NORMOBARIC HYPOXIA: METABOLIC RESPONSES FOLLOWING 10-DAY HYPOXIC CONFINEMENT

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Doctoral Dissertation
Jožef Stefan International Postgraduate School
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MEDNARODNA PODIPLOMSKA ŠOLA JOŽEFA STEFANA
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NORMOBARIČNA HIPOKSIJA: METABOLNI ODZIVI PO 10-DNEVNI HIPOKSIČNI IZPOSTAVITVI

Doktorska disertacija

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Abstract

The aim of the present thesis was to examine the effect of normobaric hypoxic confinement on selected metabolic responses. This was investigated in two separate studies:

Study I investigated the effect of normobaric hypoxia, as frequently used by athletes for altitude training, on metabolism. The metabolic responses were assessed in eleven normal weight aerobically well-trained healthy males after a 10-day hypoxic confinement.

Study II tested the hypothesis that altitude exposure initiates body weight loss in overweight individuals. Therefore, we evaluated the effects of 10-day normobaric hypoxic confinement on metabolism in eight overweight males.

Subjects were confined to a normobaric hypoxic environment (HYPOXIA; simulated altitude ranging from 2800 m to 3400 m) for 10 days, and the responses in the hypoxic confinement trial compared to those observed in a normoxic confinement trial (NORMOXIA) of similar duration. The studies were conducted in a facility situated at an altitude of 940 m and were designed as randomized cross-over studies. The wash-out period between trials was 3 weeks. During each 10-day period, participants were restricted from any strenuous physical activity to eliminate the confounding factor of exercise, and were under continuous nutritional control. Before, and at the end of each (NORMOXIA and HYPOXIA) confinement, participants completed a meal tolerance test (MTT) to investigate the postprandial metabolic responses. Resting energy expenditure (REE), metabolic factors (circulating glucose, GLP-1, insulin, catecholamines, ghrelin, peptide-YY (PYY), leptin), gastro-intestinal blood flow and appetite sensations were measured in the fasted and postprandial (2 hrs) states.

Study I: In normal weight individuals (73.0±7.7 kg; 23.7±4.0 yrs, BMI 22.2±2.4 $kg \cdot m^{-2}$) body weight was significantly reduced by both confinements (NORMOXIA: -0.7±0.2 kg; HYPOXIA: -0.9±0.2 kg). There was an increase in body fat mass in the NORMOXIA (0.23±0.45 kg) trial, but no change in fat mass in the HYPOXIA (0.08±0.08 kg) trial. Hypoxic confinement increased REE and minute ventilation ($\dot{V}E$) during rest. Decreased energy intake was attributable to an increased fasting level of leptin in normal weight aerobically trained individuals. A trend for increased values of blood glucose and insulin as a response to a test meal were observed after HYPOXIA.

Study II: In overweight individuals (125.0±17.7 kg; 30.5±11.1 yrs, BMI 37.6±6.2 $kg \cdot m^{-2}$) body weight loss was observed in the HYPOXIA trial in overweight individuals. After the continuous 10-day hypoxic confinement, REE increased significantly. Furthermore, concomitant with a tendency for decreased energy intake, there was a significant increase in PYY at the end of the HYPOXIC trial.

The present studies demonstrate that 10-day normobaric HYPOXIC confinement increased REE of both normal weight aerobically trained, and overweight individuals. Although there were no significant differences in subjective satiety scores after HYPOXIA, we speculate that increased leptin (*Study I*) and the trend for increased PYY values (*Study II*) could be partly responsible for the observed decrease in energy intake during HYPOXIA. With the exception of the increased postprandial blood glucose response, 10-day hypoxic confinement did not affect any of the measured blood

parameters and gut blood flow. To conclude, 10-day normobaric hypoxia *per se* has an effect on body weight in normal weight and overweight individuals. This is most likely due to increased REE and increased work of the respiratory muscles associated with the elevated ventilation during HYPOXIA.

Povzetek

Cilj pričujoče raziskave je bil proučiti učinek izpostavitve normobaričnemu hipoksičnemu okolju na izbrane metabolne odzive zdravih posameznikov v času mirovanja. Cilj raziskave je bil dosežen na podlagi dveh različnih, spodaj opisanih študij.

Namen *Študije I* je bil ovrednotiti učinek normobarične hipoksije, navadno v uporabi kot višinski trening, na metabolizem. Preiskovali smo metabolne odzive po 10 dneh hipoksične izpostavitve enajstih zdravih, aerobno treniranih posameznikov z normalno telesno težo.

Namen *Študije II* je bil ovrednotiti predlagano povezanost procesa hujšanja z višinsko izpostavitvijo. Preiskovali smo metabolne odzive po 10 dneh hipoksične izpostavitve pri osmih posameznikih s prekomerno telesno težo.

V obeh študijah smo ovrednotili učinek 10-dnevne normobarične hipoksične izpostavitve na metabolizem. Pri obeh študijah smo uporabili enako metodologijo. Da smo izključili potencialno vpletene dejavnike telesne aktivnosti ali spremenjene prehrane so vsi preiskovanci 2 x 10 dni živeli v nadzorovanem okolju. Fiziološke odgovore hipoksične izpostavitve (normobarična HIPOKSIJA; simulirana nadmorska višina od 2800 m do 3400 m) smo primerjali z odgovori po 10-dnevni normoksični izpostavitvi (normobarična NORMOKSIJA). Študije so bile izvedene v infrastrukturi Olimpijskega športnega centra Planica na nadmorski višini 940 m. Protokol obeh študij je zajemal dva križnovezana protiutežna poskusa. Med obema poskusoma vsake študije je bilo 3-tedensko obdobje prekinitve – "izpiranja učinkov". Med 10-dnevno izpostavitvijo je bila omejena telesna aktivnost preiskovancev na zgornjo dovoljeno aktivnost prosto gibanje po stanovanju (brez izjemnejših telesnih naporov). Preiskovanci so bili ves čas pod strokovnim nadzorom. Prav tako smo nadzorovali celodnevni energetski vnos posameznikov. Pred in po vsaki 10-dnevni izpostavitvi smo opravili metabolni tolerančni test (MTT) za preiskovanje vplivov hipoksije na metabolne odzive po hranjenju. Izmerili smo metabolno energetsko porabo v mirovanju (REE), metabolne dejavnike (krvni sladkor, GLP-1, inzulin, kateholamine, grelin, peptid-YY in leptin), črevesni pretok, subjektivno oceno apetita na tešče in v času dveh ur po hranjenju.

Študija I: Rezultati so pri posameznikih z normalno telesno težo (73.0±7.7 kg; 23.7±4.0 let, ITM 22.2±2.4 $kg \cdot m^{-2}$) pokazali značilno zmanjšano telesno težo po obeh 10-dnevnih izpostavitvah (NORMOKSIJA:-0.7±0.2 kg; HIPOKSIJA:-0.9±0.2 kg). Opazili smo povečanje celotne telesne maščobe po NORMOKSIJI (0.23±0.45 kg), medtem ko po HIPOKSIJI ni bilo značilnih sprememb v masi maščobnega tkiva (0.08±0.08 kg). HIPOKSIJA je povečala metabolno energetsko porabo v mirovanju (REE) in minutno ventilacijo ($\dot{V}E$) v mirovanju. Med HIPOKSIJO se je zmanjšal energetski vnos, kar so deloma potrdile tudi povečane vrednosti leptina (hormona sitosti) pri posameznikih z normalno telesno težo. Opazili smo trend povišanih vrednosti krvnega sladkorja in povišanih vrednosti inzulina po HIPOKSIJI.

Študija II: Rezultati so pokazali pri posameznikih s prekomerno telesno težo (125.0±17.7 kg; 30.5±11.1 let, ITM 37.6±6.2 $kg \cdot m^{-2}$) značilno izgubo telesne teže po 10-dnevni HIPOKSIJI in ne po enako trajajoči NORMOKSIJI. Po neprekinjeni 10-dnevni hipoksični izpostavitvi smo opazili povečano metabolno energetsko porabo v mirovanju (REE). Rezultati so nakazovali zmanjšan energetski vnos, ki je bil podprt z opaženimi

višjimi vrednostmi peptida-YY (PYY) po HIPOKSIJI.

S pričujočujočo raziskavo smo ugotovili, da je 10-dnevna normobarična hipoksična izpostavitev značilno povečala metabolno energetsko porabo (REE) v mirovanju tako pri zdravih posameznikih z normalno telesno težo kot tudi pri posameznikih s prekomerno telesno težo. Čeprav subjektivna ocena sitosti ni pokazala značilne spremembe apetita po hipoksiji, lahko sklepamo, da je trend povišane vrednosti leptina v *Študiji I* in trend povečane vrednosti PYY v *Študiji II* deloma odgovoren za opažen zmanjšan eneretski vnos v času 10-dnevne HIPOKSIJE. Razen povečanih vrednosti krvnega sladkorja in inzulina po 10-dnevni HIPOKSIJI, ni bilo značilnih sprememb številnih krvnih parametrov ali črevesnega pretoka. Glede na rezultate predstavljenih študij lahko povzamemo, da ima HIPOKSIJA sama po sebi učinek na telesno težo pri posameznikih z normalno kot tudi pri posameznikih s prekomerno telesno težo. To je zelo verjetno zaradi povečane metabolne energetske porabe (REE) in povečanega dela respiratorne muskulature, ki je povezano s povečano minutno ventilacijo v HIPOKSIJI.

Abbreviations

A-a	=	alveo-arterial difference
ANOVA	=	analysis of variance
AUC	=	area under curve
BMI	=	body mass index
BMR	=	basal metabolic rate
Cap Dens	=	capillary density
CNS	=	central nervous system
CO_2	=	carbon dioxide
CSS	=	composite satiety score
DAP	=	diastolic arterial pressure
DEXA	=	dual emission X-ray absorptiometry
EE	=	energy expenditure
F_iO_2	=	fraction of inspired oxygen
GLP-1	=	glucagon-like peptide-1
Hb	=	haemoglobin concentration
HCVR	=	hypercapnic ventilatory response
HDL	=	high density lipoprotein
HOMA	=	homeostatic model assessment
HR	=	heart rate
Ht	=	haematocrit
HVR	=	hypoxic ventilatory response
LDL	=	low density lipoprotein
LLS	=	Lake Louise Score
MTT	=	meal tolerance test
O_2	=	oxygen
P_B	=	barometric pressure
PA,CO_2	=	alveolar partial pressure of CO_2
PA,O_2	=	alveolar partial pressure of O_2
PO_2	=	(ambient) partial pressure of O_2
PHPR	=	pulmonary hypoxic pressure response
PYY	=	peptide YY
REE	=	resting energy expenditure
SAP	=	systolic arterial pressure
S_PO_2	=	arterial oxygen saturation
$\dot{V}E$	=	minute ventilation
$\dot{V}O_2$	=	O_2 consumption
$\dot{V}O_{2peak}$	=	peak O_2 consumption

1 Introduction

The ancient Greeks were the first to recognise air as a key element of the Earth environment. As a consequence of the pioneering work of chemists such as Joseph Priestley, Antoine Lavoisier and Henry Cavendish, we now know that the composition of a dry atmosphere (mole fractions) is 78.084 % of nitrogen (N_2), 20.946 % of oxygen (O_2), 0.934 % of argon (Ar), 0.031 of carbon dioxide (CO_2), and smaller fractions of other common gases. Oxygen is a vital element for the existence and sustainment of aerobic organisms (Priestley, 1775). It is essential in cellular metabolism, cell growth and differentiation. Adequate O_2 availability has a pivotal role in human performance and overall health. Therefore, manipulation of O_2 levels in the inspired air has been considered for a variety of hyperoxic (Treacher and Leach, 1998; Keramidas 2011) and hypoxia (Jelkman et al., 1992; Richardson et al., 2009, Millet et al., 2010, Mekjavić et al., 2012) therapies.

Hypoxia as a decrease in ambient O_2 partial pressure (PO_2), is established by either lowering barometric pressure and maintaining the environmental oxygen fraction (FO_2) constant (hypobaric hypoxia, altitude), or by lowering FO_2 and maintaining the ambient pressure constant (normobaric hypoxia). Protocols incorporating normobaric hypoxia (simulated altitude) are most frequently used for altitude acclimatization, and in athletic training to enhance altitude and sea level performance (Billaut et al., 2012).

Among the many physiological adaptations of humans to altitude, the adaptation of metabolism, and its subsequent effect on body composition, remains unresolved. The available evidence suggests that exposure to high altitude causes a reduction in food intake due to loss of appetite, and changes in endocrine parameters controlling homeostasis (appetite hormones), metabolism of nutrients, and basal metabolic needs. In addition, these adaptations are also affected by factors such as cold, exertion, lack of comfort, food palatability and availability. Despite the numerous field studies to date, that have investigated metabolic adaptations to high altitude, the exact mechanism of high altitude anorexia remains unresolved.

1.1 Physiological responses to hypoxia

The effect of hypoxia has been studied intensively since Paul Bert (1878) first highlighted the danger of ascent to high altitude to early balloonists. The effects of sudden exposure to high altitude depend on the level and duration of the hypoxic exposure. Most prominent responses are breathlessness and elevated heart rate on exertion, as well as an effect on central nervous system function.

At levels as low as 1500 m night vision is impaired, and at higher altitudes (4000–5000 m) some tingling of fingers and mouth is experienced. At altitudes above 5000 m consciousness may become compromised in some subjects, whereas above 7000 m most unacclimatised individuals will lose consciousness. The effects of acute and chronic hypoxia on physiological systems appear to have an initial transient response followed by a return to original or slightly elevated values (Figure 1.1). As an example, an initial exposure to hypoxia will cause an immediate transient increase in heart rate in the first minutes of exposure, followed by a continuous fall towards an asymptotic value over the

next weeks of exposure, with the final values being higher than the original heart rate observed in normoxia. Similarly, the transient ventilatory response to hypoxia is followed by a decrease in ventilation with prolonged exposure to hypoxia, due to changes in both central and peripheral chemoreceptor response over 1–20 days. The transient elevation in hemoglobin concentration is due to an initial decrease in plasma volume, followed by a slow increase in red cell mass (West et al., 2007; Figure 1.2).

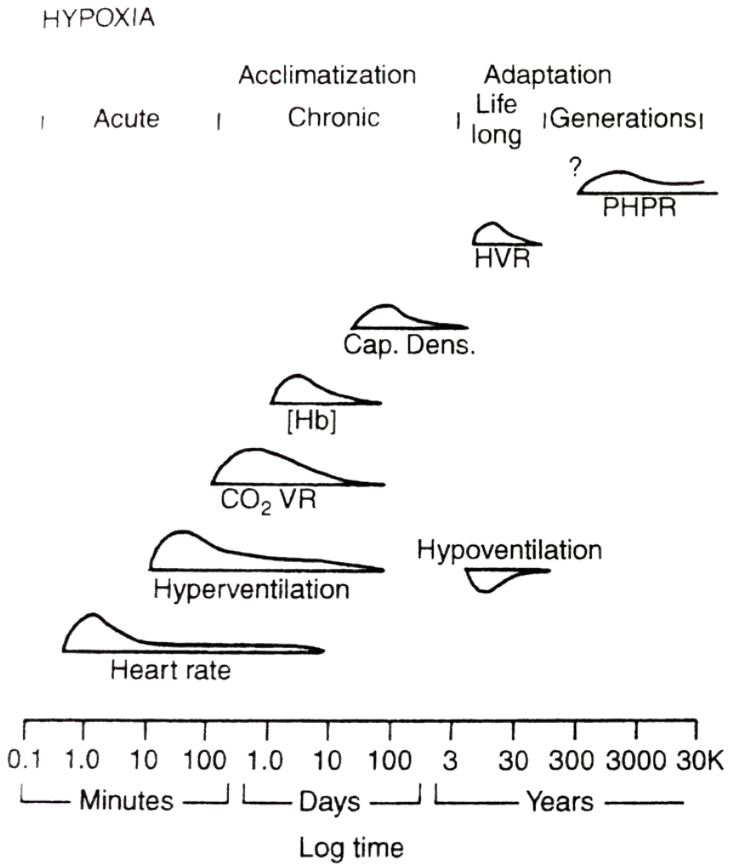

Figure 1.1: *The time courses of a number of acclimatization and adaptive changes plotted on a log time scale, the curve of each response denoting the rate of change, which is fast at first then tails off.* Included are: heart rate, hyperventilation and hypoventilation, the carbon dioxide ventilatory response (CO_2VR), hemoglobin concentration (Hb), changes in capillary density (Cap. Dens.), hypoxic ventilatory response (HVR) and pulmonary hypoxic pressure response (PHPR) (Adapted from West et al., 2007 using data from Lundby et al., 2004).

Minute ventilation ($\dot{V}_E$) is one of the most important physiological responses at altitude. Namely, during prolonged altitude exposure, the increase in ventilation is initiated in response to the reduced partial pressure of oxygen (PO_2) in the inspired air. As shown in Figure 1.3, representing the oxygen cascade, PO_2 decreases progressively as it passes from the lungs to the mitochondria. At sea level there is a drop of about 50 mmHg in the O_2 transport system, which depends, in part, on the metabolic rate (CO_2 production, O_2 consumption). However, it also depends on alveolar ventilation, and for a given O_2 uptake and CO_2 output, the size of this reduction is entirely due to ventilation.

