 3000 data points for the 66-day validation experiment in Phase 2 (Fig. 1).

Overall, we observed improvements in blood markers, electrolyte content, metabolic efficiency, and gut health following high altitude exposure in both experiments. The athlete noticed feelings of increased vitality and energy both within the first week (between days 5 and 8) and within the second week (in days 13 and 14) upon returning to baseline, which recapitulate the LHTH protocol. However, performance related hematologic parameters, such as red blood cell count, hematocrit and hemoglobin reached maximum values precisely after 45 nights under the SHTL model declining thereafter in both phases (Supplemental Fig. 1) rather than after the 21 days stipulated by the standardized LHTH model protocol. These 45 nights with an average nightly exposure of roughly 8hrs sum 360hrs or 15 days, which are fewer days compared to the 21 days recommended by the LHTH protocol. This observation assumes that hypobaric altitude exposure (real, under the LHTH model) and normobaric altitude exposure (artificial, under the SHTL model) yield very similar results in hematologic benefits as demonstrated in various studies, despite the differing physiological effects these two methods induce [9]. Therefore, the noted discrepancy in reaching maximum hematologic measures in this particular case, may reflect the individual athlete's quicker adaptation time to high altitude compared to the standardized protocol. Hence, it is imperative to determine the individual adaptation process and duration when devising a successful high altitude protocol for peak performance.

2. Case presentation

2.1. Experimental design

An elite endurance athlete was monitored for 91 days during the main experiment of Phase 1 in 2022, which occurred during their off-season, and for 66 days during the validation experiment of Phase 2 in 2023, which took place during their in-season (Supplemental Table 1 and Fig. 1). Both phases included a 14-day baseline period in which the athlete slept in their bed at sea-level altitude (125ft). The baseline period was followed by either a 56-day period (for Phase 1) or a 45-day period (for Phase 2) during which the athlete slept in a normobaric high altitude simulation tent assembled in their bed. The high altitude simulation settings were set as following: 7 nights of acclimatization at progressive high altitude increments: starting at 4,000ft (1 night) and increasing to 5,000ft (1 night), 7,000ft (1 night), 9,000ft (1 night) and finally 11,000ft (3 nights). The acclimatization week was followed by 49 nights (for Phase 1) or 38 nights (for Phase 2) of continuous sleeping at 11,000ft. This was then followed by 21 nights (for Phase 1) or 7 nights (for Phase 2) during which the athlete returned to sleeping at the baseline altitude close to sea-level at 125ft (Fig. 1).

Throughout the experiments, the athlete diligently maintained their weekly training load, characterized by weekly total activity, training frequency, volume, and intensity – recorded as TRIMP factor [16] (Supplemental Fig. 2). The athlete also ensured consistency in their lifestyle parameters throughout the duration of both experiments including hours of sleep, sleep quality, hours of total activity,

