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HYPOXIA • SHORT COMMUNICATION

Intermittent hypoxia revisited: a promising non-pharmaceutical strategy to reduce cardio-metabolic risk factors?

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Abstract
Purpose The study aims to investigate the effects of moderate intermittent hypoxia (IH) on key cardio-metabolic risk factors in overweight and obese subjects.
Methods Six subjects were exposed to 10 sessions of moderate IH over 2 weeks (based on $\overline{SpO_2} = 80\%$; ~70 min per session). Measures were made of blood glucose (GLU) and lactate (La^-); high (HDLc) and low-density lipoproteins (LDLc); triglycerides (TRG), systolic (SBP), and diastolic blood pressure (DBP); and cardiac autonomic indices [root mean square of successive R-R interval differences (RMSSD) and short-term fractal scaling exponent (DFAα1)].
Results GLU decreased and La^- increased following a single IH session (6.21 ± 1.62 vs. 5.32 ± 1.03 mmol L^{-1}; $p < 0.05$; 1.14 ± 0.21 vs. 1.47 ± 0.22 mmol L^{-1}), but no sustained change after 10 sessions of IH occurred ($p > 0.05$). Conversely, LDLc (3.00 ± 0.68 vs. 2.51 ± 0.60 mmol L^{-1}; $p < 0.05$), LDLc/HDLc ratio (2.52 ± 0.66 vs. 2.26 ± 0.70 mmol L^{-1}; $p < 0.05$), and SBP (118.6 ± 13.3 vs. 109.6 ± 11.3 mmHg; $p < 0.05$) were all significantly decreased after 10 sessions.
Conclusion A short course of recurrent IH appears to be a safe and effective non-pharmacological method of reducing key cardiovascular risk factors associated with metabolic disorders.

Keywords Moderate intermittent hypoxia · Cardio-metabolic risk factors · Treatment strategy · Obesity

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Introduction

Repeated episodes of low oxygen interspersed with re-oxygenation (intermittent hypoxia (IH)) are well known in sleep medicine and are characteristic of obstructive sleep apnea [1]. Sleep apnea-induced IH has been linked to detrimental cardiovascular, respiratory, cognitive, and metabolic outcomes [2]. Despite considerable heterogeneity among IH protocols, these studies are often associated with severe exposure to hypoxia (2–8% inspired O_2) along with high frequencies of hypoxemia-re-oxygenation cycles (48–2400 cycles day^{-1}) [3]. By contrast, beneficial effects of low-dose IH (9–16% inspired O_2) with 3–15 cycles day^{-1} have been reported in humans to treat clinical disorders ranging from psychiatric depression to hypertension [3].

We tested the hypothesis that a two-week exposure to passive moderate IH would elicit beneficial outcomes by diminishing key cardio-metabolic risk factors in overweight or obese adults. In addition, this study details an alternative to the standard IH methodology. Since the hypoxic ventilatory response is known to be highly variable, the proposed methodology is based on mean arterial oxygen saturation $(\overline{SpO_2})$,

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to ensure that the same "hypoxic dose" was administered to the all participants.

Materials and methods

Subjects

Six participants (3 overweight and 3 obese; 4 males and 2 females) were recruited (body mass index, 30.6 ± 1.4 kg m^{-2}; age, 56.2 ± 10.0 years). Baseline values of the main metabolic and cardiovascular markers were 5.86 ± 1.23 mmol L^{-1} (GLU); 1.32 ± 0.39 mmol L^{-1} (TRG); 1.27 ± 0.42 mmol L^{-1} (HDLc); 3.00 ± 0.68 mmol L^{-1} (LDLc); 120.3 ± 15.2 mmHg (SBP); and 79.5 ± 8.1 mmHg (DBP).

Experimental design

Based on a single-blinded approach, the experimental design is presented in Fig. 1. Pre-treatment measures were taken prior to 5 days of daily sham sessions (mask breathing room air) followed by 10 IH sessions (mask breathing normobaric IH) over 2 weeks (5 days per week). For normobaric IH, the duration of hypoxic and normoxic intervals were tailored to each participant depending on their speed of desaturation and re-saturation [4]. Briefly, the underlying strategy was to ensure that the participants maintained an $\overline{SpO_2}$ of 80%, over 70 min of repeated cycles of hypoxemia followed by re-oxygenation (Fig. 2). Before pre-measurements, all participants were given a short "hypoxic test" consisting in a few cycles of IH to estimate their individual speed of desaturation and re-saturation. Based on this short hypoxic test, the two criteria we used to achieve a mean SpO_2 over 70 min were as follows:

- Asking the participants to take the mask-off when SpO_2 reaches a threshold of 70%
- Then asking the participants to put the mask-on when SpO_2 returns to 95%