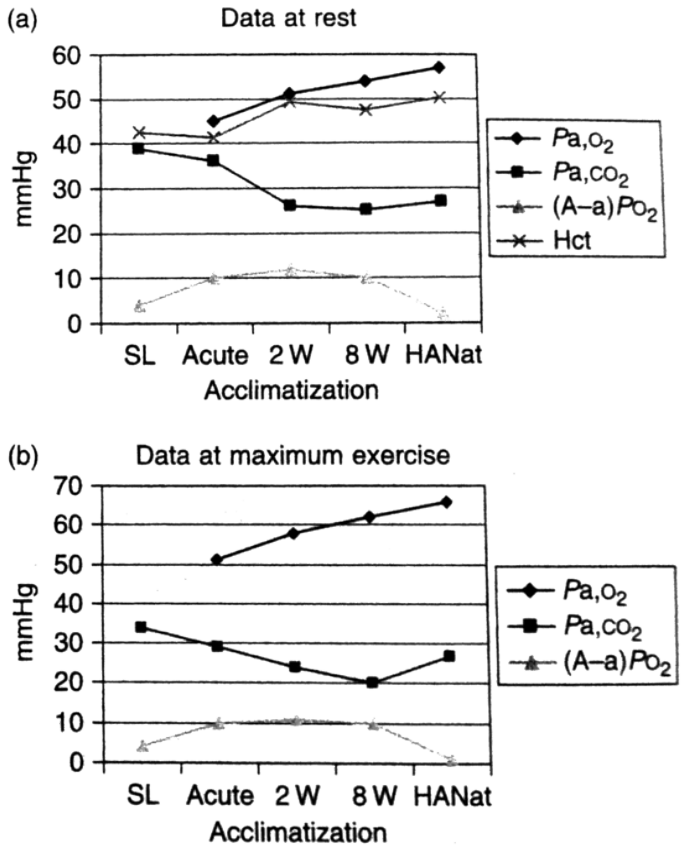

Figure 1.2: *Changes in Pa,O_2, Pa,CO_2, (A-a) PO_2 and hematocrit (Hct) at sea level (SL) under normoxia and acute hypoxia, at altitude (4100 m) after 2 weeks (2W) and 8 weeks (8W) acclimatization, mean results in six lowlanders and eight Amarya high altitude natives (HA Nat); at rest (a) and maximum exercise (b)* (Adapted from West et al., 2007 using data from Lundby et al., 2004).

The final decrease in PO_2 shown in Figure 1.3 is the decrease observed from arterial to mixed venous blood, and is due to the uptake of O_2 by the tissues. The magnitude of this decrease is influenced by metabolic rate, the cardiac output and the O_2 carrying capacity of the blood, i.e. the hemoglobin concentration. Moreover, following the first decrease of oxygen saturation of arterial haemoglobin (S_PO_2), the levels increase after a few days of altitude exposure (West et al., 2007).

The peripheral chemoreceptors (the carotid and aortic bodies) principally respond to CO_2 and pH, whereas the central chemoreceptors (medulla) sense changes in pH, which are frequently due to changes in PCO_2. With increasing ventilation in response to hypoxia, CO_2 falls, thus the CO_2 drive to breathing is reduced and the hypoxic response is masked (unless measures are taken to prevent this fall in PCO_2). There are some indications that increased ventilation does not always begin until the inspired PO_2 is reduced to approximately 100 mmHg which is equivalent to about 3000 m altitude (Rahn and Otis, 1949). However, hypoxia stimulates the peripheral chemoreceptors resulting in increased ventilation, decreased P_aCO_2 and hence respiratory alkalosis. The kidneys respond to the increased pH by excreting bicarbonate in the urine, and plasma bicarbonate concentrations falls. Moreover, with hypoxia there is a partial switch in cerebral metabolism of glucose from the aerobic to the anaerobic pathway (West et al., 2007).

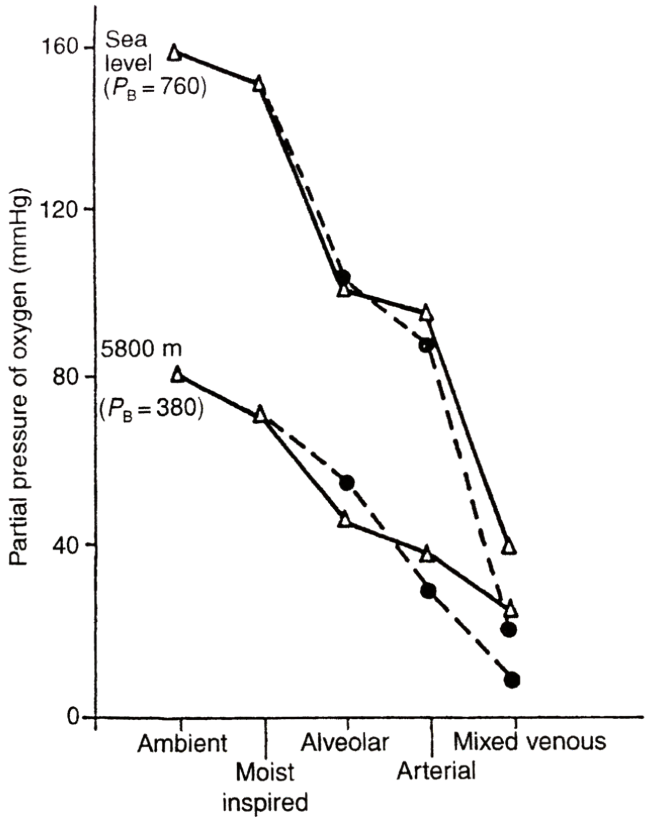

Figure 1.3*: The oxygen transport system from outside air through the body at sea level and at altitude of 5800 m. P_B barometric pressure; full circle rest; triangle maximum work* (Modified by Ward et al., 2000 from Pugh 1964).

Energy expenditure (EE) is also influenced by oxygen supply. Many studies derived from expeditions to high altitude report daily EE values in climbers that are comparable to highly trained endurance athletes at sea level (Westerterp et al., 1992, 1994). Furthermore, some studies have reported an increase of REE during a prolonged stay at 5800 m (Gill and Pugh, 1964). Increased REE was also reported in obese individuals after a 3 week sojourn at 3300 m (Lippl et al., 2010). There is some discrepancy regarding the change in REE at altitude relative to sea level values among studies. This discrepancy may be due to methodological limitations of field measurements, and/or due to the presence of confounding factors such as strenuous physical activity of climbers, cold, comfort level, limited availability and palatability of food. In addition, decreased appetite, and the associated decrease in energy intake were the suggested cause for the observed body-weight loss at altitude (Kalson et al., 2010).

1.2 Practical application of normobaric hypoxia

Recently athletes have begun to incorporate normobaric hypoxia, which is an acceptable alternative to altitude hypobaric hypoxia, in their training regimens (Evetts et al., 2005; Self et al., 2011, Singh et al., 2010), to improve aerobic performance, by enhancing the oxygen carrying capacity of blood (Sawka et al., 2000; Rusko et al., 2004). Improvement of aerobic performance induced by hypoxic training is due to both »central« and »peripheral« mechanisms. The former mediates oxygen transport enhancement (Levine and Stray-Gundersen, 2005), whereas the latter supposedly mediates muscular adaptations (Gore and Hopkins, 2005). Hypoxic exposure stimulates erythropoiesis leading to an increase in erythrocyte formation (Gunga et al., 1994), and causes a

moderate increase in blood oxygen carrying capacity. It also induces ventilatory acclimatization. The magnitude of these haematological and respiratory changes depends on the hypoxic stimulus. The minimal time required in hypoxia appears to be 12 h/day for 18 days (Richalet and Gore, 2008). The altitude normally chosen by athletes for hypoxic training is such that it does not induce detrimental effects in performance and has a minimal risk for mountain sickness.

The benefits of administering hypoxic mixtures to athletes or patients must outweigh the risks. Furthermore, there must be a scientific evidence of any proposed benefits of such protocols. Presently there is much anecdotal and some scientific evidence of the direct effects of hypoxia *per se* on metabolism, however as yet not sufficient to explain the phenomenon of »high altitude anorexia«. The purpose of the present thesis is to provide further evidence regarding factors that may contribute to this phenomenon.

1.3 Hypoxic environment and metabolism

Altitude exposure above 2500 m has been implicated in the unexplained loss of body weight (Barry and Pollard, 2003; Boyer and Blume, 1984; Guilland and Klepping, 1985; Pulfrey and Jones, 1996; Rose et al., 1988; Westerterp et al., 1992), which appears to be dependent on the nature of the hypoxic stimulus (Kayser, 1994; Mazzeo, 2008). Weight loss at high altitude was observed even in the absence of symptoms of mountain sickness (Tschöp and Morrison, 2001), which is known to affect appetite. Most of the field studies conducted to date have not been able to control for potentially confounding variables, such as cold, exertion, lack of comfort, limited palatable food at altitude, thus the effect of hypoxia *per se* on the aetiology of “high altitude anorexia” remains unresolved.

Decreased appetite and the associated decrease in energy intake have been observed at altitude (Kalson et al., 2010, Westerterp-Plantenga et al., 1999). Furthermore, different appetite hormones have also been suggested to mediate altitude anorexia (Tschöp et al., 1998, Shukla et al., 2005, Wasse et al., 2012). Laboratory trials have demonstrated appetite suppression after a simulated 31-day hypobaric hypoxic exposure to 8848 m (Westerterp-Plantenga et al. 1999), and it was suggested that the hormone leptin may mediate altitude anorexia (Tschöp et al. 1998). Leptin serves as an adiposity signal to inform the brain of the adipose tissue mass in a negative feedback loop regulating food intake and energy expenditure. However, observations of the effect of hypoxia on leptin levels are conflicting. Namely, studies have reported increased (Shukla et al. 2005; Snyder et al. 2008), decreased (Vats et al. 2007, Zaccaria et al. 2004) or unchanged (Barnholt et al. 2006) leptin levels during hypoxic exposure. Moreover, the endocrine factors that contribute to the observed changes in body weight at altitude remain unclear. It has been suggested that absorption of nutrients is slowed, and possibly impaired, at altitude (Milledge 1972; Schoots et al. 2006). Recently, the observation of suppression of energy intake and of the appetite hormone, ghrelin, after a 7 hour normobaric hypoxic exposure, suggested that short-term hypoxia in the absence of cold and other stressors may be implicated in high altitude anorexia (Wasse et al. 2012). After prolonged hypoxia (range: 7 days to 7 wks), ghrelin was unchanged at altitude (Shukla et al., 2005). In contrast, Shukla et al. (2005) reported that the peptide YY (PYY), which reduces appetite or promotes satiety, was not significantly altered after acute normobaric hypoxia. The effect of prolonged (a few days) normobaric hypoxia on this gut hormone, which could potentially contribute to weight loss, remains unresolved. Hoverever, the endocrine factors that contribute to the observed changes in body weight at altitude remain unclear. It has been suggested that absorption of nutrients is slowed, and possibly impaired, at altitude (Milledge, 1972; Schoots et al., 2006). Furthermore, it was demonstrated that carbohydrate ingestion can improve oxygen delivery during hypoxia (Golja et al., 2008).

However, there have been no studies investigating prolonged (a few days) effects of normobaric hypoxia on the gut hormones, which could potentially contribute to weight loss.

Energy expenditure (EE) is influenced by oxygen supply. However, the observations of the effect of hypoxia on resting energy expenditure (REE) are conflicting. Though the majority of studies report an increase in REE (Picon-Reategaui 1961, Grover 1963, Gill and Pugh 1964, Butterfield et. al., 1992), some (Durnin and Brockway 1959, Westerterp et al., 1992, 1994) report no change in altitude REE. It has been found that, when energy intake is not allowed to fall below the sea level values, acute altitude exposure elevates REE by about 12–27 % (Nair et al., 1971, Butterfield et al., 1992). Of the former, values of EE in climbers have been reported to be comparable to highly trained endurance athletes at sea level (Westerterp et al., 1992). However, the data regarding REE at altitude is not consistent. Additionally, hypoxia is known to stimulate the sympathoadrenal system, resulting in an increased secretion of norepinephrine within the first three weeks of exposure (Mazzeo et al., 1991; Reeves et al., 1992; Young et al., 1989; Brooks et al., 1971). These effects may be responsible for some of the metabolic changes seen at altitude, such as augmentation of the basal metabolic rate (BMR) during rest (Hill et al., 2011).

The mechanism of weight loss, normally a consequence of the imbalance between energy intake and expenditure, is also related to other factors such as appetite, nutrient intake, digestibility and altered fluid balance (Kayser, 1994). Weight loss at altitude has also been attributed to the initial loss of water, and subsequent loss of fat and muscle mass due to malnutrition (Kayser, 1994). Westerterp (2001) concluded that weight loss is mainly caused by malnutrition due to hypoxia–related satiety, independent of acute mountain sickness. Moreover, decreased xylose absorption with more severe desaturation was noted (Milledge, 1972), confirming the notion that hypoxia followed by reoxygenation impairs nutrient absorption (Schoots et al., 2006). However, hypoxia is believed to be a major factor in the development, and progression of metabolic alterations in glucose metabolism (Louis and Punjabi, 2009; Stock et al., 1978). The observed reduction in baseline and postprandial gut blood flow (superior mesenteric artery) during acute altitude exposure has been attributed to increased intestinal sympathetic tone, and has been suggested could lead to reduced energy intake during prolonged exposure (Loshbaugh et al., 2006). However, most of the field studies conducted to date have not been able to control for potentially confounding variables at altitude: cold, exertion, lack of comfort, limited palatable food at altitude, thus the effect of hypoxia *per se* on the aetiology of “high altitude anorexia” remains unresolved.

1.4 Normobaric hypoxic confinement and body weight reduction

During altitude training of athletes, adaptation of several physiological systems occurs as a result of these challenging environmental conditions (Bartch and Saltin, 2008; Kraemer and Rogol, 2005). The human body is able to develop remarkable physiological processes to cope with reduced oxygen level in such extreme environments. Moreover, body weight reduction may be related to the duration of exposure and altitude reached (Kayser, 1994), namely hypoxic dose. It's evident after several days or more and appears to be an inevitable consequence of prolonged hypobaric hypoxia (Boyer 1984; Guilland and Klepping, 1985; Rose et al., 1988; Westerterp et al., 1992). However, an alternative to hypobaric hypoxia that induces similar physiological responses (Richard and Koehle, 2012) is normobaric hypoxia, which has not been investigated as extensively as hypobaric hypoxia. With the exception of the studies of Wasse et al. (2012) investigating short term effects of normobaric hypoxia (1-hour, 7-hours), there have been no other studies

investigating the effect of continuous normobaric hypoxia on human metabolism to our knowledge.

The observation that high altitude exposure leads to considerable weight loss in alpinists has led to the suggestion that it might be beneficial to incorporate hypoxic training in weight management programmes for obese individuals. It is known that hypoxia stimulates the sympathetic nervous system and field studies have commonly reported weight loss during exposures to high altitude (Consolazio et al., 1968; Krzywicki et al., 1969; Gill and Pugh, 1962; Surks et al., 1966). From these studies, it is not possible to discern whether weight reduction is due to the increased energy expended during hard physical work, nonshivering and shivering thermogenesis in the cold environment, limited availability or palatability of food, dehydration, malabsorbtion, acute mountain sickness, or a combination of these factors (Boyer, 1984). Nevertheless, Rose et al. (1988) suggested that hypoxia *per se* might be a sufficient cause for the weight loss and decreased food consumption reported by mountain expeditions at high altitude and Netzer et al. (2008) reported an average reduction of 1.14 kg in body weight following an 8-wk exercise programme conducted under normobaric hypoxic conditions (inspired fraction of O_2, F_IO_2=15 %) in obese individuals, but the loss of fat mass was not defined. Moreover, loss of appetite was reported after 31-days of hypobaric hypoxic exposure (Westerterp-Plantenga et al., 1999). Recently, Wasse et al. (2012) investigated the effects of a 7-hr exposure to normobaric hypoxia and reported a similar suppression of energy intake.

The manner in which metabolic adaptations at high altitude affect human performance is still unknown. Without knowledge of the mechanism of the hypoxia-induced reductions in body mass, advocating hypoxic exposure/training in weight-loss programmes may be unwarranted (Netzer et al., 2008, Wasse et al., 2012). Therefore, the present thesis investigated the effects of 10-day hypoxic confinement in healthy normal weight and in overweight male individuals.

2 Aims and Hypothesis

The present thesis investigated the effect of hypoxia on specific metabolic responses during rest. The general purpose was evaluated in two separate studies:

Study I: Athletes use hypoxia as a part of altitude acclimatization or hypoxic training to increase elite sports performance, but the side effects of hypoxia on metabolism are still unknown. Therefore, the aim of this study was to examine the effect of normobaric hypoxia on selected metabolic responses during rest in healthy, normal weight, aerobically well trained individuals.

Study II: Metabolic changes indicating body weight reduction were associated with hypoxia. Therefore, the aim of this study was to examine the effect of normobaric hypoxia on selected metabolic responses during rest in overweight individuals.

In Studies I and *II,* the following null hypothesis (H_{01-6}) were tested:

- H_{01}: *Body weight and body composition.*
  Prolonged exposure to hypoxia has no significant effect on body weight reduction and changes in body composition.

- H_{02}: *Cardiovascular and hematological variables.*
  10-day hypoxic confinement has no significant effect on cardiovascular and heamatological function.

- H_{03}: *Resting energy expenditure.*
  10-day hypoxic confinement has no significant effect on metabolic requirements.

- H_{04}: *Appetite.*
  10-day hypoxic confinement has no significant effect on appetite.

- H_{05}: *Gastro-intestinal blood flow.*
  10-day hypoxic confinement has no significant effect on intestinal blood flow.

- H_{06}: *Postprandial hormonal metabolic.*
  10-day hypoxic confinement has no significant effect on select blood variables: glucose, insulin, GLP-1, noradrenaline, adrenaline, leptin, ghrelin, peptides – YY (PYY).

3 Thesis structure

The hypotheses outlined above have been addressed in two separate research studies, which are reported in two main chapters (Chapter 4, 5).

In particular, Chapter 4 presents the metabolic effect 10-day normobaric hypoxic confinement in normal weight, aerobically well-trained, males (recreational athletes).

Chapter 5 presents the metabolic effect of 10-day normobaric hypoxic confinement in overweight males.

The findings of the present thesis are summarized in Chapter 6.

The ethic's approvement of the Study I and Study II is attached in the Appendix A.

The individual's data of Study I and Study II are attached in the Appendix B.