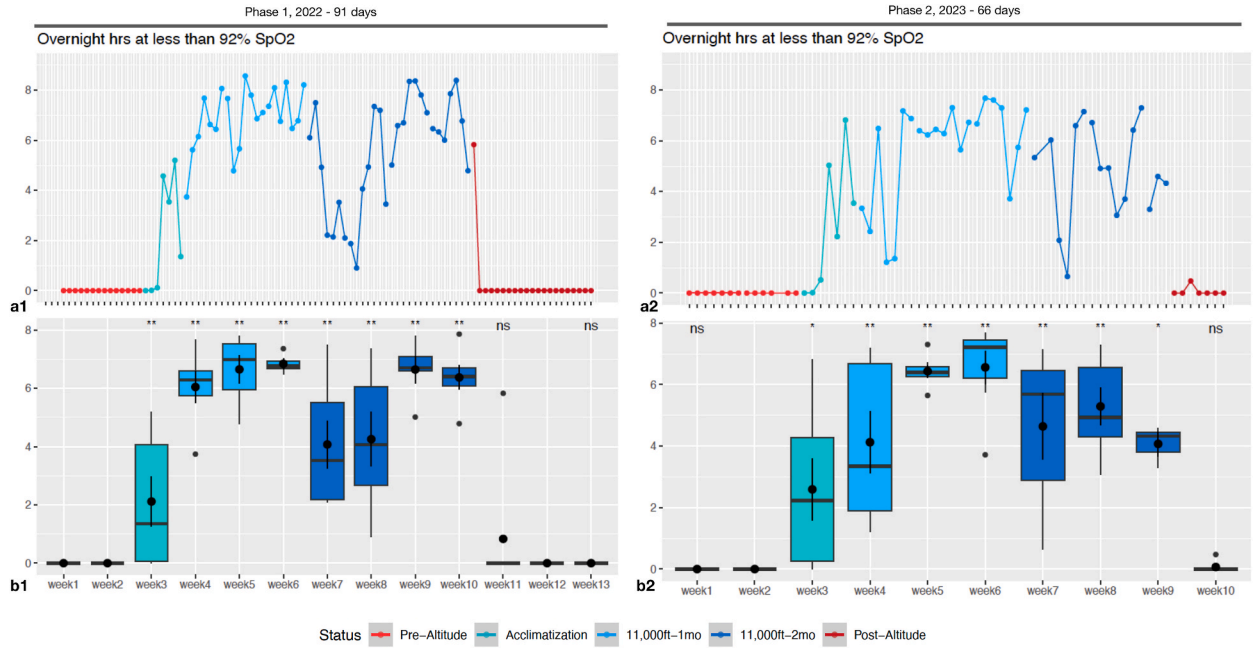

Fig. 2. Daily (a1, a2) and weekly (b1, b2) average hours spent at less than 92 % blood oxygen saturation levels (SpO_2) for Phase 1 and Phase 2. The data confirm an average mild hypoxic exposure of 6.1hrs/night for Phase 1 and 5.3hrs/night for Phase 2. Statistical analyses showed significantly higher number of hours spent at 92 % SpO_2 during the high altitude period compared to Pre-Altitude week2. [Note: all changes of mean values were calculated with the Wilcoxon rank sum test compared to week 2 Pre-Altitude and significance is indicated with the p-value cutoff limits as *p-value <0.05, **p-value <0.01].

stress tolerance, and gastrointestinal health (Supplemental Fig. 2). Other environmental parameters such as daily room temperature and humidity inside and outside the high altitude tent remained stable albeit subjected to minor seasonal variations (for complete data and trends, see Supplemental Files).

To assess changes in the athlete's physiology, a comprehensive set of tests was conducted. These tests included 7 blood tests in Phase 1 and 6 blood tests in Phase 2 performed before, during and after the high altitude exposure. In addition, gut microbiome tests were completed through fecal metagenomic shotgun sequencing involving 2 tests for each of Phase 1 and Phase 2 before and during the high altitude exposure. Daily measures of body weight and composition were recorded as well as 2 min tests of heart rate variability and blood pressure upon awaking. Lastly, continuous recordings were made for overnight heart rate and blood oxygen saturation levels (for complete data and trends see Fig. 1 and Supplemental Files).

3. Results

3.1. Significant changes in overnight blood oxygen saturation during the high altitude nights confirmed exposure to hypoxia

To track the athlete's time spent at or below 92 % of oxygen saturation (SpO_2), which is indicative of a mild hypoxic state, continuous blood oxygen saturation levels and heart rate were measured throughout each night's sleep. During Phase 1, spanning 49 nights of sleep at 11,000ft with an average duration of 8.3hrs per night, there was an average of 6.1hrs per week spent at SpO_2 levels below 92 % (± 1.9hrs) (Fig. 2(a1, b1)). During Phase 2, spanning 38 nights of sleep at 11,000ft with an average duration of 7.9hrs per night, there was an average of 5.3hrs per week spent at SpO_2 levels below 92 % (± 2hrs) (Fig. 2(a2, b2)). Elevated minimum heart rate was observed in both phases during the nights spent at high altitude (Supplemental Fig. 4).