Acute hypoxic conditions (5000 m, i.e., FiO_2 = 10%) were provided by a hypoxicator (ATS-HP, Pulford Air & Gas Pty LTD, Australia) while SpO_2 was continuously recorded with a finger probe oximeter (CMS60D, Contect TM, Qinhuangdao, China). The sham sessions were treated like the experimental sessions, except that the air breathed through the facemask

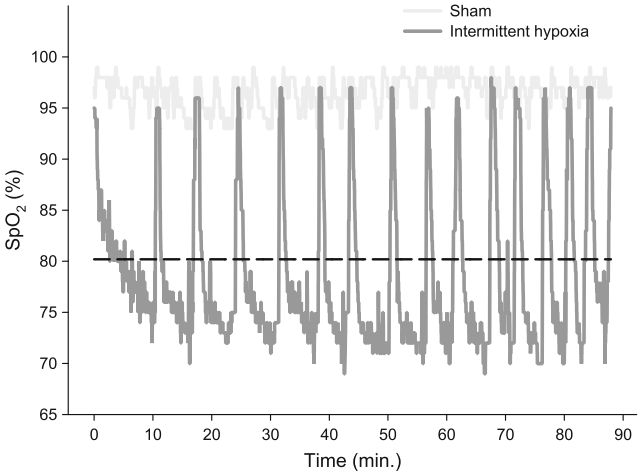

Fig. 2 Kinetics of both desaturation and re-saturation throughout a single IH session in a subject. As indicated by the horizontal dotted line, the overall "hypoxic dose" is based on mean peripheral oxygen saturation $\left(\overline{SpO_2} = 80\%\right)$

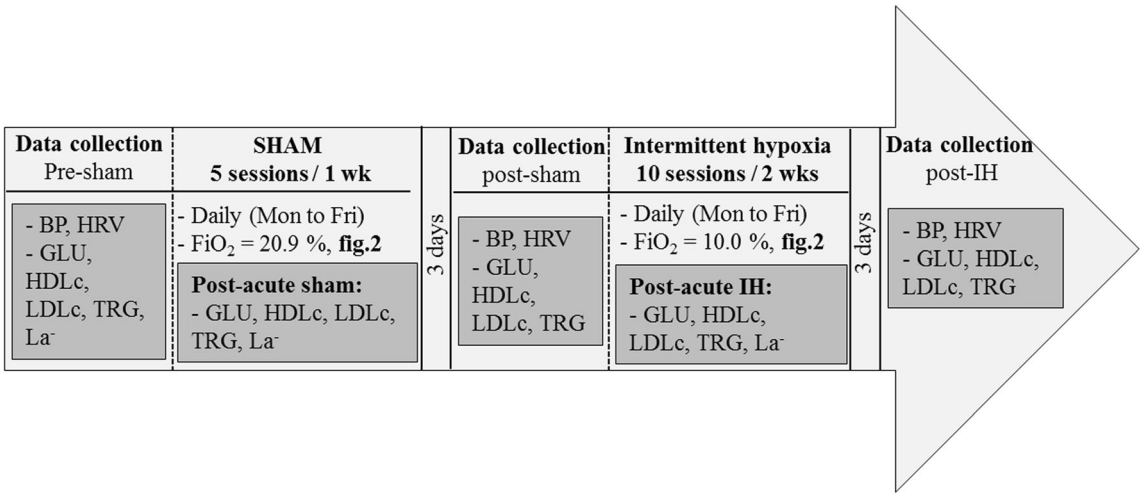

Fig. 1 Timeline illustrating the design of the experiment. *GLU* arterial blood glucose, *TRG* triglycerides, *HDLc* high-density lipoproteins, *LDLc* low-density lipoproteins, La^- Lactatemia, *BP* Blood pressure, *HRV* heart rate variability, FiO_2 fraction of inspired oxygen

was normoxic (FiO_2 = 20.9%). All samples were collected in the early morning under strictly fasted conditions. Participants were asked not to make any significant lifestyle changes throughout the study; none took medication or suffered from any known diseases.

Lipid, cholesterol, and blood glucose profiles

Fasting concentrations of high- and low-density lipoproteins (HDLc and LDLc); triglycerides (TRG); and arterial blood glucose (GLU) concentration were determined from arterialized capillaries via a finger prick sample, taken before and after the first session (sham and IH) as well as 3 days after each treatment (sham and IH), using a Cholestech LDX device (Alere, San Diego, California).

Lactate

Blood lactate samples (0.3 μL) were drawn from arterialized capillaries via a finger prick before and after the first session (sham and IH) then analyzed with a hand-held portable analyzer (Lactate pro 2, LP, Arkray KDK, Japan) to obtain the concentration of lactate (La^-).