4 Metabolic effect of normobaric hypoxia in recreational athletes

The empirical evidence, and also anecdotal evidence of weight loss following high altitude mountain climbing expeditions, suggests that hypoxia may induce weight loss in athletes conducting hypoxic training (simulated altitude training) to improve performance (Richalet and Gore 2008; Siebenmann et al. 2012). Such weight loss may be beneficial, if it affected the fat tissue compartment, but detrimental if it reduced muscle mass and caused dehydration. Without knowledge of the nature of hypoxia-induced reductions in body mass, advocating hypoxic training in weight-loss programmes may be unwarranted (Netzer et al. 2008; Wasse et al. 2012). The primary aim of the present study was to test the hypothesis that a continuous 10-day HYPOXIC confinement in healthy normal weight males would have no significant effect on resting energy expenditure, gastrointestinal hormones and appetite, which were indicated that may lead to loss of body weight, and may provide some insight into the phenomenon of high altitude anorexia.

4.1 Material and Methods

4.1.1 Subjects

Eleven healthy males, all low altitude (351±103 m) residents, participated in two 10-day trials. Subject exclusion criteria included a history of physician-diagnosed medical problems, recent prolonged exposure to normobaric or hypobaric hypoxia, or recent weight loss, participation in any dietary manipulations in the past six months, and use of any medications or drugs. All participants gave their written informed consent to participate in the study. The study protocol was approved by the National Committee for Medical Ethics at the Ministry of Health of the Republic of Slovenia and conformed to the Declaration of Helsinki.

4.1.2 Experimental procedure

The study was conducted at the Olympic Sport Centre Planica (Planica, Slovenia) situated at an altitude of 940 m. Subjects participated in two trials, during which they were confined to one floor of the facility. In one trial, the ambient conditions were normoxic (NORMOXIA), and in the other they were rendered hypoxic (HYPOXIA). The study was designed as a randomized cross-over study. Participants were assigned to two groups: initially one group (N=6) was confined to a normobaric normoxic environment (NORMOXIA; inspired fraction of O_2, F_IO_2=0.2093) for 10 days and the other (N=5) to a controlled normobaric hypoxic environment (HYPOXIA, F_IO_2=0.1613). As shown in Figure 4.1, the subjects were exposed to a simulated altitude of 2800 m (F_IO_2=0.1683) for the first two days (days 1 and 2). Thereafter the fraction of oxygen in the facility was reduced every two days, so that the subjects were exposed to a simulated altitude of 3000 m (F_IO_2=0.1643) on days 3 and 4, to 3200 m (F_IO_2=0.1603) on days 5 and 6, and finally to 3400 m (F_IO_2=0.1567) for the remaining 4 days (Figure 4.1).

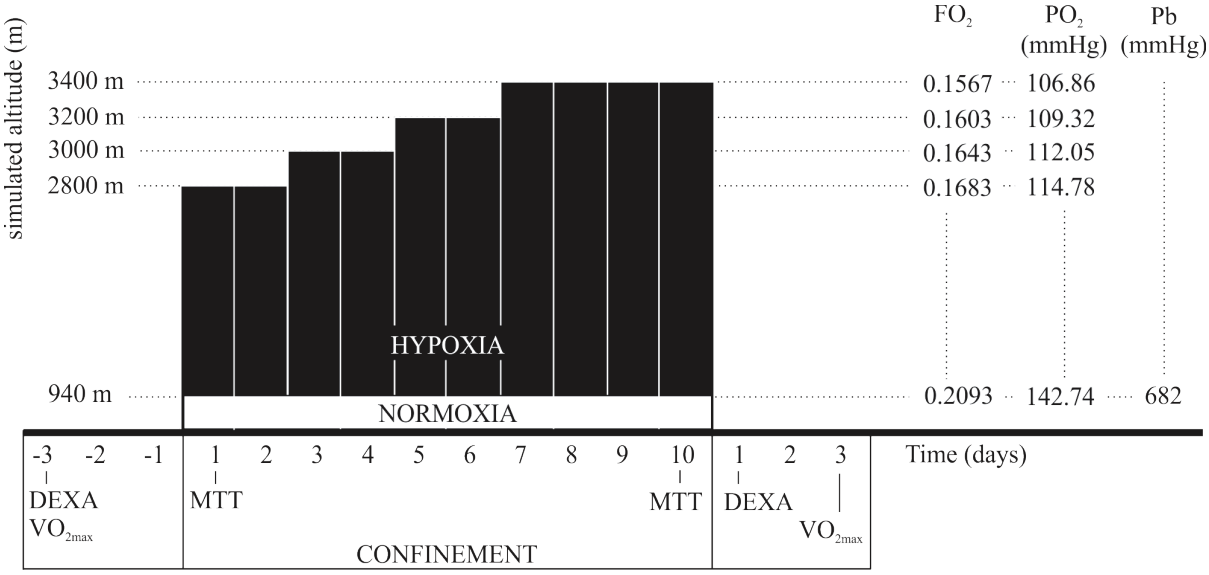

Figure 4.1: *Schematic representation of the overall experimental protocol of the present study.*

In both trials, the participants arrived at the facility 3 days prior to the onset of the 10-day confinement. During these 3 days, they were familiarised with the experimental protocol and equipment. The baseline measurements were obtained (Figure 4.2) with the performance test (VO_{2max}) and meal tolerance test (MTT) including fasting and postprandial REE. Those pre-confinment tests were performed in the normoxic environment before the NORMOXIA and HYPOXIA confinement. Upon completion of the 10-day confinements, subjects remained at the facility for an additional 3 days for the post-confinement tests. The post-confinement meal tolerance test (MTT) and fasting REE measurements in the NORMOXIA and HYPOXIA conditions were performed in normoxic and hypoxic environments, respectively. In the HYPOXIA trial, once these tests were completed, the subjects remained under normoxic conditions for the remaining two days.

After a 3-week wash-out period the subjects returned to the Olympic Sport Centre Planica, and the trials were crossed. During both the NORMOXIA and HYPOXIA trials, subjects were confined to the living quarters (each group had at their disposal 3 double sleeping rooms and one living/dining room; total area of ~ 90 m^2). In the HYPOXIA trial, the reduction in room oxygen fraction (FO_2) was achieved with an oxygen dilution system (B-cat, the Netherlands), based on the Vacuum-Pressure Swing Adsorption principle. The oxygen levels in each room were monitored and recorded at 15-min intervals throughout the 10-day period. If the FO_2 in any given room would decrease below the pre-set value, delivery of the hypoxic gas mixture to that room would be stopped. If the FO_2 would drop by more than 0.5% of the pre-set value, the control system would activate a fan, which would delivere external ambient air into that room. As a consequence of the fan being activated, the FO_2 in the room would increase rapidly to the desired level. Once the FO_2 would attaine the pre-set value, the fan would be de-activated. During the HYPOXIA trials, the control system maintained the FO_2 with the facility stable, thus there was never a need for the fans to be activated. Each subject was also requested to either wear, or have in close proximity, a personal clip-on type of environmental oxygen analyser (Rae PGM-1100, California, USA) with an audible alarm that would be activated if the oxygen level would decrease below the pre-set level.

Prior to the onset of the study, subjects completed questionnaires regarding their current and past health status, habitual physical activity levels, dietary habits, and food preferences. During the 3-day period prior to each confinement, subjects were requested to record their 3-day dietary intake in a food diary. During the 10-day confinement, subjects were restricted from any high-intensity, or aerobic exercise. Physical activity was restricted to slow walks in the living area. Nutritional choices and energy intake were documented in daily nutritional diaries during both trials. The food menu comprised typical national foods, freely available, and an effort was made to accommodate individual food preferences. The subjects received the same food menu during each 10-day exposure, but without any restriction regarding the quantity consumed; they ate and drank *ad libitum*. The daily energy intake was recorded and analysed with a dietary assessment program (OPKP, Jožef Stefan Institute, Ljubljana, Slovenia). Subjects' wellbeing was monitored by medical personnel. All participants had personal pulse *oxymeters (*Nonin, Medicals 3100 WristOx*, Minnesota, USA)* monitoring arterial blood oxygen saturation (SpO_2) and heart-rate (HR). Symptoms of mountain sickness and individual mood and appetite were monitored daily with the Lake Louise Scoring system (LLS) and Visual Analog Scale (VAS) for Mood and Appetite, respectively. Fasting and postprandial metabolic rate measurements were conducted at the same time of day for each subject (COSMED, Quark PFT, Rome, Italy). The metabolic assessments were conducted in a normoxic environment, 1 day prior to the onset of each 10-day confinement (pre-test), and on day 10 of the confinement period (post-test) in either hypoxic or normoxic environments.

4.1.2.1 Anthropometry

Body composition was analysed before and after each 10-day confinement with Dual-Emission X-ray absorptiometry (Discovery, Hologic, Inc, Bedford USA). Measurements were made of total body fat mass and regional fat mass (abdominal, right thigh, left thigh) and fat-free mass. Body weight and height were measured with a weighing scale and a stadiometer, respectively (Seca 703, Seca, Hamburg, Germany).

4.1.2.2 Aerobic capacity

All subjects performed an incremental exercise test to exhaustion on a cycle-ergometer (Daum Electronics, Fürth, Germany) 3 days prior to and one day after each confinement, to determine their peak oxygen consumption ($\dot{V}O_{2peak}$). The $\dot{V}O_{2peak}$ testing protocol comprised a 15-min resting period, followed by a 2-min warm-up at 60 W. Thereafter, the workload was incremented each minute by 25 W, until exhaustion. Inability to maintain the cycling cadence above 60 rpm, plateau in $\dot{V}O_2$ and/or a respiratory exchange ratio >1.1, were the criteria used, to confirm the attainment of the $\dot{V}O_{2peak}$ (calculated as the highest $\dot{V}O_2$ averaged over 60 s during the test). $\dot{V}O_2$ and minute ventilation ($\dot{V}E$) were measured breath-by-breath during rest and exercise with a Quark CPET metabolic cart (Cosmed, Rome, Italy).

4.1.2.3 Metabolic test

Prior to, and on the final day of each 10-day confinement, subjects completed a meal tolerance test (MTT) to assess their fasting metabolic status and the postprandial metabolic responses. For 3 days before the pre-confinement metabolic experiments subjects refrained from exercising and were under dietary control with limited caffeine (daily maximum caffeine content: 150 mg) and alcohol (daily maximum alcohol content: 8 g or 10 ml) consumption. The dietary intake diaries obtained prior to each MTT revealed that the macronutrient composition was similar for the NORMOXIA and

HYPOXIA trials. The last meal prior to the MTT was the evening meal the day before the test. For each subject, the composition of the last meal prior to the 12-hour fast was the same for each MTT. For the MTT, subjects consumed a standardized mixed nutrient liquid test meal (Ensure, Nutrition shake, vanilla flavour; Abbott) based on their individual body weight (5 $ml \cdot kg^{-1}$, 1.5 $kcal \cdot ml^{-1}$), determined on the day of the experiment. Additionally, ^{13}C-labelled glucose (9.2 $mg \cdot kg^{-1}$) was added to the test meal as an indicator of gastric emptying and glucose uptake and use (expired $^{13}CO_2$ was measured). The average meal volume was 361.4±3.4 ml and contained 27.4 g of protein, 48.5 g of fat, and 88.4 g of carbohydrate, plus significant amounts of vitamins and minerals. Participants were asked to consume the entire meal portion provided (Figure 4.2).

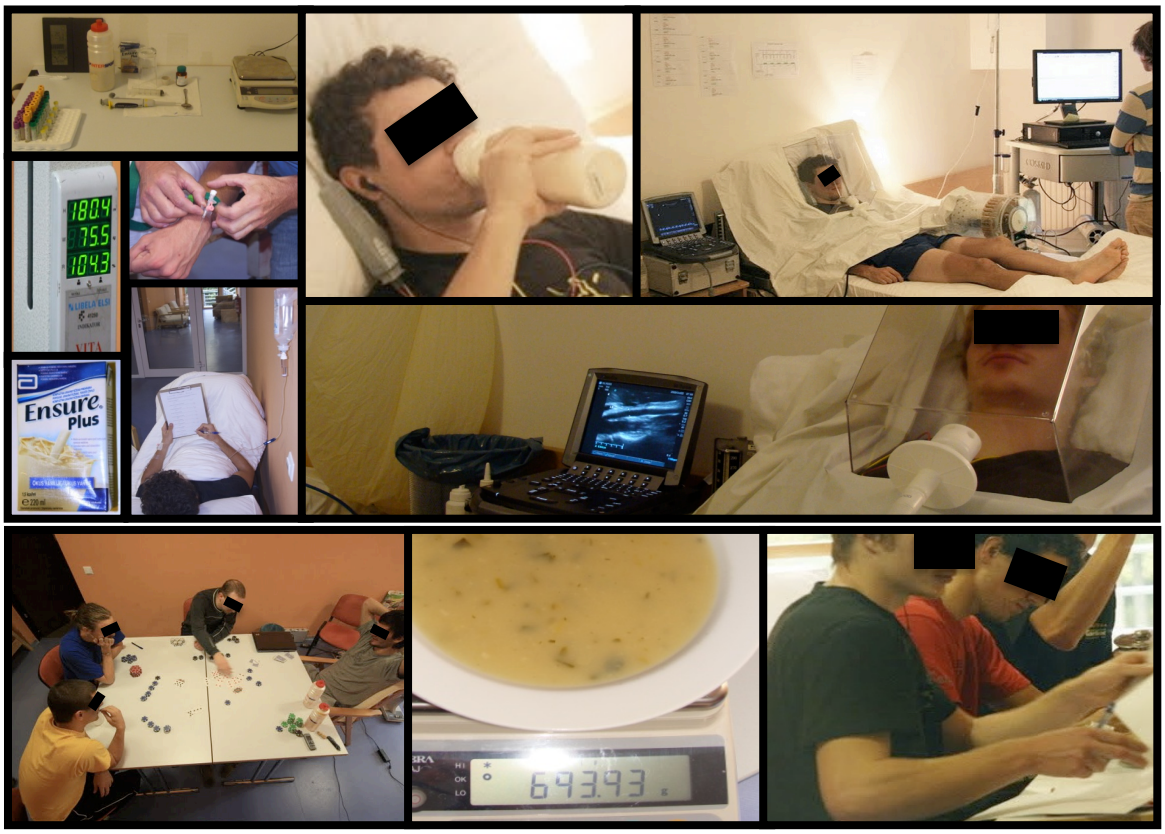

Figure 4.2: *Testing (upper) before and after the controlled 10-day confinement (lower) in normal weight individuals.*

4.1.2.4 Blood sampling

Blood samples (6 ml) were drawn at regular intervals through a catheter (Baxter Health Care, Valencia, CA) inserted into a dorsal hand vein at the beginning of the experiment. The subject's catheterised hand was placed in a hot air box (55–60 °C) to maintain a constant high hand skin temperature and provide arterialised venous blood. Arterialised venous blood samples were collected in the fasted state prior to the test meal (one sample 15 minutes before, and another approximately 10 seconds before, the meal), and at regular intervals during the 2 hours following the ingestion of the test meal, to monitor blood glucose (every 10 min), and to analyse the responses of serum insulin and plasma glucagon-like peptide (GLP-1), peptide YY (PYY) and ghrelin (every 15 min). Plasma catecholamine (noradrenaline and adrenaline) responses were additionally

measured in the fasting state and postprandially. The plasma level of leptin was also measured in the fasted state before and after each condition.

Blood glucose level was analysed immediately from each arterialised venous blood sample (HemoCue, HMC-201-PROMO, Sweden). For subsequent hormone analyses, all blood samples were either immediately (or after 10 min, in the case of the insulin tube to allow clotting) centrifuged at 3000 rpm for 10 min (at a temperature of 4 °C), and aliquots kept on ice until the end of the MTT and stored at -20 °C for 1 day, and thereafter at -70 °C for further analyses. The analysis of all plasma samples was conducted in duplicate using the assays described below.

Insulin concentrations were determined using radio-immunoassay (RIA) (Insulin Coat-A-Count, Diagnostic Products Corp., Los Angeles, USA); GLP-1 concentrations (comprising GLP-1 7-36 amide and 7-37) using Enzyme-Linked ImmunoSorbent Assay (ELISA) (Merck Millipore, Missouri, USA); PYY using RIA for total PYY (Merck Millipore, Missouri, USA) which recognised both PYY1-36 and PYY3-36 in EDTA plasma plus aprotinin; ghrelin was determined using RIA for total ghrelin (Merck Millipore, Missouri, USA) and leptin was determined using a human leptin RIA (Merck Millipore, Missouri, USA). Catecholamines were measured using extraction of the adrenaline and noradrenaline from the plasma (which had been treated with EGTA/glutathione (Sigma-Aldrich, Dorset, UK) as a preservative) followed by high performance liquid chromatography (HPLC) with electrochemical detection (Forster and Macdonald 1998).

Labelled glucose artificially enriched with (U-^{13}C) glucose (^{13}C/C>99 %; Isotec, Miamisburg, OH, USA) was dissolved in each individual's liquid meal so that the appearance of $^{13}CO_2$ in the expired air could be used as a marker of the combination of gastric emptying, uptake and oxidation of the test meal. This breath testing is based on the principle that an ingested substrate is metabolised, and a measurable metabolite is then expelled by the respiratory system. Therefore, breath samples were collected simultaneously with the blood samples before and after the meal (at -15, 0, 15, 30, 45, 60, 75, 90, 105 and 120 min) using a breath-sampling bag (500 ml) with a one-way valve for capture of normal exhaled air. To allow analysis of $^{13}C/^{12}C$ in expired CO_2, 20 ml samples of expired gases were collected from the breath-sampling bag via a catheter (Baxter Health Care, Valencia, CA) into evacuated tubes (vacutainers: Becton Dickinson, Franklin Lakes, NJ) and stored until further analysis. All samples were subsequently analysed in triplicate with mass spectrometry (Prism, VG, Manchester, UK) and ^{13}C abundance was calculated for all time points. The incremental postprandial response (i.e. the ^{13}C enrichment curve) was integrated and presented as an area under the curve (AUC).