3.2. Changes in hematologic parameters revealed optimal performance profile after 45 nights of high altitude exposure in both Phase 1 and Phase 2 experiments

A total of 7 comprehensive blood tests were performed during Phase 1 and a total of 6 were performed during Phase 2 (Fig. 1). The tests included blood composition measures, complete lipid, electrolyte, metabolic and hormonal profiles (Supplemental Files).

Data trends indicated that overall, significant improvements in measures associated with athletic performance were observed after high altitude exposure reaching the athlete's personal peak after precisely 45 nights (Supplemental Fig. 1 and Supplemental Files). Even higher values were achieved in the follow-up experiment during Phase 2 and were recorded after 45 nights similarly to Phase 1. These improved blood measures included enhanced electrolyte content (potassium and sodium), increased levels of calcium, and elevated levels of total red blood cell counts, hematocrit, and hemoglobin (Fig. 3). In both experimental phases, the athlete's blood markers transitioned from being within lower or median values (before high altitude sleep) to higher and improved values (after high

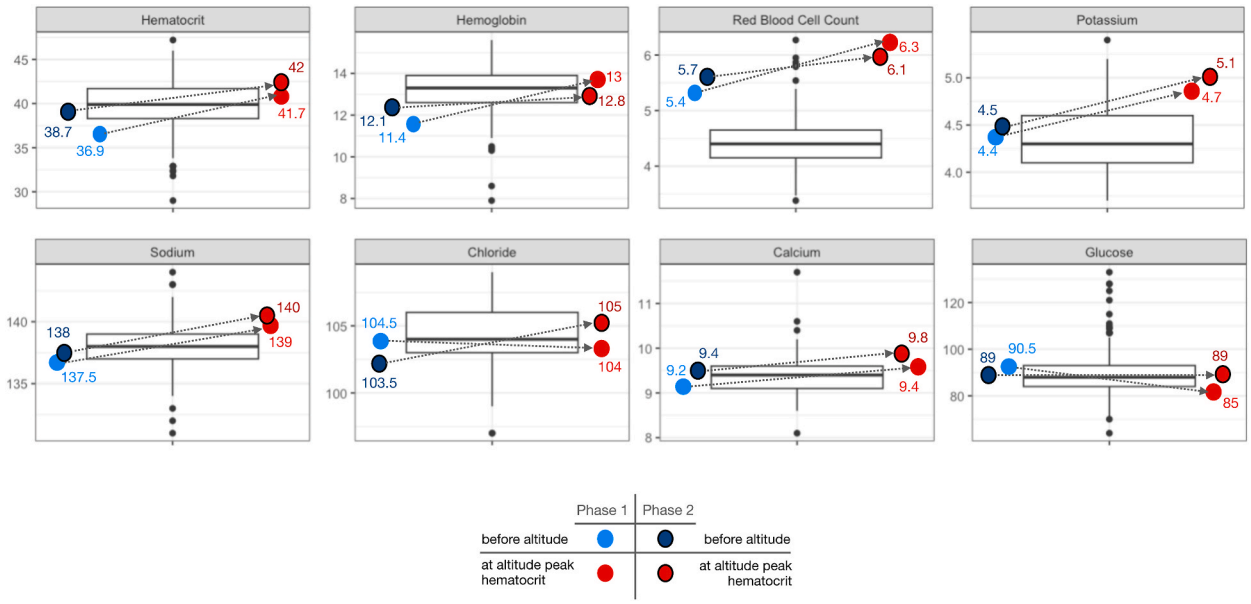

Fig. 3. Key markers from comprehensive blood tests before (blue circles) and after (red circles) 45 nights of high attitude exposure at peak hematologic parameters compared to a healthy population (box and whisker). For Phase 1 (simple circles) and Phase 2 (lined circles), hematologic and metabolic markers were improved including decreased glucose levels, increased red blood cell counts, hematocrit, hemoglobin, calcium, and electrolytes (potassium, sodium, chloride). For comparison, box and whisker plots indicate the distribution (median value and 1st and 3rd quartiles) of blood markers from over two hundred samples of a healthy cohort with the same sex and age bracket as the athlete. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

altitude sleep) when compared to a quartile range derived from the same gender and age group in the general population (box and whisker plots in Fig. 3).