Blood pressure and cardiac autonomic regulation

Beat-to-beat systolic (SBP) and diastolic blood pressure (DBP) were continuously recorded during a 15-min rest period by means of a servo-controlled finger photoplethysmograph (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands). Simultaneous inter-beat intervals were recorded using a heart rate monitor (Suunto Memory belt, Suunto Oy, Vantaa, Finland) to estimate cardiac autonomic regulation. A widely accepted time-domain index, the root mean square of successive R-R interval differences (RMSSD), was used to estimate the parasympathetic outflow to the heart [5]. In addition, cardiac autonomic co-activation was estimated through the short-term fractal scaling exponent (DFAα1) [6]. These measures were taken at three time points: prior to commencement of the study, after 5 sessions of sham, and after 10 sessions of IH.

Statistical analysis

Friedman's test and multiple pairwise comparisons (adjusted with Tukey's test) were used for all comparisons. A p value <0.05 was considered statistically significant for all analyses.

Results

Initial sham or IH

Arterial GLU was similar for the first pre- and post-sham (5.86 ± 1.23 vs. 5.67 ± 1.20 mmol L^{-1}, respectively; p = 0.58; Fig. 3a). However, arterial GLU was significantly lower following the first IH session (6.21 ± 1.62 vs. 5.32 ± 1.03 mmol L^{-1}; $p < 0.05$, Fig. 3a). Conversely, La^- following the first IH was significantly higher (1.47 ± 0.22 vs. 1.14 ± 0.21 mmol L^{-1}; $p < 0.05$). There was no difference in La^- before and after the first sham session (1.25 ± 0.22 vs. 1.12 ± 0.21 mmol L^{-1}, respectively; $p > 0.05$).

Metabolic and cardiovascular markers after 10 sessions of IH compared to sham treatment

The IH treatment had a significant effect on LDLc and the LDLc/HDLc ratio. Pairwise comparisons revealed that LDLc was lower at the end of the 10 sessions of IH than before it (pre- 3.00 ± 0.68 vs post- 2.51 ± 0.60 mmol L^{-1}, $p < 0.05$). The LDLc at the end of the 10 sessions of the IH protocol was lower than after 5 days of sham (2.51 ± 0.60 vs. 2.90 ± 0.82 mmol L^{-1}, respectively, $p < 0.01$) (Fig. 3b). The LDLc/HDLc ratio was significantly lower after 10 sessions of IH than it was after the sham treatments (2.26 ± 0.70 vs. 2.52 ± 0.66 mmol L^{-1}, respectively, $p < 0.05$).

No significant effects on diastolic blood pressure, heart rate, RMSSD, and DFAα1 were observed between treatment types. Conversely, the treatment type did have a significant effect on systolic blood pressure. Pairwise comparison showed that systolic blood pressure decreased following the 10 sessions of IH treatment when compared to sham treatment alone ($p < 0.05$; Fig. 3c).

Discussion and Conclusion

This study revealed that intermittent moderate hypoxic stress significantly altered glycaemia in both overweight and obese subjects. The results showed an instantaneous drop in arterial GLU following a single IH session while it did not change after a single placebo control session (sham) (Fig. 3a). These encouraging preliminary results are in line with the recent research reporting a sharp decrease in glycaemia (~25%) in type II diabetes following 5 IH cycles of 6 min [7]. Interestingly, our study revealed that the decrease in arterial GLU was associated with a significant elevation in La^- (~29%). Consequently, the post-IH hypoglycemic effect observed might be attributable to increased glycolytic processes, the Pasteur effect [8]. Nonetheless, the 10 IH sessions, over 2 weeks were not sufficient to induce persistent changes in baseline