4.1.2.5 Assessment of metabolic rate during rest

One hour after the subjects completed their morning personal hygiene and morning body weighing, they relaxed and rested supine for 3 hours during the metabolic test. The metabolic tests were conducted at the same time of the day for each subject (between 07:00 am and 01:00 pm); the environmental conditions were kept constant: the mean ambient temperature, relative humidity and barometric pressure were 25±0.9 ˚C, 35.8±7.6 %. The barometric pressure of 682 mmHg was verified with the Slovenian Meteorological Agency. The conditions of the laboratory were thermally comfortable.

Resting energy expenditure (REE) was measured using indirect respiratory calorimetry with an open-circuit spirometer canopy system (Quark RMR, Cosmed, Italy). A transparent ventilated hood system was placed over the subject’s head with a hose connecting the hood to the gas analysis system. The flow of ambient air through the hood was controlled by a pump. The analyser was calibrated in a normoxic environment for all the tests. Reference gas standards were used to calibrate the system, and all measurements

were automatically corrected for environmental temperature, pressure, and humidity. The post-tests in the HYPOXIA trial were performed in a hypoxic environment. During the hypoxic post-tests the metabolic analyser was calibrated in a normoxic environment, but fasting and postprandial REE were monitored in the hypoxic environment of the room. Since the hardware and software of the metabolic analyser (Quark RMR, Cosmed, Italy) was not capable of conducting on-line calculations of REE in a normobaric hypoxic environment, the values of REE in the hypoxic environment were derived manually from the measurements of the FO_2 entering and exiting the canopy placed on the subject's head, and the air flow through the canopy. Basal measurements of $\dot{V}O_2$ and CO_2 production ($\dot{C}O_2$) were conducted at 15-min intervals with the individuals awake, before the standard meal and at time-points 15, 45, 75, 105 min, postprandially. To disregard the artefacts that occur during the first few minutes of measurement, when the canopy is placed over a subject's head and the measurement initiated, the calculation of REE was made on the values measured after the first 2 minutes of the test.

Additionally, HR (Polar, RS400, Finland), arterial pressure (aneroid sphygmomanometer, Welch Allyn, Inc., USA), and SpO_2 (Nonin Medicals 3100 WristOx, Minnesota, USA) were recorded at 15-min intervals.

4.1.2.6 Appetite Sensation

Subjective perceptions of hunger, fullness, desire to eat, thirst and prospective food consumption were assessed using a validated visual analogue scale (VAS; Stubbs et al. 2000). The VAS scale was a 100 mm line, anchored to the left with 'sensation not felt at all' and to the right with 'sensation felt the greatest' and subjects were asked to place a vertical line in relation to their feeling at that particular point in time, these scores were then summed to form the Composite Satiety Score (CSS) according to the following equation (the higher the score, the higher the level of subjective satiety; Stubbs et al. 2000):

$$CSS = (Full + (100 - Desire) + (100 - Hunger) + (100 - PFC))/4.$$

4.1.2.7 Intestinal blood flow

Blood flow was measured in the proximal portion of the superior mesenteric artery (SMA), 2–5 cm distally to its origin in the aorta. Flow was estimated by measurements of vessel-lumen diameter and mean flow-velocity, using ultrasonographic / Doppler techniques (Philips CX50, Bothel, Washington).

Flow velocity was measured using a 3–12 MHz linear array Doppler transducer that was kept aligned with the vessel; the angle correction of the transducer was maintained at less than 60° and its sample volume was adjusted to cover more than 75 % of the vessel lumen.

The diameter of the SMA was measured in B-mode image during end-diastole (determined from the ECG), as wall-to-wall distance in the sagittal section. Assuming that the artery had a circular cross-section, flow was subsequently calculated by multiplying vessel cross-sectional area by the mean flow-velocity. Each flow determination was the average of measurements from 3–4 consecutive heart beats, repeated 2–3 times, i.e. the average of data from 6–12 beats. The same sonographer performed all measurements.

4.1.2.8 Calculations and statistical methods

Mass spectrometer analysis of breath samples provided a delta value (δ), which was used to calculate abundance (atom %) at each time point using standard methods (Pouteau et al. 1998). Enrichment of breath samples was then obtained by standardising

postprandial values to those at baseline.

The homeostatic model assessment (HOMA) method was used to quantify fasting insulin resistance and β-cell function (Matthews et al. 1985). The nonlinear model of two types of HOMA scores were used:

HOMA IR = insulin resistance =
= (fasting insulin in $mU \cdot l^{-1}$) × (fasting plasma glucose in $mmol \cdot l^{-1}$) / 22.5
HOMA β = β-cell function [%] =
= 20 × (fasting insulin in $mU \cdot l^{-1}$) / ((fasting glucose in $mmol \cdot l^{-1}$) - 3.5).

A 2-way ANOVA (NORMOXIA-HYPOXIA, Pre-Post) with repeated measures was used to define the effect of the 10-day confinements on the measured variables. A Tukey *post hoc* test was used to assign the specific differences in the analysis of variance. Additionally, some data were presented as calculated area under curve (AUC) and compared with the same type of ANOVA. Values are mean±SD unless indicated otherwise. The alfa level of significance was set *a priori* at 0.05.

4.2 Results

4.2.1 Anthropometry

The (mean±SD) age, mass, percent total body fat, and body mass index (BMI) of the present study participants were 23.7±4.0 yrs, 73.0±7.7 kg and 22.3±2.4 $kg \cdot m^{-2}$, respectively (Table 4.1).

Table 4.1: *Descriptive characteristics (age, body weight, stature, body mass index) of the present study participants.*

Subject	Age (years)	Body weight (kg)	Stature (cm)	BMI ($kg^{-1} \cdot m^{-2}$)
S1	24	76.2	179.0	23.8
S2	21	69.5	183.0	20.8
S3	21	66.9	164.0	24.9
S4	24	86.7	184.0	25.6
S5	30	76.0	184.0	22.4
S6	21	86.4	185.5	25.1
S7	25	68.4	198.0	17.4
S8	20	66.7	178.0	21.1
S9	20	73.2	185.0	21.4
S10	32	69.6	181.0	21.2
S11	23	63.8	171.0	21.8
Mean	23.7	73.0	181.1	22.3
SD	4.0	7.7	8.7	2.4

Body mass decreased by -0.7±0.2 kg after NORMOXIA, and by -0.9±0.2 kg after HYPOXIA, there being no statistically significant difference between the NORMOXIA and HYPOXIA (p=0.77). Total body fat mass significantly increased in the NORMOXIA (p=0.04), whereas no difference between pre- and post-measurements was observed in the HYPOXIA (Table 4.2). In the abdominal region, absolute fat content increased significantly in the NORMOXIA (p=0.01), but exhibited a tendency towards a decrease in the HYPOXIA (p=0.08). There was also a tendency, albeit not significant, of a reduction in lean body mass after normoxic confinement (p=0.06, Table 4.2).

Table 4.2: *Body composition before (PRE) and after (POST) the 10-day NORMOXIA (F_IO_2 = 0.21) and HYPOXIA (F_IO_2 = 0.16) confinements in the facility situated at 940 m altitude.* Values are mean ± SD, n=11.

	NORMOXIA		HYPOXIA	
Variable	PRE	POST	PRE	POST
Body composition				
Body mass (kg)	73.0 ± 7.7	72.4 ± 7.0	72.3 ± 5.9	71.4 ± 6.3
BMI ($kg \cdot m^{-2}$)	22.3 ± 2.4	22.0 ± 2.7	22.1 ± 1.8	21.8 ± 2.0
Total fat mass (%)	14.6 ± 5.8	15.0 ± 6.1	14.6 ± 6.1	14.6 ± 5.5
(kg)	10.9 ± 5.5	11.1 ± 5.4 *	10.7 ± 5.3	10.6 ± 4.8
Abdominal fat mass (%)	11.9 ± 6.3	12.7 ± 6.7 *	11.9 ± 6.6	11.8 ± 5.8
Right thigh (%)	14.9 ± 6.9	15.9 ± 7.3	14.9 ± 6.6	14.5 ± 6.7
Left thigh (%)	15.3 ± 6.3	15.5 ± 6.2	14.9 ± 6.5	14.9 ± 6.0
Fat free mass (%)	85.4 ± 5.8	85.0 ± 6.0 *	85.4 ± 6.1	85.4 ± 5.5
(kg)	62.2 ± 5.2	61.3 ± 5.0	61.6 ± 4.9	60.8 ± 4.7

4.2.2 Cardiovascular response

The average nocturnal arterial blood oxygen saturation (SpO_2) during the course of the 10-day confinement was lower ($p<0.001$) in HYPOXIA (88.9±0.2 %) than in NORMOXIA (97.2±0.2 %). In contrast, heart rate (HR) was higher ($p=0.04$) in HYPOXIA (64.4±0.7 min^{-1}) than NORMOXIA (60.1±0.4 min^{-1}, Figure 4.3).

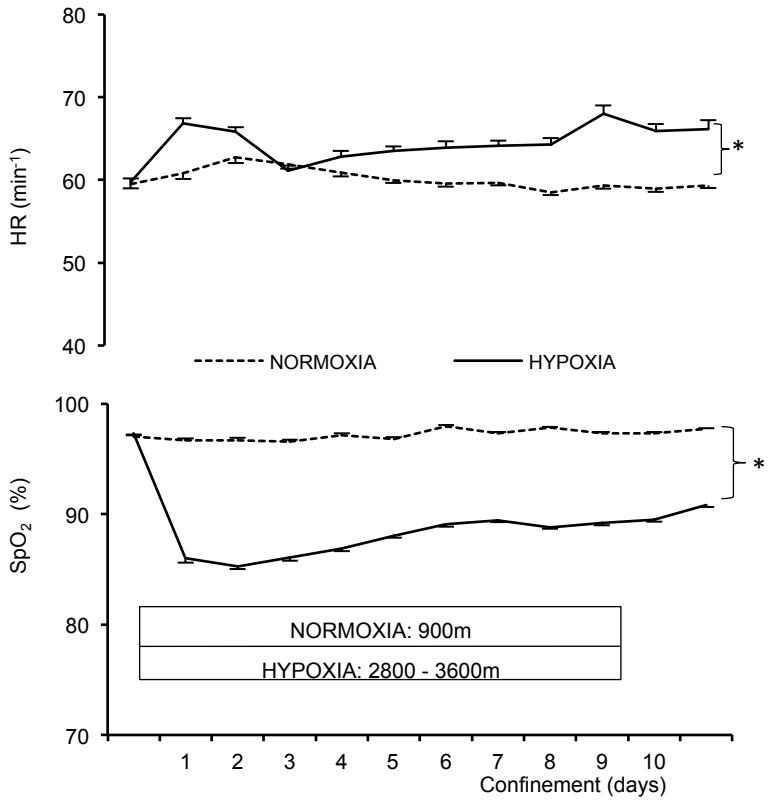

Figure 4.3: *Nocturnal heart rate (HR, min^{-1}) and blood oxygen saturation (SpO_2, %) before (PRE), during, and at the end (POST) of the NORMOXIA and HYPOXIA confinements.* Values are mean±SEM, n=8. (*): Significant differences between the NORMOXIA and HYPOXIA confinement; $p<0.05$.

Peak aerobic performance ($\dot{V}O_{2peak}$) was not significantly affected by NORMOXIA (61.2±7.2 ml·kg^{-1}·min^{-1}; 61.8±7.0 ml·kg^{-1}·min^{-1}) or HYPOXIA (62.6±6.1 ml·kg^{-1}·min^{-1}; 62.4±5.9 ml·kg^{-1}·min^{-1}).

Resting cardiorespiratory response resulted in significantly elevated minute ventilation ($\dot{V}$E) after HYPOXIA (p=0.01), but not after NORMOXIA (Table 4.3). Furthermore, no symptoms of mountain sickness (Lake Louise Score) were detected during the HYPOXIC confinement.

Table 4.3: *Resting cardiorespiratory responses before (PRE) and after (POST) the 10-day NORMOXIA (F_IO_2 = 0.21) and HYPOXIA (F_IO_2 = 0.16) confinements in the facility situated at 940 m altitude*. $\dot{V}O_2$: oxygen uptake, $\dot{V}E$: minute ventilation; (*): significant differences between PRE and POST confinement; p<0.05. Values are mean ± SD, n=11.

Cardiorespiratory variables	NORMOXIA		HYPOXIA	
	PRE	POST	PRE	POST
Heart rate (min^{-1})	59.0 ± 11.8	63.1 ± 11.5	63.6 ± 12.0	61.3 ± 13.7
$\dot{V}O_2$ (ml·kg^{-1}·min^{-1})	3.8 ± 0.7	4.2 ± 0.6	4.0 ± 0.3	5.4 ± 1.0 *
$\dot{V}E$ (l·min^{-1})	15.2 ± 2.0	15.0 ± 2.1	15.2 ± 2.0	16.8 ± 2.0 *

In addition, during rest there were no significant differences observed in systolic arterial pressure (SAP) or diastolic arterial pressure (DAP) before and after the NORMOXIA (SAP: 118.0±7.7 mmHg; 114.6±8.2 mmHg; DAP: 78.9±6.0 mmHg; 74.6±6.6 mmHg) and HYPOXIA (SAP: 119.3±9.2 mmHg; 123.0±9.3 mmHg; DAP: 80.2 ± 6.3 mmHg; 85.5 ± 8.7 mmHg).

4.2.3 Resting energy expenditure

The resting energy expenditures (REE) in fasted state and during the meal tolerance test (MTT), before and after the 10-day NORMOXIA and HYPOXIA trials is presented in Figure 4.4. REE increased after the meal (Breakfast) and remained elevated 2 hrs postprandially.

No differences were observed before and after the 10-day period in NORMOXIA. By comparison, fasting REE was elevated (p=0.01) in HYPOXIA, but the REE response to the test meal was similar such that absolute postprandial values were higher after hypoxic confinement (p=0.01) compared to values observed before the confinement.

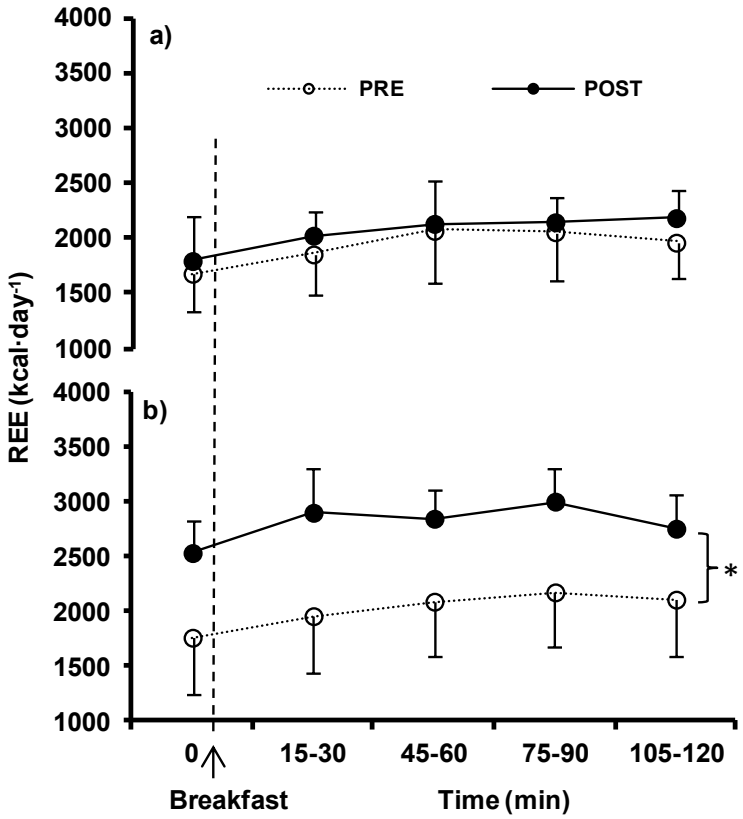

Figure 4.4: *Postprandial resting energy expenditure (REE) before (PRE) and after (POST) 10-day NORMOXIC (a) and 10-day HYPOXIC (b) confinement.* Values are mean±SD. (*): Statistically significant differences between PRE and POST confinement; $p<0.05$.

4.2.4 Energy intake

A reduction in energy intake was observed in the HYPOXIA ($p=0.02$), with mean daily energy intake being 2847±241 kcal·day^{-1} and 2472±251 kcal·day^{-1}, in NORMOXIA and HYPOXIA, respectively.

4.2.5 Haematological and laboratory variables

The changes in haemoglobin did not reach the level of significance before and after the NORMOXIA (Pre: 146.4±0.9 g·L^{-1}; Post: 144.5±0.8 g·L^{-1}) or HYPOXIA (Pre: 147.2±0.9 g·L^{-1}; Post: 148.4±0.9 g·L^{-1}).

Blood glucose levels in the fasted state were similar after NORMOXIA, while after HYPOXIA a trend ($p=0.09$) towards decreased fasting blood glucose was observed (Figure 4.5) compared to pre-confinement values. Fasting insulin and fasting GLP-1 were higher after the NORMOXIA ($p=0.01$; $p=0.02$), but not after the HYPOXIA.