3.3. Changes in gut bacteria showed improved overall gut health after 45 nights of high altitude exposure in both Phase 1 and Phase 2 experiments

The athlete conducted 2 at-home fecal microbiome tests during Phase 1 and another 2 during Phase 2. One test was performed before the high altitude exposure and the other took place immediately after the 45 night duration when the hematologic peak occurred. The purpose of these fecal microbiome tests was to assess changes in the gut bacterial composition and metabolism (Gut Health Test, Thorne HealthTech, Inc.) [17]. Data trends from the tests showed that sleeping at high altitude can improve digestion, lower inflammation, reduce dysbiosis and intestinal permeability, and improve immune system and readiness (Gut Health Test reports, Table 1). For detailed microbial composition in each test, see Supplemental Files.

3.4. Significantly lower body weight during high altitude exposure was maintained after return to baseline

The athlete's body weight and body composition were monitored daily upon waking. Notably, without any reported changes in the athlete's diet or activity, the data showed significant body weight reduction during the weeks of high altitude exposure when compared to the week prior to high altitude (Wilcoxon test p-value <0.05, Fig. 4, Supplemental Fig. 2). Trends also revealed a reduction in % change in body fat as well as reduction in % change in muscle mass and body water although these reductions did not reach statistical significance (Supplemental Fig. 5). Interestingly, the significant reduction in body weight persisted throughout the weeks of returning to baseline for both experiments.

3.5. Significant changes in heart rate variability morning measures showed altered sympathovagal balance of the autonomic nervous system

All metrics of heart rate variability (HRV) of the athlete were assessed in daily 2min measures upon waking. These metrics included the time domain indexes of RMSSD (the root mean square of successive differences between normal heartbeats), SDNN (the standard deviation of NN intervals, where NN intervals are the RR intervals when artifacts are removed), PNN50(%) (percent of successive NN intervals that differ by more than 50 ms), and MeanRR (average of RR interval duration) as well as the frequency domain indexes of total power, LF (Low frequency), HF (High frequency) and LF/HF ratio (Supplemental Files) [18].

Compared to the baseline week 2, RMSSD showed significant increase between week 5 and week 8 during Phase 1 (Fig. 5 a1) and in week 9 during Phase 2 (Fig. 5 a2). The LF/HF ratio exhibited substantial decline over the entire duration of Phase 1 spent at high altitude (Fig. 5 b1). Similarly, in Phase 2, the LF/HF ratio displayed a significant decline during most of the high altitude weeks (Fig. 5 b2).

4. Discussion

In this study, we aimed to systematically address the need for personalization when designing a high altitude protocol to achieve peak performance parameters. Towards that end, we applied and extended the standardized LHTH protocol [1] using an SHTL model while closely monitoring an elite endurance athlete for a two year period. We conducted a multi-dimensional, N-of-1 case study in two experimental phases: Phase 1 to determine the personalized protocol for peak hematologic parameters (during the off-season of 2022), and Phase 2 to validate the protocol of Phase 1 (during the in-season of 2023).