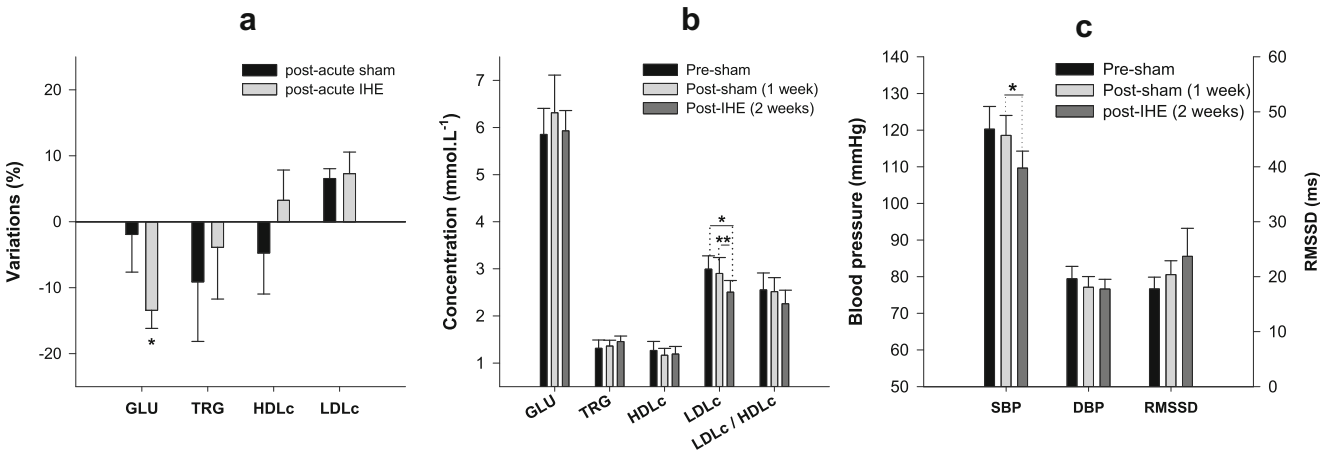

Fig. 3 Bar charts describing the cardio-metabolic measures after one session (**a**) and following the 10 sessions of IH intervention (**b**, **c**). *GLU* arterial blood glucose, *TRG* triglycerides, *HDLc* high-density lipoproteins, *LDLc* low-density lipoproteins, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *RMSSD* root mean square of successive R-R interval differences. *$p < 0.05$ versus corresponding value; **$p < 0.01$ versus corresponding value

GLU. This may indicate an insufficient hypoxic dose, a criterion which is also decisive in eliciting significant metabolic changes in healthy subjects such as elite athletes [9]. An alternative explanation might be that subjects with high fasting glycaemia levels derive more benefit from a program of IH conditioning than those with normal baseline GLU. It is worth noting that one of the participants meeting the clinical criterion for diabetes mellitus (i.e., fasting GLU > 7 mmol L^{-1}) had a larger drop in GLU (~24%) following a single IH session than other participants; this substantial decrease was maintained until the end of the 10 sessions of IH (~20%).

Comparison of the blood lipid levels between sham and IH revealed a drop in LDLc at the end of 10 sessions of IH (Fig. 3b), leading to a decreased LDLc/HDLc ratio following 10 sessions of IH. Hypoxia is known to inhibit the HMG-CoA reductase, an enzyme playing a pivotal role in cholesterol synthesis [10]. Consequently, the promising ability of an appropriate hypoxic dose to mimic lipid-lowering medications would deserve further attention.

Our IH intervention also had positive effects on SBP, a hypotensive effect likely to be beneficial to subjects with metabolic disorders. Epidemiological studies have indeed demonstrated that diagnosis of hypertension increases as body mass index increases (adjusted odds ratio)—1.7 in overweight subjects and more than 4.8 in some severe cases of obesity [11]. It is unlikely that the observed hypotensive effect came from an increased sensitivity of the baroreflex, as vagal-related index (RMSSD) and resting heart rate remained unchanged throughout the protocol (Fig. 3c). Consequently, the rationale behind IH-induced antihypertensive effect could most likely be explained at the endothelium level, since moderate hypoxic conditioning prevents vasoconstriction by increasing the bioavailability of vasodilator molecules such as nitric oxide [12].

The finding that DFAα1, a predictive index of cardiac abnormalities [13] and a surrogate measure of cardiac-autonomic co-activation [6] remained unchanged throughout the protocol, indicates that the short-term IH protocol administered to the participants did not affect sympatho-vagal interactions.

Finally, the proposed methodology is significantly different in terms of hypoxic dose than those previously used to prevent a variety of diseases [3, 12]. In the present study, the criterion defining the hypoxic *dose* is based on a $\overline{SpO_2}$ target (i.e., 80%, Fig. 2), while other investigations set up their protocol by using a predetermined time for hypoxia/re-oxygenation cycles (e.g., 5 min of hypoxia followed by 5 min of normoxia). Since the human hypoxic ventilatory response is highly variable [14], fixed cycles might induce significant inter-individual differences in the kinetics of desaturation and re-saturation, possibly leading to heterogeneous *hypoxic doses* between participants. By contrast, our study takes into account this variability by evaluating the hypoxic dose based on a standard $\overline{SpO_2}$ to ensure its homogeneity between subjects throughout the intervention [4].

The main limitation of the study is the small sample size that might increase the risk of type II error. One could also question the carry over effect that might alter the present results. As breathing air through a facemask (sham sessions) likely had little effect on SpO_2, it is reasonable to assume that this possible effect has not much altered the main outcomes.

To conclude, a short course of recurrent IH appears to be a safe and effective non-pharmacological method of reducing key cardiovascular risk factors associated with metabolic disorders.

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Compliance with ethical standards

Funding Funding was provided by an internal grant from Griffith University.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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