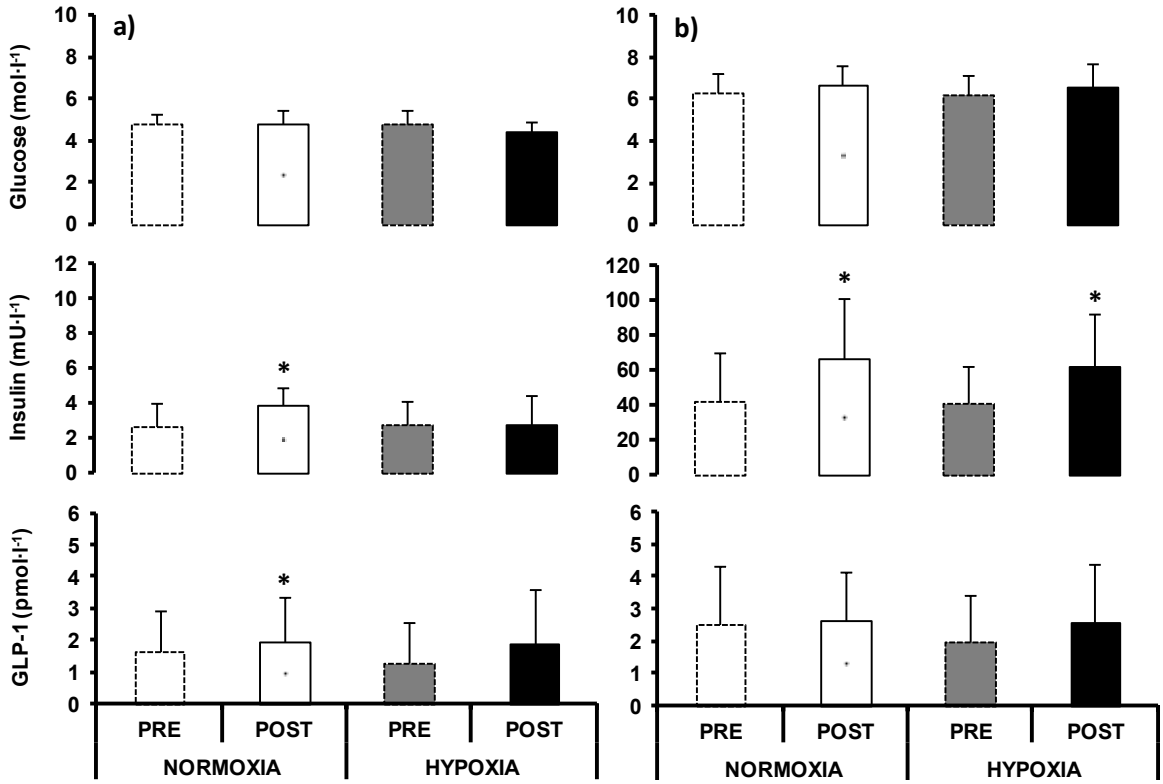

Figure 4.5: *Blood glucose, serum insulin and GLP-1 values in fasted (**a**), and postprandial state (mean of 2 hours, **b**), before (PRE) and after (POST) 10-day normoxic (NORMOXIA) and hypoxic (HYPOXIA) confinement.* Values are mean±SEM, (*): statistically significant differences between PRE and POST confinement; $p<0.05$.

Postprandially, circulating glucose was elevated in NORMOXIA and HYPOXIA until the 40th min, and then gradually decreased (Figure 4.6). There was a tendency, albeit not significant, of higher glucose levels ($p=0.06$) after HYPOXIA (Table 4.5, 4.6). Postprandially, insulin initially increased in all trials, and then gradually decreased until the end of the 2-hour measurement. After the 10-day period, insulin was higher ($p<0.05$) in both the NORMOXIA and HYPOXIA compared with the values observed in the pretests (Figure 4.6). GLP-1 increased after the meal, and the response was similar for both the NORMOXIA and HYPOXIA trials (Figure 4.5).

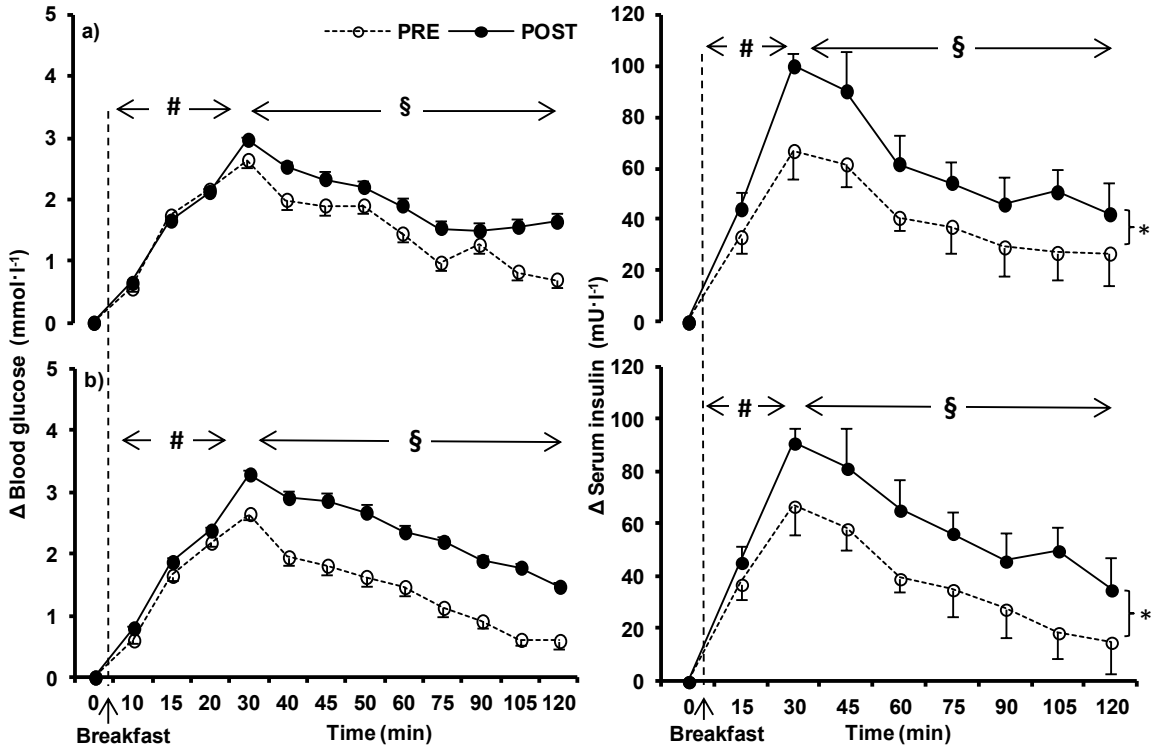

Figure 4.6: *Delta postprandial blood glucose, and serum insulin values before (PRE) and after (POST) the 10-day NORMOXIC (**a**) and HYPOXIC confinement (**b**). Values are mean±SEM.* (*): Statistically significant differences between PRE and POST confinement, (#): statistically significant differences with time from the fasted state; (§): statistically significant differences with time from the peak values; $p<0.05$.

HOMA IR significantly increased in the NORMOXIA trial (pre: 0.6±0.3; post: 0.9±0.4; p=0.03), while no differences were observed in the HYPOXIA trial (pre: 0.5±0.3; post: 0.5±0.4). HOMA-β was significantly different after each confinement (p=0.03) with no differences between (p=0.77) NORMOXIA (pre: 46.9±33.8; post: 81.5±45.3) and HYPOXIA (pre: 57.7±52.0; post: 64.5±44.2).

The enrichment of ^{13}C in expired air, derived from labelled glucose, increased after the meal (Figure 4.7; $p<0.001$), although this was not different between confinements (p=0.71). Thus, there was no evidence of impaired dietary glucose availability following a period of hypoxic confinement, and the speed with which ingested glucose was absorbed and metabolised was not altered by this intervention.

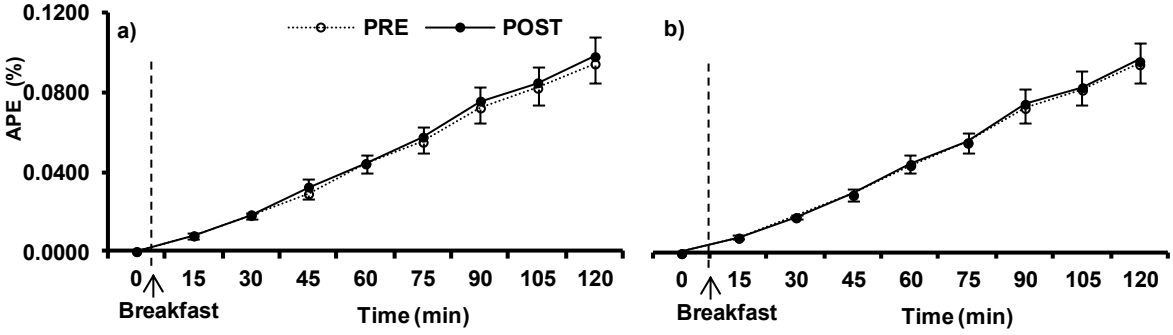

*Figure 4.7: Isotopic enrichment of expired CO_2 expressed in atom percent excess (APE) in postprandial response before (PRE) and after (POST) the 10-day NORMOXIC (**a**) and HYPOXIC (**b**) confinement.* Values are mean±SEM.

The noradrenaline level in the fasted state was significantly higher after the HYPOXIC confinement (p=0.04) compared to NORMOXIC confinement, whereas no differences in fasting adrenaline were observed in both trials. There was a tendency for elevated postprandial levels of noradrenaline in the HYPOXIA (p=0.07) trial compared to NORMOXIA, whereas there were no significant postprandial changes of adrenaline before or after the NORMOXIA or HYPOXIA (Table 4.5).

There were no changes in fasting ghrelin levels after each confinement (Table 4.5). Ghrelin decreased postprandially in all confinements (p<0.001), but there were no statistically significant differences between the pre- and post-confinement tests within each trial, nor between the NORMOXIA and HYPOXIA (Table 4.5).

Leptin levels in the fasted state significantly increased after both the NORMOXIA and HYPOXIA trails (p=0.02; Table 4.5). There was no significant difference between the responses in the NORMOXIA and HYPOXIA trials (p=0.53) both with and without the change in fat mass used as a co-variate (p=0.52).

In the fasted state PYY was not significantly different between the conditions. Postprandially, PYY increased significantly (p<0.001) in both the NORMOXIA and HYPOXIA trials (Table 4.5), but there were no significant differences between NORMOXIA and HYPOXIA (p=0.46).

Table 4.4: *Fasted and mean postprandial level of ghrelin, leptin, peptide YY_{3-36} (PYY), adrenaline and noradrenaline before (PRE) and after (POST) the 10-day NORMOXIA (F_IO_2 = 0.21) and HYPOXIA (F_IO_2 = 0.145) confinements in the facility situated at 940 m altitude.* Values are mean±SEM, n=11. (*): Statistically significantly differently between PRE and POST confinement; (#): Statistically significantly different between fasted and postprandial condition; p<0.05.

	NORMOXIA PRE		POST		HYPOXIA PRE		POST	
Variables	Fasted state	Postprandial state	Fasted state	Postprandial state	Fasted state	Postprandial state	Fasted state	Postprandial state
Adrenaline ($nmol \cdot L^{-1}$)	0.31±0.01	0.22±0.01	0.27±0.01	0.19±0.01	0.30±0.02	0.21±0.02	0.26±0.01	0.19±0.01
Noradrenaline (nmol·L-1)	0.89±0.02	1.01±0.03	0.77±0.02	0.87±0.03	1.01±0.03	1.07±0.03	1.30±0.04*	1.53±0.05
Ghrelin ($pg \cdot mL^{-1}$)	1139.4±29.5	990.0±22.4#	1088.1±31.5	906.8±24.7#	1002.5±21.7	864.1±19.8#	1130.3±28.2	914.0±24.6#
Leptin ($ng \cdot mL^{-1}$)	3.0±0.2	-	3.6±0.2*	-	2.6±0.2	-	3.6±0.2*	-
PYY ($pg \cdot mL^{-1}$)	99.9±3.4	122.1±2.2#	114.9±2.6†	132.4±2.2#	95.1±2.5	124.6±3.3#	107.2±1.8	138.5±2.8#

4.2.6 Intestinal blood flow

The postprandial blood flow in the superior mesenteric artery increased after the meal, with peak values being observed 30 min postprandially (mean increase of 456±15 $ml \cdot min^{-1}$). Thereafter, mesenteric arterial flow decreased, but remained elevated above the baseline value (by 123±6 $ml \cdot min^{-1}$) for the remainder of the postprandial period. Mesenteric arterial flow response was not significantly different after the 10-day NORMOXIA or HYPOXIA trial (Table 4.4).

Table 4.5: *Fasted and mean postprandial mesenteric arterial blood flow before (PRE) and after (POST) the 10-day NORMOXIA (F_IO_2 = 0.21) and HYPOXIA (F_IO_2 = 0.145) confinements in the facility situated at 940 m altitude.* Values are mean±SEM, n=11.

Condition		Fasted state	Postprandial state			
	Time (min)	0	30	60	90	120
		Mesenteric arterial blood flow (ml·min^{-1})				
NORMOXIA	Pre	149.7±6.7	530.6±26.1	400.6±20.7	279.0±13.9	263.6±14.7
	Post	131.8±8.5	593.1±20.8	409.5±14.7	316.5±13.7	251.7±10.3
HYPOXIA	Pre	146.0±8.0	627.1±29.4	455.9±22.8	287.0±13.8	233.6±10.5
	Post	142.8±5.4	646.0±19.1	420.5±9.6	332.4±13.2	316.2±12.2

4.2.7 Subjective satiety evaluation

Subjective satiety (composite satiety score; CSS) in the fasted state before (pre) and after (post) confinement in the NORMOXIA (Pre: 31.8±2.0, Post: 31.1±2.1) or HYPOXIA (pre: 38.3±2.2; post: 37.3±2.0) was not significantly different (p=0.19). CSS increased after the test meal, but there were no differences before or after NORMOXIA (pre: 45.9±9.2; post: 42.6±4.0) or HYPOXIA (pre: 51.0±4.7, post: 50.3±5.8).

4.3 Discussion

The principal finding of the present study is that a continuous 10-day exposure to normobaric HYPOXIA without the confounding factor of strenuous physical activity causes a decrease in dietary intake and a concomitant increase in resting energy expenditure (REE).

In addition, body fat mass increased slightly during the NORMOXIC confinement, whereas no change was observed during the HYPOXIC confinement. Following the HYPOXIA, there was also a trend for changes in the plasma glucose responses to a test meal which is consistent with the development of postprandial insulin resistance.

4.3.1 Energy intake inhibition

Our observation of reduced energy intake during the HYPOXIA trial concurs with the reported loss of appetite after a 31-day hypobaric hypoxic exposure in laboratory conditions (Westerterp-Plantenga et al. 1999), and suppressed energy intake after a 7-hour exposure to normobaric hypoxia (Wasse et al. 2012).

The subjects ate *ad libitum*, and no change in appetite was detected by the composite satiety score after the test meal. A reduction in energy intake is consistent with the suggested altitude anorexia mediated by leptin (Tschöp et al. 1998), which is thought to regulate food intake and energy expenditure. In the NORMOXIA trial, the increased fasting leptin could be explained on the basis of the tendency for increased body fat mass, whereas in the HYPOXIA trial leptin increased, despite a trend for a reduced total fat content. This increase in leptin levels might be related to the decreased food intake as well as the increased REE. Our observed leptin response is in agreement with studies reporting increased leptin levels after hypoxic exposure (Mazzeo 2008; Shukla 2005; Snyder 2008). Furthermore, it has been reported that hypoxia-treated cells up-regulate obese gene transcription, suggesting that enhancement of leptin secretion *in vivo* under hypoxic conditions may be a mechanism to consider when developing therapeutic methods for

obesity treatment (Yingzhong et al. 2006). However, equivocal leptin levels after HYPOXIA, could be due to high intra-individual responses as well as differences in the degree of hypoxic exposure (Mazzeo 2008).

Similar to other studies, we also observed no change in ghrelin levels during the HYPOXIA trial, although the ghrelin level decreased after the meal as expected in a normal postprandial response (Cummings et al. 2001). In agreement with others (Lippl et al. 2010), a significant decrease in fasting ghrelin after the hypoxic confinement was not observed, most likely due to the fact that the absolute amount of weight loss was small. Previously, unchanged ghrelin levels were reported despite a reduction of 5 kg in body mass (Benso et al. 2007). It has been suggested that PYY can inhibit ghrelin neurons and consequently ghrelin secretion (Riediger et al. 2004). In the present study PYY was unchanged after HYPOXIA, which does not support the theory that it contributes to high-altitude anorexia.

4.3.2 Increased metabolic rate

Westerterp et al. (1992, 1994), who observed reduced body weight mainly due to fat loss during a Mt. Everest climb (>5000 m, 3 weeks) reported no significant differences in resting metabolic rate measured at sea level by respiratory gas analysis and at high altitude. In most of the field studies a number of environmental factors (hypobaric hypoxia, cold) and intense physical activity might affect metabolic rate. However, in agreement with our observation, there are indications of increased REE in altitude studies (Gill and Pugh, 1964; Grover, 1963; Stock et al., 1978). Furthermore, Pulfrey and Jones (1996) reported that climbing to nearly 8000 m required 536 kcal/day just for an acclimatization to altitude, which did not include energy expenditure (EE) for physical exertion. Moreover, inline with our observations, a 27 % increase of REE was reported on the day 2 at altitude which decreased, but reached plateau at 17 % increase above the sea level REE by day 10 (Butterfield et al. 1992). Reynolds et al. (1999) reported EE ranged from 1.85 up to 3.82 times the REE measured at sea level before the expedition, with the mean of 2.98 ± 0.70 for the climbers and of 2.43 ± 0.45 for the base camp individuals. Again, all the previous evidence of increased REE at high altitude were related to even lower O_2 availability due to pressure change at high altitude and it is interesting that we have found similar results. Lippl et al. (2010) confirmed that hypobaric hypoxia (with no physical activity) contributed to increase REE, but there were no evidences if daily normobaric hypoxic confinement (frequently used as hypoxic training for athletes) could affect metabolic rate. Therefore, our observation of increased REE suggests that hypoxia *per se* has a pivotal role in the elevated REE at high altitude.