Data collection encompassed measurements of overnight blood oxygen saturation levels, heart rate and heart rate variability, hematologic and metabolic blood markers, gut microbiome tests, training parameters, body composition and lifestyle metrics. In both experimental phases, the analyses of results revealed significant changes occurring during the period of sleeping in the high altitude tent (Supplemental Fig. 4). Peak hematologic values such as red blood cell count, hematocrit, hemoglobin as well as electrolyte content were attained after 45 nights of high altitude exposure (Fig. 3). The average sleep duration was 8.3hrs during Phase 1 and 7.9hrs during Phase 2, totaling 373.5hrs or 15.6 days in Phase 1 and 355.5hrs or 14.8 days in Phase 2.

Table 1
Summary of key gut health metrics. The metrics were calculated based on levels of associated bacteria and their metabolic activity in the gut through the reports of Gut Health Test, a commercial gut test (Thorne HealthTech, Inc., Supplemental Files).

DNA GUT HEALTH TEST					
Direction/Effect	Gut Metric	Phase 1		Phase 2	
		before altitude	at altitude peak hematocrit	before altitude	at altitude peak hematocrit
Higher/Better	**Digestion**	67.8	71.3	**57.3**	76
Lower/Better	**Inflammation**	43.8	29.9	**66.4**	49.1
Lower/Better	**Gut dysbiosis**	77.6	70.4	**72.6**	68.4
Lower/Better	**Intestinal permeability**	47.9	24.4	**51.9**	45.9
Lower/Worse	**Gut diversity**	88	68	**94**	89
Higher/Better	**Immune readiness**	41	48	**47**	48

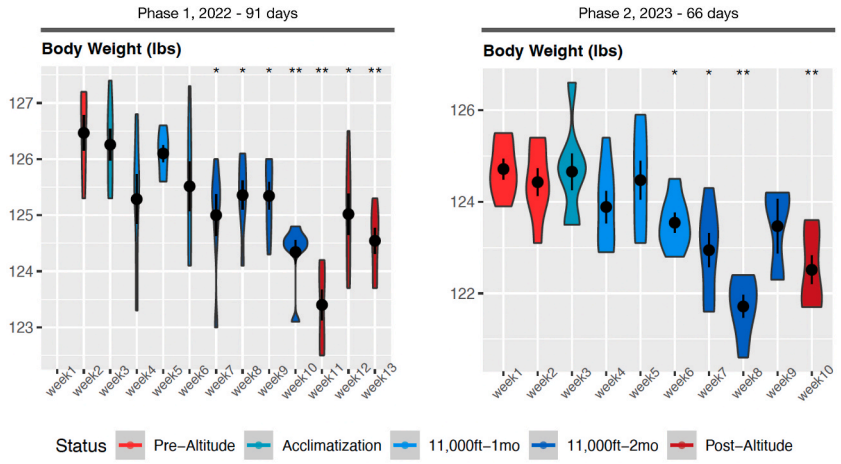

Fig. 4. Weekly changes in body weight (lbs.) during the Phase 1 and Phase 2 experiments. In both experimental phases, there was a significant reduction in body weight during the weeks of altitude which was maintained after return to baseline (week 11–13 for Phase 1 and week 10 for Phase 2). [Note: all changes of mean values were calculated with the Wilcoxon rank sum test compared to week 2 of baseline and significance is indicated with the p-value cutoff limits as *p-value <0.05, **p-value <0.01].

During both phases, the approximately 15 days needed to reach peak hematologic values differed from the 21 days recommended by the LHTH model protocol designed for hypobaric high altitude settings. This observation is based on the notion that hypobaric altitude exposure (real, under the LHTH model) and normobaric altitude exposure (artificial, under the SHTL model) confer similar results in hematologic benefits, something that has been demonstrated in various studies despite the physiological differences they impose such as minute ventilation and nitric oxide [10].

In general, the hematologic benefits of high altitude exposure have been extensively studied previously, but the results have shown variability and they have been challenging to replicate due to numerous confounding factors including individual physiological adaptations to high altitude [11–14]. Here, we aimed to develop and validate a personalized protocol to achieve optimal blood markers while also recording other cardiovascular and metabolic benefits.

It is noteworthy that, considering there were no significant changes in the athlete's dietary and lifestyle habits, the additional recorded benefits in HRV, body composition (weight and fat % reduction) and gut health are intriguing. In mountaineers and short-term visitors of high altitude environments, gastrointestinal problems typically manifest as nausea and vomiting. Anorexia has also been observed and although a multifactorial causality is considered, hormonal changes in leptin and cholecystokinin are hypothesized, due to hypoxia [19]. In this study, after 45 nights of high altitude exposure, improved digestion and lowered inflammation were observed in both experimental phases although there was a decrease in the gut microbial diversity.

To delve more deeply into the subject, an examination of the complete breakdown of the microbial community revealed that high altitude exposure led to an increase in some beneficial bacteria (Supplemental Files and Supplemental Fig. 6). For instance, there was an elevation in short chain fatty acid levels of butyrate, lactate, propionate and valerate [20] (Phase 1, Supplemental Fig. 6), and an elevation in the health promoting species, *Faecalibacterium prausnitzii* [21] (Phases 1 and 2, Supplemental Fig. 6). Conversely, some other beneficial bacteria decreased such as the pluripotent probiotics species, *Akkermansia muciniphila* [22] and *Bifidobacterium* [23]. On the other hand, some pathogenic bacteria decreased, such as *Alistipes* [24] (Phase 1) and *Eggerthella lenta* [25] (Phases 1 and 2, Supplemental Fig. 6). In summary, despite a reduction in gut diversity, the 45-night period of high altitude exposure improved the overall gut health, digestion, and metabolic capabilities of the athlete. These improvements occurred without imposing any restrictions to dietary habits or without any additional reported negative gastrointestinal symptoms.

It is also worth noting that during both experimental phases, the athlete lost significant weight and fat percent. Similar changes in body composition as a result to exposure in hypoxic environments have been reported previously [26]. However, the body composition alterations may vary across studies, depending on factors such as the duration of exposure, the altitude setting, and individual responses based on activity background, sex, and age. Nevertheless, the overall trends are consistent towards lower body weight and reduced body fat [26].

Lastly, it is worth reporting the cardiovascular and recovery benefits of the high altitude exposure observed from the HRV metrics. In general, all HRV metrics describe changes in time intervals between consecutive heartbeats reflecting the adjustments that occur as the autonomic nervous system (ANS) regulates unconscious functions including respiration, digestion, blood pressure and cardiac function [18]. The ANS is a complex network of cells and acts primarily unconsciously to control bodily functions by regulating a balance between the sympathetic nervous system (SNS, "fight of flight" response) and the parasympathetic nervous system (PNS, "rest and digest" response). The exact association between the HRV metrics and the ANS control or balance between SNS and PNS in healthy individuals remains controversial [27], but recent research has indicated that the HRV metrics of RMSSD and HF associate primarily with the activation of the PNS and enhanced parasympathetic activity [28,29]. The enhanced parasympathetic activity is associated to improved rest and recovery [30]. It is interesting to note that a significant increase of the RMSSD was observed in both experimental