The observed increase in REE induced by hypoxic confinement is most likely attributable to increased pulmonary ventilation, hyperkinetic circulation as well as to other adaptive responses to sustained hypoxia (Gilmartin et al. 2008). Gill and Pugh (1964) reported a 10 % increase of REE during a prolonged stay at 5800 m, whereas Butterfield et al. (1992) reported a 27 % increase in REE on the 2nd day at 4300 m, which thereafter decreased to 17 % on the 10th day. Our observations of a 31.4 % increase in REE following a 10-day hypoxic confinement is, to our knowledge, the first such measurement conducted in normobaric hypoxia, and concurs with the magnitudes of the hypoxia-induced increases in REE reported by earlier studies. Although the present 10-day HYPOXIA confinement did not result in statistically significant increase in haemoglobin concentration it is reasonable to assume that it did increase erythropoietin secretion (Berglund et al. 2002, Gunga et al. 1994), and there is evidence suggesting that increased erythropoietin concentration could be linked with increased REE (Christensen et al. 2012).

However, the tendency for insulin resistance induced by present HYPOXIA confinement is also attributable to an increased erythropoietin level (Biolo et al. 2010). In addition, circulating catecholamines can stimulate energy expenditure (Cori and Buchwald 1930). Our finding of increased noradrenaline after HYPOXIA is in line with numerous studies (Calbet 2003; Richalet et al. 2010), indicating activation of the sympathetic nervous system (SNS) by hypoxia (Cutler et al. 2004; Gilmartin et al. 2008). It has been demonstrated that variability in REE can be explained by differences in SNS activity (Webber and Macdonald 2000), and hence, SNS activation may have contributed to the increased REE during the present hypoxic confinement. The increase in REE induced by hypoxia *per se* may not be desirable for athletes training in hypoxic conditions, as their energy requirements may be increased. By contrast, this response to hypoxia might be beneficial for obese individuals, in whom exercise limitation can profoundly restrict daily activities, and lead to lower energy expenditure. Hypoxia-induced enhancement of REE and additionally the reduced *ad libitum* energy intake observed in our study after normobaric HYPOXIC confinement might contribute to weight loss in the obese.

4.3.3 Sustained intestinal blood flow

The weight loss at altitude may not be entirely due to an imbalance between the amount of food (energy) ingested and energy expenditure. Slowed, and possibly impaired, absorption of nutrients at altitude has also been suggested (Schoots et al. 2006) to reduce the availability of the ingested energy. In contrast, it was reported that, at least up to an altitude of 5000 m, malabsorption does not seem to play a role in altitude-related weight loss (Kayser 1994).

In the present study, HYPOXIA did not compromise the gut blood flow response to the test meal. We did not observe any significant differences from the normal, anticipated increase after the meal (Sidery and Macdonald 1994; Totman et al. 2009), nor were there differences in the responses of superior mesenteric arterial flow between the NORMOXIA and HYPOXIA trials. Recently, it was suggested that the suppression of acylated ghrelin during 7 hours of hypoxic exposure might be linked to impaired gut blood flow in response to acute hypoxia (Wasse et al. 2012). In addition, the observation of impaired postprandial gut blood flow (superior mesenteric artery) during acute altitude exposure as a consequence of increased intestinal sympathetic tone, suggested that, if sustained, it may be related to reduced energy intake, during prolonged exposure (Loshbaugh et al. 2006). However, our results concur with the already reported loss of appetite, but no reductions in gut blood flow during several days of exposure to hypobaric hypoxia (Kalson et al. 2010). Thus, it is unlikely that impaired gut blood flow is responsible for high-altitude anorexia, as previously proposed. In addition, there were no changes in the postprandial $^{13}CO_2$ level in expired air (derived from the ingested ^{13}C-glucose) after confinement in NORMOXIA or after confinement in HYPOXIA. This, together with the finding of unaltered gut blood flow in both conditions, provides strong evidence that a 10-day hypoxic confinement does not induce malabsorption, and thus does not reduce the availability of ingested energy. There is no evidence that gut function was affected by HYPOXIA in the present study.

4.3.4 Insulin sensitivity

Fasted insulin and GLP-1 were increased after the NORMOXIA, but not after the HYPOXIA trial. Interestingly, a trend ($p=0.09$) towards decreased fasting blood glucose after the 10-day hypoxic confinement was noted. Consequently, the HOMA IR and

HOMA-β index were elevated only after the NORMOXIA trial due to increased fasting insulin. Postprandially, a trend for elevated blood glucose only after the HYPOXIA trial was concomitant with the elevated insulin response, which might suggests increased insulin resistance due to hypoxia or the imposed inactivity (Hamburg et al. 2007, Olsen et al. 2008) in the physically well-trained participants.

Moreover, the reduction in insulin mediated peripheral glucose uptake could also be compounded by the small decrease of fat-free mass and presumably also by the increase in SNS activation in hypoxia. Recently, Peltonen et al. (2012) demonstrated that SNS activation was also associated with the disruption of glucose control. Therefore the observed tendency for insulin resistance could be, in part, due to a hypoxia-induced SNS activation. Stock et al. (1978) reported no changes either in fasting blood glucose levels, or in the postprandial blood glucose response during the 1st week of exposure to altitude (3650 m above sea level), while after the 2nd week at high altitude there was a reduction in fasting and postprandial blood glucose and insulin levels. In contrast to our study, the subjects in this study were exercising. In addition, compared to our study the technique of blood sampling was different, in particular, blood samples were drawn from the antecubital vein in the field study, whereas in the present study arterialised venous blood samples were obtained. The former would lead to an underestimation of the glucose response to a meal due to tissue extraction. The observed tendency for an elevated postprandial blood glucose response observed in the HYPOXIA trial was concomitant with unaltered adrenaline levels, in accordance with previous observations (Pulfrey and Jones 1996). Moreover, our findings of significantly higher noradrenaline levels in the fasted state in hypoxia, with a tendency of elevated postprandial noradrenaline levels only after the HYPOXIA trial are consistent with the observations of increased activity of the SNS, when oxygen availability is decreased, as in hypoxia (Gilmartin et al. 2008, Peltonen et al. 2012). Increased SNS activity might be partly responsible for the elevated REE in the HYPOXIA trial.

Moreover, our finding of a significantly higher resting ventilation following the 10-day hypoxic confinement concurs with the findings of others (Evetts et al., 2005), and would cause an increase in respiratory muscle oxygen consumption. This would also contribute to the observed increase in hypoxia-induced increase in REE.

The observed reduction of the *ad libitum* energy intake in the HYPOXIA compared to the NORMOXIA trial, most likely contributed to the loss of mass in the former condition. This concurs with the results of Abete et al. (2010), who reported a weight loss of 0.5–1.0 kg·week^{-1} in subjects whose energy intake was restricted by 500–1000 kcal·day^{-1} compared to the usual diet.

4.3.5 Summary

To summarise, in contrast to other studies, particularly field studies, we have minimised and/or eliminated certain confounding factors, which may contribute to weight loss during longer exposures at higher altitudes, including cold stress, strenuous physical activity, detraining, lack of comfort, and unpalatable food. By carefully monitoring nutritional intake and minimising physical activity of the subjects, our results focus on the direct effects of normobaric HYPOXIA in the fasted state on postprandial metabolic responses.

Our results indicate metabolic changes, which may lead to reduction in body weight, but it remains speculative whether hypoxia of greater magnitude might induce more pronounced weight loss. In agreement with previous observations of increased REE after hypobaric hypoxia (Butterfield et al. 1992), normobaric HYPOXIA induced a similar response in the present study.

The observed significant increase in REE is most likely the reason that restriction of activity in otherwise active and aerobically well-trained young males did not induce an increase in body weight. Specifically, the trend for greater loss of body weight after the 10-day HYPOXIA (compared to the NORMOXIA) could be explained on the basis of the substantial increase in REE during the HYPOXIA. In conclusion, athletes and alpinists conducting hypoxic training should be aware that hypoxia may lead to a negative energy balance as a consequence of increased REE and reduced energy intake, and should monitor their energy intake to prevent such loss in mass, which may ultimately have a detrimental effect on performance.

5 Metabolic effects of normobaric hypoxia in overweight individuals

Obesity has become a global epidemic and novel strategies to achieve effective weight loss are being sought. As a prelude to studies investigating the effect of hypoxic exercise on metabolism, as a novel weight management intervention, we initiated a series of studies to examine resting metabolism during 10-day hypoxic confinement. These initial studies were designed to reveal the effect of hypoxia *per se* on metabolism, without any confounding effects of exercise. Interest in this area arises from anecdotal evidence of »high altitude anorexia«, and results of controlled studies reporting hypoxia-induced alterations in metabolism (Haufe et al., 2008; Wisner et al., 2009). The aim of the present study was to test the hypothesis ($H_{0\text{-}6}$) and assess whether hypoxia might initiate similar significant metabolic responses in obese individuals, and whether this would result in body weight loss.

5.1 Materials and Methods

5.1.1 Subjects

Eight overweight males, all low altitude (351.6±103.7 m) residents, participated in two 10-day trials. Overweight status was defined as total body fat > 30 % and body mass index (BMI) > 27.5 $kg \cdot m^{-2}$. Subject exclusion criteria included a history of physician-diagnosed medical problems, recent prolonged exposure to normobaric or hypobaric hypoxia, or recent weight loss, participation in any dietary manipulations in the past six months, and use of any medications or drugs. All participants gave their written informed consent to participate in the study. The study protocol was approved by the National Committee for Medical Ethics at the Ministry of Health of the Republic of Slovenia and conformed to the Declaration of Helsinki.

5.1.2 Experimental procedure

The study was conducted at the Olympic Sport Centre Planica (Planica, Slovenia) situated at an altitude of 940 m. Subjects participated in two trials, during which they were confined to one floor of the facility. In one trial, the ambient conditions were normoxic (NORMOXIA trial), and in the other they were rendered hypoxic (HYPOXIA trial). The study was designed as a randomized cross-over study.

Participants were assigned to two groups: initially one group (N=4) was confined to a normobaric normoxic environment (NORMOXIA; F_IO_2=0.2093) for 10 days and the other (N=4) to a controlled normobaric hypoxic environment (HYPOXIA) for the same period. During the HYPOXIA trial, the 10-day exposure to a simulated altitude commenced at 2800 m (F_IO_2=0.1683) on days 1 and 2, and continued with a daily increase of 200 m, until a simulated altitude of 3400 m (F_IO_2=0.1567) was attained.

The subjects remained at the simulated altitude of 3400 m for the remaining 4 days. In both trials, the participants arrived at the facility 3 days prior to the onset of the 10-day confinement.

During these 3 days, they were familiarised with the experimental protocol and equipment, and baseline measurements were obtained.

Upon completion of the 10-day confinements, subjects remained at the facility for an additional 3 days for the post-confinement tests. After a 3-week wash-out period the subjects returned to the Olympic Sport Centre, and the conditions were crossed-over. During both the NORMOXIA and HYPOXIA trials, subjects were confined to the living quarters (each group had at their disposal 3 double sleeping rooms and one living/dining room; total area of ~ 90 m^2).

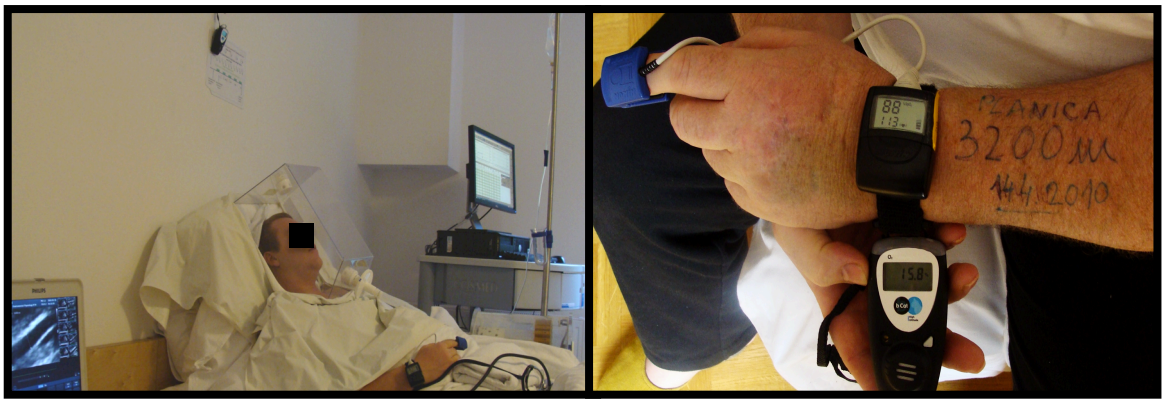

Figure 5.1: *Testing (left) before and after the 10-day confinement (right) in overweight individuals.*

Furthermore, all the Methodology (Experimental protocol: Figure 4.1 and testing Figure 5.1) was exactly the same as previously used in Study I. (Chapter 4.1) with the normal weight individuals. Except that the overweight individuals did not perform maximal performance test (VO_{2max} testing) and additionally, circulating bood lipids were also measured in this Study.

5.2 Results

5.2.1 Anthropometry

The (mean±SD) age, mass, percent total body fat, and body mass index (BMI) of the present study participants were 30.5±11.1 yrs, 125.0±17.7 kg, 30.8±6.1% and 37.6±6.2 $kg \cdot m^{-2}$, respectively (Table 5.1).

Table 5.1: *Descriptive characteristics (age, body weight, stature, body mass index) of the present study participants.*

Subject	Age (years)	Body weight (kg)	Stature (cm)	BMI ($kg^{-1} \cdot m^{-2}$)
S1	21	103.60	180.3	31.87
S2	26	134.10	193.2	35.93
S3	21	123.30	189	34.52
S4	22	120.80	180.9	36.91
S5	34	150.50	182.5	45.19
S6	45	143.60	176.6	46.04
S7	49	124.50	172.8	41.69
S8	26	99.70	186.3	28.73
Mean	30.5	125.0	182.7	37.6
SD	11.1	17.7	6.6	6.2

The changes in body weight were different (p=0.02) between the two 10-day confinements. In particular, body weight decreased by 0.7±0.2 kg in HYPOXIA, whereas it increased by 1.0±0.2 kg in NORMOXIA; a difference of 1.7 kg. Neither the HYPOXIC nor the NORMOXIC confinement affected the total or regional body fat mass (Table 5.2).

Table 5.2: *Anthropometric variables before (PRE), and at the end (POST) of the 10-day NORMOXIC and HYPOXIC trials.* Values are mean±SD.

	NORMOXIA		HYPOXIA	
	PRE	POST	PRE	POST
Body weight (kg)	125.0±17.7	126.0±19.3	123.9±18.0	123.1±19.0
BMI ($kg \cdot m^{-2}$)	37.6±6.2	37.9±6.7	37.3±6.3	37.1±6.6
Total fat mass (%)	30.8±6.1	31.6±5.3	32.1±6.7	31.8±6.1
Abdominal fat (%)	35.1±5.4	36.0±5.2	36.5±5.7	36.2±6.0
Right thigh fat (%)	29.0±6.3	30.3±5.5	30.0±5.9	30.6±6.2
Left thigh fat (%)	28.1±6.3	29.9±5.7	28.4±5.8	30.9±8.0

5.2.2 Cardiovascular response

The average nocturnal arterial blood oxygen saturation (SpO_2) during the course of the 10-day confinement was lower (p<0.001) in HYPOXIA (90.3±0.2 %) than in NORMOXIA (97.4±0.1 %). In contrast, heart rate (HR) was higher (p=0.04) in HYPOXIA (82.7±0.8 min^{-1}) than NORMOXIA (78.8±1.0 min^{-1}, Figure 5.2).

Furthermore, arterial pressures were similar before and after both the NORMOXIC (pre: systolic arterial pressure, SAP= 144±15 mmHg, diastolic arterial pressure, DAP= 88±10 mmHg; post: SAP= 138±18 mmHg, DAP= 87±12 mmHg), and HYPOXIC (pre: SAP= 145±14 mmHg, DAP= 89±11 mmHg; post: SAP= 137±9 mmHg, DAP= 87±10 mmHg) confinements. Furthermore, no symptoms of mountain sickness (Lake Louise Score) were detected during the HYPOXIC confinement.

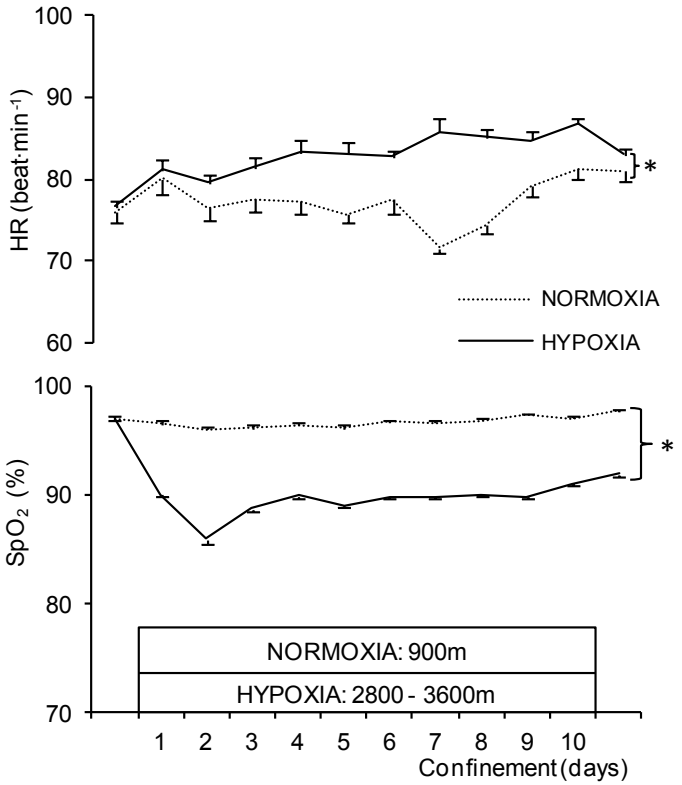

Figure 5.2: *Nocturnal heart rate (HR, beats·min^{-1}) and blood oxygen saturation (SpO_2, %) before (PRE), during, and at the end (POST) of the NORMOXIA and HYPOXIA confinements.* Values are mean±SEM, n=8. (*): Significant differences between the NORMOXIA and HYPOXIA confinement; $p<0.05$.