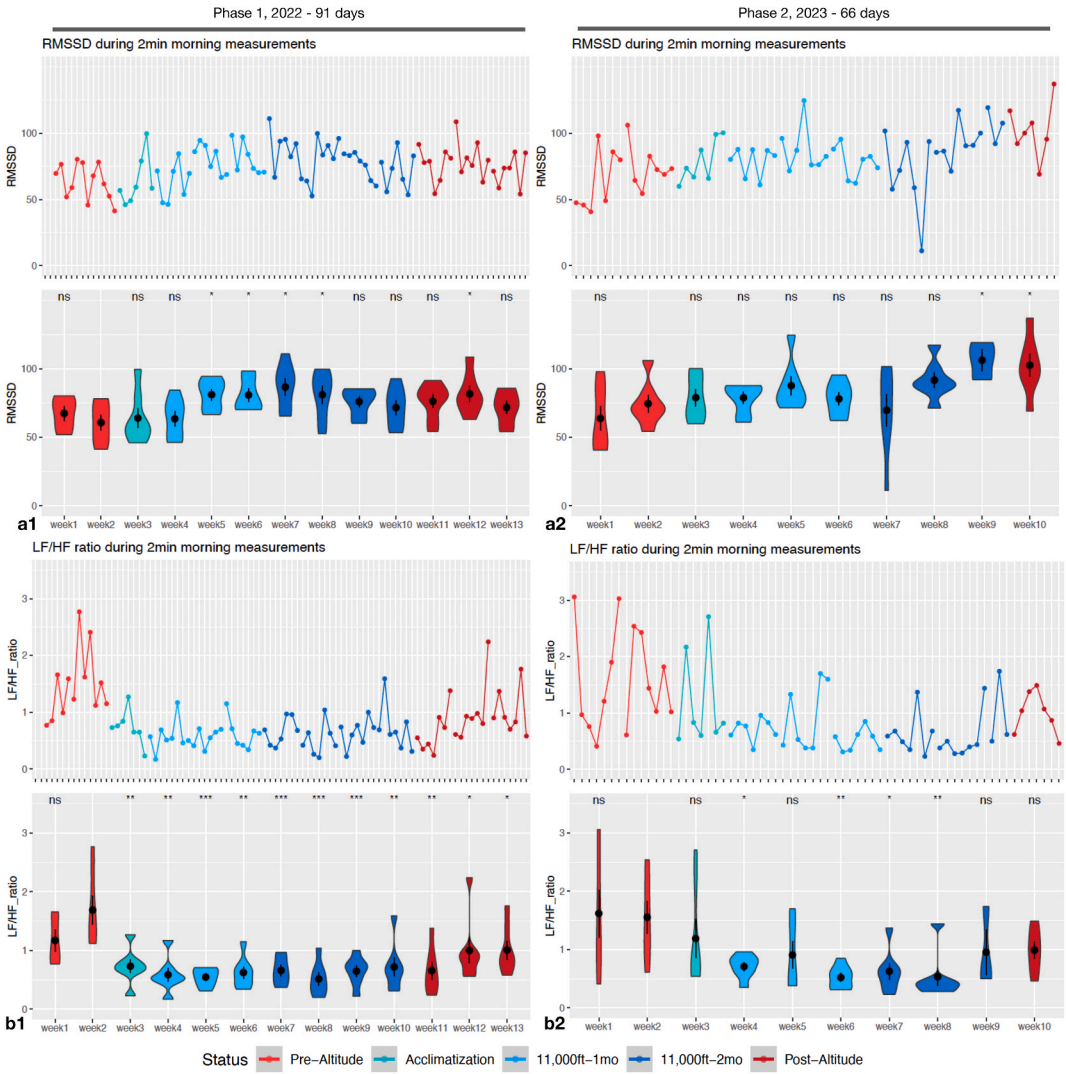

Fig. 5. Daily and weekly measures of RMSSD (a1, a2) and LF/HF ratio (b1, b2) during short-term 2min HRV upon waking for Phase 1 (a1, b1) and Phase 2 (a2, b2) experiments. Significant increase in RMSSD values during weeks 5–8 for Phase 1, and in week 9 for Phase 2. Significant decrease of LF/HF ratio during the entire high altitude period and post-altitude 3 week period for Phase 1, and during most high altitude weeks for Phase 2 [Wilcoxon rank sum test compared to baseline week 2, *p-value <0.05, **p-value <0.01, ***p-value <0.001].

phases. This observation may indicate that during the high altitude period, the athlete showed a change in their ANS balance, characterized by increased parasympathetic activity and activated PNS. This change possibly contributed to better recovery and digestion as also supported by the observed alterations in the athlete's gut microbial composition and activity.

5. Conclusion

Conducting a unique, multi-dimensional, N-of-1 study, we underscored the significance of personalization in designing high altitude protocols to attain performance oriented, hematologic parameters. We applied the standardized LHTH protocol within the SHTL model to develop a personalized protocol for the athlete and achieve peak hematologic parameters during their off-season. We then repeated the personalized protocol and validated it during their in-season in the following year. The results demonstrated that for this athlete, peak hematologic and metabolic parameters were achieved earlier than the LHTH protocol recommendation. In addition to the improved blood results, the athlete exhibited enhanced cardiovascular and recovery metrics, positive changes in body composition and advancements in gut health. Despite the limitations inherent in case studies focused on a single individual, this research work endeavored to collect multiple measurements to mitigate confounding variables and included a follow up experiment to ensure the initial observations validity. The outcomes of this work highlighted the paramount importance of developing a high altitude protocol at the individual level to consistently achieve peak hematologic and metabolic parameters that contribute to optimal aerobic

capacity and performance. In practical applications, athletes seeking to leverage high altitude exposure as a means to improve their performance, may experience more successful and reproducible results by determining their personalized protocol according to this study's methodology:

- Identify the precise high altitude exposure duration needed to achieve peak hematologic values during the off-season
- Establish this inferred optimal time as a personalized protocol
- Replicate this personalized protocol during the in-season

Ethics declarations statement

The participant provided informed consent to participate in the study.

The participant provided informed consent for the publication of their anonymized case details and data analyses.

Review and/or approval by an ethics committee was not needed for this study because this is a case report. Case reports do not meet the regulatory definition of research because they would not qualify as a systematic investigation that contributes to generalizable knowledge.

This study report is prepared in accordance with the requirements of the HIPAA privacy regulations and all information and data written and provided in this work is de-identified.

Data availability statement

All data to support the conclusions have been provided in the Supplemental Material.

CRediT authorship contribution statement

Loukia Lili: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Cem Meydan:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis, Data curation. **Nate Rickard:** Writing – review & editing, Conceptualization. **Bodi Zhang:** Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Loukia Lili reports financial support and equipment, drugs, or supplies were provided by Thorne HealthTech, Inc. Loukia Lili reports equipment, drugs, or supplies was provided by Mile High Training, LLC. Loukia Lili reports equipment, drugs, or supplies was provided by Polar Electro Oy. Cem Meydan reports financial support was provided by Thorne HealthTech, Inc. Nate Rickard reports financial support was provided by Thorne HealthTech, Inc. Bodi Zhang reports financial support was provided by Thorne HealthTech, Inc. Loukia Lili reports a relationship with Thorne HealthTech, Inc. that includes: employment and equity or stocks. Cem Meydan reports a relationship with Thorne HealthTech, Inc. that includes: employment and equity or stocks. Nate Rickard reports a relationship with Thorne HealthTech, Inc. that includes: employment and equity or stocks. Bodi Zhang reports a relationship with Thorne HealthTech, Inc. that includes: employment and equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The normobaric, high altitude simulation tent was provided by Mile High Training, LLC (https://milehightraining.com/). The training load and all activity metrics were monitored by wrist GPS watches provided by Polar Electro, USA (https://www.polar.com/us-en). The at-home blood (Biological Age Health Panel) and gut DNA (Gut Health Test) tests were provided by Thorne HealthTech, Inc. (https://www.thorne.com/).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23159.

List Of Abbreviations

LHTH	Live High Train High
SHTL	Sleep High Train Low
SpO_2	Oxygen saturation
HR	Heart rate
HRV	Heart rate variability
RMSSD	The root mean square of successive differences between normal heart beats

SDNN The standard deviation of all normal RR (NN) intervals
PNN50(%) The mean number of times an hour in which the change in successive normal RR (NN) intervals exceeds 50 ms
meanRR Average RR interval duration
LF Low frequency
HF High frequency
ANS Autonomic nervous system
PNS Parasympathetic nervous system
SNS Sympathetic nervous system

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