5.2.3 Resting energy expenditure

Resting energy expenditure (REE) in the fasted state was elevated after HYPOXIC confinement (358±49 kcal·day^{-1}; p=0.03); after NORMOXIC confinement fasting REE remained at similar levels (33±18 kcal·day^{-1}) compared to pre-confinement values.

Furthermore, after HYPOXIC confinement postprandial REE increased (p=0.05), while no differences were observed after NORMOXIC confinement (Figure 5.3).

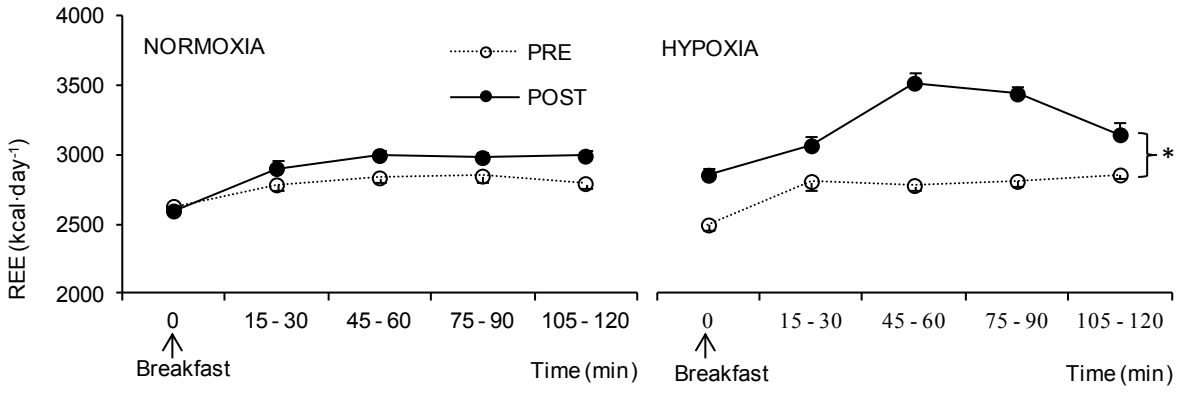

Figure 5.3: *Postprandial resting energy expenditure (REE) before (PRE), and at the end (POST) of the NORMOXIA and HYPOXIA trials.* Values are mean±SEM, n=8. (*): Significant differences between PRE and POST confinement; $p<0.05$.

5.2.4 Energy intake

The mean energy intake was not significantly different during the NORMOXIC and HYPOXIC confinements, although there was a tendency for it to be lower in HYPOXIA ($p=0.08$). Specifically, energy intake was 3497±189 kcal·day^{-1} in NORMOXIA and 3264±164 kcal·day^{-1} in HYPOXIA.

5.2.5 Haematological and laboratory variables

The haemoglobin level was unaffected by the HYPOXIC (pre: 154.8±1.7 g·L^{-1}; post: 156.0±1.4 g·L^{-1}) confinement, whereas it decreased after the NORMOXIC (pre: 154.1±1.5 g·L^{-1}; post: 147.6±1.7 g·L^{-1}) confinement. Cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were unaffected by both confinements (Table 5.3).

Table 5.3: *Cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels before (Pre) and after (Post) 10-day normoxic confinement (NORMOXIA) and 10-day hypoxic confinement (HYPOXIA).*

Lipids	NORMOXIA		HYPOXIA	
	PRE	POST	PRE	POST
Cholesterol (mmol·L^{-1})	4.9±0.1	4.4±0.1	4.9±0.1	4.2±0.1
Triglyceride (mmol·L^{-1})	2.3±0.2	1.9±0.2	2.4±0.2	2.1±0.2
HDL (mmol·L^{-1})	1.1±0.1	0.9±0.0	1.1±0.1	0.9±0.0
LDL (mmol·L^{-1})	2.9±0.1	2.7±0.1	2.9±0.1	2.5±0.1

The blood glucose level increased after each MTT. The postprandial blood glucose response was higher after the HYPOXIA confinement than after the NORMOXIA confinement ($p<0.001$, Figure 5.4).

Insulin levels also increased after the test meals, but no significant increases in insulin in the post-HYPOXIC confinement were observed (Figure 5.4).

In fasted state the level of GLP-1 did not significantly differ before and after the NORMOXIA (pre: 2.1±0.1 pM; post: 2.4±0.2 pM) or HYPOXIA (pre: 1.9±0.1 pM; post 2.2±0.1 pM; $p=0.8$). Similarly, the postprandial levels of GLP-1 were not significantly different before and after NORMOXIA (pre: 3.2±0.2 pM; post: 3.2±0.2 pM) or HYPOXIA (pre: 3.4±0.3 pM; post: 3.3±0.1 pM).

No significant differences were observed in HOMA-IR before and after the NORMOXIA (pre: 0.7±0.1; post: 0.6±0.1) and HYPOXIA (pre: 0.5±0.1; post: 0.6±0.1).

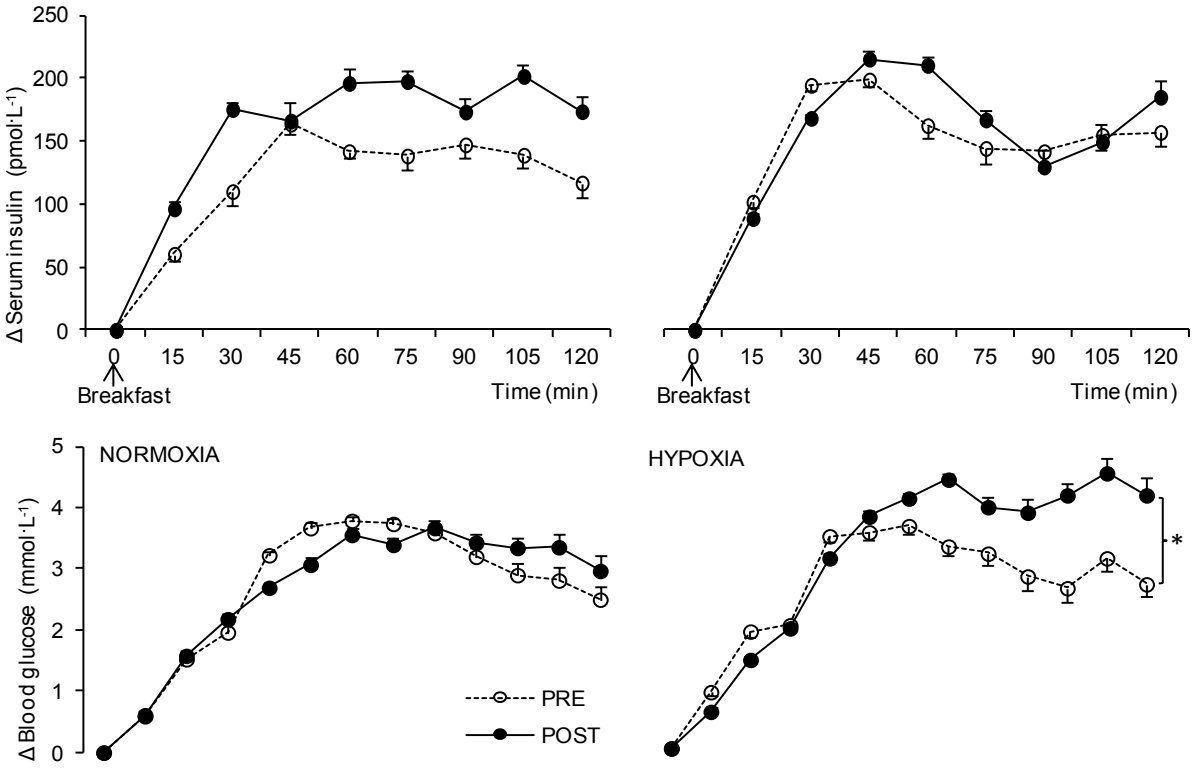

Figure 5.4*: Postprandial delta blood glucose and serum insulin before (PRE), and at the end (POST) of the 10-day normoxic (NORMOXIA) and hypoxic (HYPOXIA) confinements.* Values are mean±SEM, n=8. (*): Significant differences between PRE and POST confinement; $p<0.05$.

The hormone and metabolite concentrations before and after the NORMOXIA and HYPOXIA confinements in the fasted and postprandial states are presented in Table 2. Fasting PYY was significantly decreased both by the NORMOXIC and HYPOXIC confinement. In the fasted state, all other blood variables remained unaltered by the NORMOXIC as well as the HYPOXIC confinement. Moreover, there were no significant changes in postprandial adrenaline level, while noradrenaline levels increased ($p<0.001$) after the meal in both the NORMOXIC and HYPOXIC trials. Postprandial ghrelin levels decreased after the meal (Table 5.2, $p<0.001$), there was no difference between the NORMOXIA and HYPOXIA ($p=0.16$). PYY values (Table 5.3) were increased after the meal ($p<0.001$), with higher responses after the HYPOXIC confinement ($p=0.01$).

Table 5.4: *The hormone and metabolite concentrations in fasted state after the meal before (PRE) and at the end (POST) of the NORMOXIC and HYPOXIC trials.* Values are mean±SD. GLP-1: glucagon-like peptide-1, PYY: peptide YY_{3-36}. (#): Significant differences postprandially; (†): significant differences between NORMOXIA and HYPOXIA in the same state; (*): significant differences between pre and post in the same confinement ($p \leq 0.05$).

Hormone metabolic	NORMOXIA PRE		POST		HYPOXIA PRE		POST	
	Fasted state	Postprandial state	Fasted state	Postprandial state	Fasted state	Postprandial state	Fasted state	Postprandial state
Adrenaline ($nmol \cdot L^{-1}$)	0.18±0.01	0.11±0.01	0.17±0.01	0.10±0.01	0.14±0.01	0.11±0.01	0.11±0.01	0.09±0.01
Noradrenaline ($nmol \cdot L^{-1}$)	1.21±0.03	1.52±0.06#	1.26±0.08	1.43±0.07#	1.11±0.03	1.28±0.02#	1.28±0.06	1.54±0.05#
Ghrelin ($pg \cdot mL^{-1}$)	925.6±41.7	833.1±30.6#	945.8±46.0	826.5±34.8#	965.1±49.3	873.2±34.2#	940.0±27.1	840.4±22#
Leptin ($ng \cdot mL^{-1}$)	18.6±1.2	-	21.1±1.5	-	17.1±1.3	-	18.5±1.2	-
PYY ($pg \cdot mL^{-1}$)	105.9±5.0	136.1±4.5#	97.2±3.1*	129.9±3.2#	103.0±2.8	137.4±6.2#	91.9±2.2*	129.8±6.0#

5.2.6 Intestinal blood flow

The increments in diameter and blood flow (Figure 5.5) of the superior mesenteric artery in response to the MTT were similar before and after both the NORMOXIC and HYPOXIC confinements.

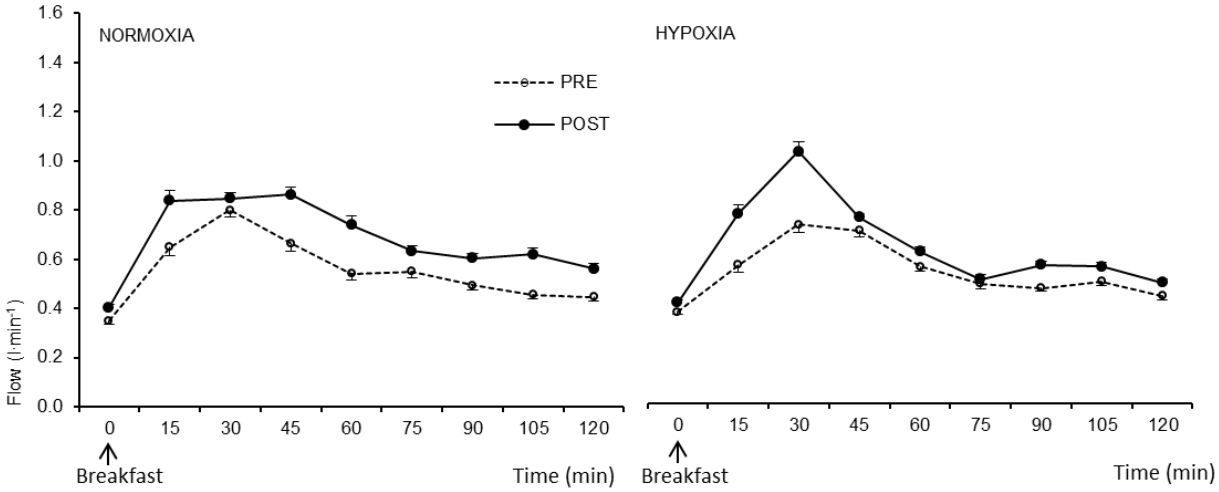

Figure 5.5**:** *Postprandial blood flow of the superior mesenteric artery before (PRE), and at the end (POST) of the 10-day normoxic (NORMOXIA) and hypoxic (HYPOXIA) confinements.* Values are mean±SD, n=8.

5.2.7 Subjective satiety evaluation

Moreover, there were no differences in subjective satiety, presented as composite satiety score (CSS), in the fasted state before compared to after NORMOXIC or HYPOXIC confinement. Similarly, there were no differences (p=0.51) postprandially in subjective satiety before compared to after the NORMOXIC or HYPOXIC confinement.

5.3 Discussion

The main observation of the present study is a significant loss in body mass in overweight individuals after a continuous 10-day normobaric hypoxic confinement, compared to an increase in body mass during a normoxic confinement of similar duration.

The present study confirms that hypoxia may lead to body weight reduction in the absence of these cofounders, predominantly due to an increase in resting energy expenditure (REE) and a loss of appetite.

5.3.1 High altitude anorexia

Our observation is in agreement with many field studies that have reported remarkable weight loss at altitudes higher than 4000 m (Pulfrey and Jones, 1996; Reynolds et al., 1999; Westerterp et al., 1992; Westerterp et al., 1994). In such field studies, it is difficult to exclude the contribution of cold, physical activity, food availability and palatability, commonly present at high altitude, from the effects of hypoxia *per se*.

In the present study, we investigated the responses to 10-days of continuous hypoxia. Gunga et al. 2003 investigated the effect of 3 wks at moderate altitude (1700 m) in male subjects with metabolic syndrome (age: 54 yrs; BMI: 30.3 $kg \cdot m^{-2}$; with hypertension, hyperlipidemia, diabetes mellitus and/or coronary heart disease). They reported a body weight decrease of 0.9 kg at day 19 at altitude, and a further reduction of 0.7 kg in body weight 6–7 wks after the altitude exposure. This weight loss was due to a reduction in body fat, whereas no change was observed in lean body mass. However, during the altitude exposure the subjects with metabolic syndrome were active, participating in activities such as mountain hiking between 1500–2500 m and swimming. In addition, in the study of Gunga et al. 2003 energy intake was analysed retrospectively from the questionnaires filled out by participants and from this an average total energy intake approximately 1900 $kcal \cdot day^{-1}$ was derived; whilst REE was not measured. This value of 1900 $kcal \cdot day^{-1}$ was likely a substantial underestimate, as the subjects weight of 92.9 kg would require at least 2222 $kcal \cdot day^{-1}$ to maintain body weight with a low level of physical activity *(1.2*; derived using the Harris-Benedict equation, revised by Roza and Shizgal, 1984), and substantially more if the level of physical activity was higher. Alternatively, if the estimate of a 1900 kcal·day energy intake correct, the body weight loss would be attributable to low energy intake rather than to any hypoxia-induced change in metabolism. Similarly, Lippl et al. 2010 observed body weight loss in obese individuals after 14 days at altitude. Therefore, and because there were no control group in those studies, it is not possible to conclude the extent to which the hypoxia *per se* or the physical activity contributed to the weight change.

Moreover, while there were some early indications of unchanged REE at altitude (Stickney and Van Liere, 1953; Chiodi 1957; Durnin and Brockway, 1959), many investigators have observed an elevated REE at altitude, most likely due to an increased activity-induced energy expenditure in climbing subjects (Kelloff et al., 1957; Picon-Reategui, 1961, Grover, 1963, Gill and Pugh, 1964; Hannon and Sudman, 1973; Klausen, 1966; Picon-Reategui, 1961; Butterfield et al., 1992; Pulfrey and Jones, 1996). In most field studies metabolic activity was measured before and after the expeditions either near to sea level, or from average daily metabolic activity determined from the activity level in the field, and the resting metabolic rate for climbers at altitude was assumed to be the same as at sea level (Westerterp et al., 1992, Westerterp et al., 1994). In concordance with previous studies, Lippl et al. 2010 concluded whatever the cause was, it seems clear that increases in REE lead to weight loss in obese individuals after 14 days at altitude.

However, high altitude anorexia was reported also in hypobaric laboratory studies

(Westerterp et al., 2000) and there are also indications of similar effects of normobaric hypoxia. Netzer et al. 2007 reported significant body weight loss after normobaric hypoxic training, but the mechanism of this weight loss remains unresolved. To our knowledge there are as yet no data regarding REE levels during normobaric hypoxic confinement in the absence of changes in environmental temperature, physical activity and diet. In the present study, the significantly higher metabolic needs (elevated REE values) after 10-day normobaric HYPOXIA in overweight individuals could be responsible for the observed body weight loss. Despite similar (but not identical) effects of hypobaric and normobaric hypoxic exposures (Richard and Koehle, 2012), the ventilatory response appears to be even more pronounced in normobaric hypoxia (Evetts et al., 2005). In part, the energy cost of such hyperpnea could explain the observed higher REE in HYPOXIA. Unfortunately, the clear cause of increases in REE under hypoxia remains the source of specific discussion. While in the present study there was no cold effects to upregulate thyroid function at altitude that was associated with the increased REE (Nair et al. 1971), the suggested role of sympathetic drive responsible for increased REE could not be fully excluded (Mawson et al., 2000).

Our observation is in agreement with studies reporting a 15 % to 26 % elevation of REE in patients with chronic obstructive pulmonary diseases (COPD; Vasconcelos et al., 2002; Sergi et al., 2006). Recently, Ramires et al. (2012) have suggested that the increased REE in COPD patients is due to hypermetabolism, greater respiratory muscle effort, higher O_2 requirements and inflammation. Increased carbohydrate requirements in COPD patients have also been reported, and attributed to increased anaerobic metabolism due to reduced ability to capture oxygen.

5.3.2 Insulin sensitivity

The endocrine factors that may have contributed to the observed changes in body weight remain unclear. Although improved short-term glycaemic control has been reported after acute hypoxia and after hypoxia combined with exercise (Mackenzie et al., 2011), we observed significantly increased glucose levels after the HYPOXIA trial. The mechanism could be a tendency for insulin resistance. Markedly reduced insulin sensitivity in healthy men and women at high altitude has been already attributed to the hypoxic stimulus (Braun et al., 2001; Larsen et al., 1997). In addition, similar responses have been observed in lean and obese mice by Reinke et al. (2011), who reported insulin resistance concomitant with significant increases in leptin, and severe systemic inflammation following two hypoxic regimens (intermittent and sustained hypoxia).

Moreover, the present subjects were overweight and adipose tissue is recognised as a source of pro-inflammatory cytokines that are linked to insulin resistance in muscle and liver (Guzik et al., 2006). There are some suggestions that this pro-inflammatory state is due, in part, to chronic hypoxia induced in the adipose tissue of obese individuals, giving rise to a cascade of biochemical events leading to the release of the proinflammatory/insulin resistance mediating cytokines (Trayhurn and Wood, 2004). Thus, it is possible that normobaric hypoxia may exacerbate this effect of the cytokines, which may lead to increased insulin resistance, but further research is needed to evaluate this.

5.3.3 Appetite hormones

Body weight reduction may be a result of an imbalance in the communication between the gastrointestinal tract and nervous system required for gut-brain signalling of the food intake control (Konturek et al., 2004). Moreover, disturbed body weight regulation at high

altitude can be caused by appetite change or altered requirements, or a combination of both. In the present study there were no significant changes in energy intake after the NORMOXIA trial, but a tendency towards decreased intake after the HYPOXIA trial.

Present observations are in agreement with those of Westerterpt et al. (1992, 1994) who reported a decreased body weight mainly due to decreased appetite and associated decrease of caloric intake at simulated high altitude (hypobaric hypoxia). It has been proposed that gut hormones may be a useful target for anti-obesity therapy (Murphy and Bloom, 2004; Cummings and Overduin, 2007). For example, PYY is thought to have a critical role in energy intake inhibition (Batterham et al., 2002). PYY is released into the circulation proportional to food intake within 1 hour post-feeding (Adrian et al., 1985). Recently, Wasse et al. (2012) investigated the acute effects of normobaric hypoxia on PYY and ghrelin (appetite stimulator). They reported suppressed energy intake after 7 hrs of normobaric hypoxia (F_IO_2=12.7, simulated altitude 4000 m) with suppressed acylated ghrelin concentrations and a tendency for increased PYY values during normoxic rest compared to hypoxic rest. Although we observed the anticipated decrease in ghrelin postprandially, there were no differences in its level and response between the 10-day NORMOXIA and HYPOXIA trials, thus not lending support to an exacerbated ghrelin-induced suppression of appetite during hypoxic exposure, as suggested by Wasse et al. (2012). Our finding of an increase in postprandial PYY after prolonged HYPOXIA concomitant with a reduction of spontaneous energy intake could support the notion of a potentially beneficial role of hypoxia in obesity prevention.

Leptin levels provide feedback regarding adipose tissue mass to central regions and regulate food intake. Although the observed levels of leptin in the subjects participating in the present study are in agreement with the higher levels normally observed in obese individuals (Rosicka et al., 2003) compared to non-obese, there were no significant changes in leptin levels as a consequence of either the NORMOXIC or HYPOXIC confinement.

5.3.4 Sustained intestinal blood flow

A supressed ghrelin level after 7 hrs of normobaric hypoxia has been associated with impaired gut blood flow at high altitude (Wasse et al., 2012). Namely, a decreased flow in the superior mesenteric artery after acute hypobaric hypoxia (2hrs, equivalent to 4800 m) compared with flow in normoxia was reported earlier by Loshbaugh et al. (2006). They hypothesised that, if reduction in blood flow was maintained during prolonged exposure, it might be responsible for reduced appetite and weight loss at altitude. In contrast, Kalson et al. (2010) reported decreased energy intake and increased resting blood flow in gastrointestinal tract during acute exposure to high altitude hypoxia (2 nights acclimatisation at 3300 m; measurements were made 24 hours after exposure to 4329 m).

Furthermore, in their study the increased mesenteric artery flow response following food ingestion was maintained. They concluded that reduced blood flow is unlikely to cause gastrointestinal responses (increase in gut hormones) and reduced appetite at high altitude. However, the proposed vascular mechanism of potential changes in acylated ghrelin or PYY (Wasse et al., 2012) during longer exposure to hypoxia was not clear.

Our observations of unchanged flow response in the mesenteric artery after 10-day HYPOXIA measured in hypoxic conditions supports the suggestion of Kalson et al. (2010) that impaired gut blood flow does not contribute to high altitude anorexia after several days. Further research is needed regarding neurohormonal and vascular satiety signalling, which in the present study did not reach significant differences, but may nevertheless contribute to reduced appetite.

5.3.5 Weight loss

The present study is in agreement with those suggesting that hypobaric hypoxia (Gunga et al., 2003; Lippl et al., 2010) and controlled normobaric hypoxia (Netzer, 2008, Wasse et al., 2012) might be incorporated in weight loss protocols.

Previous altitude studies have indicated that the decrease in weight is mainly attributable to a loss of fat (Armellini et al., 1997; Rose et al., 1988; Westerterp-Plantenga et al., 1999, Gunga et al., 2003). For example, Fusch et al. (1996) reported that 70 % of the weight loss after 2 months at high altitude (4900 m) was due to body fat loss. Similarly, Boyer et al. (1984) reported that 33 % of the weight loss after 10 days at 6000 m was due to loss of fat content. Ge et al. (2010) reported reduced waist circumference after a month at an altitude of 4638 m. In addition, the degree of weight loss positively correlated with the baseline body weight, suggesting that more body weight will be lost during a stay at high altitude, if the initial body weight is higher. In our study, the changes in body composition were too small to define whether body weight loss was due to loss of fat or lean body mass, or whether and to what extent dehydration contributed to the weight loss.

Similarly, the previously reported loss of body weight after normobaric hypoxic training in obese individuals (Netzer et al., 2008) was not defined as regards the share of the loss being contributed by fat, lean body and water. Specifically, Netzer et al. (2008) reported alterations in fat metabolism. Namely, triglycerides, low density lipoproteins (LDL), cholesterol tended to be reduced, while high density cholesterol (HDL) remained stable. However, as in our study (Table 2) none of these changes reached the level of statistical significance.

5.3.6 Summary

Normobaric hypoxic confinement (HYPOXIA) in the present study resulted in the significantly increased levels of REE, suggesting a potential value of hypoxia in achieving weight loss in obese individuals.

The observed tendency for decreased energy intake during hypoxia, combined with the enhancement of PYY secretion under hypoxic conditions, may be one of the potential mechanisms for the hypoxia induced body weight loss.

An optimal weight loss regimen should also involve physical activity to control glucose regulation, especially if it is compromised by hypoxia, but this needs further exploration.

6 Conclusions

The principal findings and conclusions of the study, based on the tests of the following null hypothesis (H_{01-6}), are :

- H_{01}: *Body weight and body composition.*
  We rejected the null hypothesis that prolonged hypoxic exposure has no effect on body weight reduction and changes in body composition. The observed significant body weight reduction demonstrates that HYPOXIA could potentially induce a loss in body mass, which may ultimately have a detrimental effect on performance for athletes, but may represent a potential therapeutic value of obese therapy.

- H_{02}: *Cardiovascular and haematological variables.*
  We accepted the null hypothesis that a 10-day hypoxic confinement has no effect on cardiovascular and haematological function. According to our observations none of the cardiovascular and haematological variables reached the level of statistical significance in the HYPOXIA trial.

- H_{03}: *Resting energy expenditure.*
  We rejected the null hypothesis that a 10-day hypoxic confinement has no effect on metabolic requirements. The observed significant increase in REE in normal weight individuals (Study I) could be partly explained with the observed increased minute ventilation in the HYPOXIA. Furthermore, significantly increased levels of REE in obese individuals, confirmed our previous observation in normal weight individuals. To conclude, the increased REE in both studies suggests a potential therapeutic value of hypoxia in achieving weight loss, particularly in obese individuals.

- H_{04}: *Appetite.*
  We rejected the null hypothesis that a 10-day hypoxic confinement has no effect on appetite. Significant appetite reduction was observed in normal weight individuals (Study I), while a tendency towards reduced appetite was observed in overweight individuals. To conclude, we suggest that athletes and alpinists conducting hypoxic training should be aware that hypoxia may lead to a negative energy balance as a consequence of increased REE and also reduced energy intake, and should monitor their energy intake to prevent such loss in mass, which may ultimately have a detrimental effect on performance.

- H_{05}: *Gastro-intestinal blood flow.*
  We accepted the null hypothesis that a 10-day hypoxic confinement has no effect on intestinal blood flow. To conclude, HYPOXIA did not affect the intestinal blood flow in normal weight individuals (Study I) or overweight individuals (Study II).

- H_{06}: *Postprandial hormonal metabolic.*
  We rejected the null hypothesis that a 10-day hypoxic confinement has no effect on the selected blood variables: glucose, insulin, noradrenaline, leptin, peptides – YY (PYY). The null hypothesis was accepted for the remainder of the metabolites (GLP-1, adrenaline and ghrelin). Together with the observed tendency for decreased energy intake during hypoxia, the increased leptin level (Study I) and enhancement of PYY secretion (Study II) after HYPOXIA may be one of the potential mechanisms for hypoxia induced weight loss. According to our results the sympathetic drive responsible for the observed body weight loss could not be fully excluded. Moreover, the observations of increased blood glucose level suggest the potential development of insulin resistance after HYPOXIA. To conclude, according to our observations, hypoxic stimulus in addition to diet and exercise can be an interesting approach to lose weight, which needs further investigations

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Keep Moving!

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Publications and Conference Presentations

Amon, M.; Keramidas, M. E.; Kounalakis, S. N.; Mekjavic, I. B. The effect of a sleep high-train low regimen on the finger cold-induced vasodilation response. *High Altitude Medicine and Biology* **13**, 32–39 (2012).

The Chapter 3–4 of this thesis represents individual research papers that have been submitted in peer-review journals for publication. The papers are listed below:

Amon, M.; Kölegård, R.; Kounalakis, S. N.; Simpson, L.; Eiken, O.; Macdonald, I.; Mekjavic, I. B. The effect of normobaric hypoxic confinement on metabolism. *High Altitude Medicine and Biology* (*in the process*).

Amon, M.; Kölegård, R.; Kounalakis, S. N.; Simpson, L.; Eiken, O.; Macdonald, I.; Mekjavic, I. B. Hypoxic confinement: A potential weight reduction strategy? *Obesity* (*in the process*).

Some of the aforementioned papers have been also presented at international conferences that are listed below:

Amon, M.; Kölegård, R.; Kounalakis, S. N.; Simpson, L.; Eiken, O.; Macdonald, I.; Mekjavic, I. B. The effect of normobaric hypoxic confinement on metabolism. In *Proceedings of the 12th European Life Sciences Symposium*: *33rd Annual International Gravitational Phsiology Meeting.* 47–48 (Aberdeen, 2012).

Amon, M.; Kölegård, R.; Kounalakis, S. N.; Simpson, L.; Eiken, O.; Macdonald, I.; Mekjavic, I. B. Effect of hypoxia on postprandial blood glucose and insulin response. In *Proceedings of the XIV International Conference on Environmental Ergonomics.* 71 (Paschalidis Medical Publisher, Nafplio, Greece 2011).

Amon, M.; Keramidas, M. E.; Debevec, T.; Kounalakis, S. N.; Mekjavic, I. B. The effect of hypoxic training regimens on pulmonary function. In: *Proceedings of 14th Annual Congress of the European College of Sport Science.* 613 (LOLAND Sigmund, Oslo, 2009).

Amon, M.; Debevec, T.; Keramidas, M. E.; Pišot, R.; Šimunič, B.; Kounalakis, S. N.; Mekjavic, I. B. Effect of intermittent normobaric hypoxic exposure on performance in hypoxic and normoxic environments. In: *Proceedings of the 13th Annual Congress of the European College of Sport Science.* 208 (Universidade Técnica de Lisboa, CABRI, Estoril, 2008).

Other publications during my PhD that I was co-author:

Mekjavic, I. B.; Debevec, T.; Amon, M.; Keramidas, M. E.; Kounalakis, S. N. Intermittent normobaric hypoxic exposures at rest: effects on performance in normoxia and hypoxia. *Aviation space and environmental medicine* **83**, 942–950 (2012).

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Keramidas, M. E.; Debevec, T.; Amon, M.; Kounalakis, S. N.; Šimunič, B.; Mekjavic, I. B. Respiratory muscle endurance training: the effect on normoxic and hypoxic exercise performance. *European Journal of Applied Physiology* **108**, 759–769 (2010).

Appendix A

KOMISIJA REPUBLIKE SLOVENIJE ZA MEDICINSKO ETIKO

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Datum: 17. 10. 2009

Spoštovani gospod prof. Mekjavic,

Komisiji za medicinsko etiko (KME) ste 17. 8. 2009[1] poslali prošnjo za oceno načrta raziskave z naslovom:

"Srčnožilne in metabolne adaptacije na hipoksijo." "Continuous exposure to hypoxia: cardiorespiratory and metabolic adaptations."

KME je ocenila, da je raziskava etično sprejemljiva, in Vam izdaja svoje soglasje.

S spoštovanjem in lepimi pozdravi,

prof. dr. Jože Trontelj
predsednik Komisije za medicinsko etiko

[1] Opravičujemo se za pozen odgovor.

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Appendix B

The metabolic responses of the all the participants obtained before and after (PRE, POST) the controlled 10-day normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA) of Study I and Study II are in the following Appendix.

Study I. Descriptive characteristics (body mass, body mass index, body fat) of the present study participants before and after (PRE, POST) the 10-day normobaric normoxic confinemnet (NORMOXIA) and the 10-day normobaric hypoxic confinemnet (HYPOXIA).

Condition	NORMOXIA					
	PRE			POST		
Subject/variable	Body mass (kg)	BMI ($kg \cdot m^{-2}$)	Body fat (%)	Body mass (kg)	BMI ($kg \cdot m^{-2}$)	Body fat (%)
S1	76.20	23.78	15.90	77.30	24.13	16.20
S2	69.50	20.75	9.60	68.40	20.42	10.60
S3	66.90	24.87	16.20	65.40	24.32	18.60
S4	86.70	25.61	28.20	82.80	24.46	29.10
S5	76.00	22.45	9.30	74.30	21.95	9.50
S6	86.40	25.11	18.80	85.10	24.73	19.50
S7	68.40	17.45	8.10	65.40	15.41	8.20
S8	66.70	21.05	13.10	68.50	21.62	13.30
S9	73.20	21.39	9.30	72.80	21.27	9.50
S10	69.60	21.24	15.40	71.70	21.89	14.30
S11	63.80	21.82	16.20	64.70	22.13	16.60
Mean	73.04	22.32	14.55	72.40	22.03	15.04
SEM	0.70	0.22	0.53	0.63	0.24	0.55
Condition	HYPOXIA					
	PRE			POST		
Subject/variable	Body mass (kg)	BMI ($kg \cdot m^{-2}$)	Body fat (%)	Body mass (kg)	BMI ($kg \cdot m^{-2}$)	Body fat (%)
S1	76.30	23.81	16.90	75.50	23.56	16.90
S2	68.90	20.57	10.10	67.50	20.16	10.40
S3	65.90	24.50	16.60	63.80	23.72	15.20
S4	83.60	24.69	28.40	80.50	23.78	27.30
S5	74.90	22.12	10.00	74.40	21.98	9.40
S6	77.90	22.64	19.60	82.80	24.06	18.70
S7	71.70	18.29	7.30	68.80	17.55	8.00
S8	68.90	21.75	11.40	66.30	20.93	12.70
S9	74.40	21.74	8.80	70.90	20.72	10.50
S10	69.40	21.18	14.10	69.90	21.34	13.70
S11	63.00	21.55	17.00	64.80	22.16	18.10
Mean	72.26	22.08	14.56	71.38	21.81	14.63
SEM	0.53	0.17	0.55	0.57	0.18	0.50

Study I. Resting energy expenditure (REE) before and after (PRE, POST) the 10-day normobaric normoxic confinemnet (NORMOXIA) and the 10-day normobaric hypoxic confinemnet (HYPOXIA).

REE			NORMOXIA PRE		
(kcal·day^{-1})	Fasted state	Postprandially			
Subject/Time (min)	0	15 - 30	45 - 60	75 - 90	105 - 120
S1	1939.4	1936.2	2014.9	1909.7	1953.0
S2	1536.0	1629.1	2092.6	1900.2	1872.0
S3	1228.0	1132.2	783.9	899.6	1111.1
S4	2236.3	1324.5	2046.7	2210.9	2080.9
S5	1227.6	1890.9	2474.5	2540.9	1766.1
S6	1694.9	2302.4	2438.5	2302.7	2260.3
S7	1843.3	2228.6	2438.9	2465.0	2251.1
S8	1741.3	2015.1	2066.4	2084.3	2003.3
S9	1851.8	1983.5	2178.6	2213.3	2225.0
S10	1936.9	2076.8	2425.6	2157.8	2104.4
S11	1245.6	1894.4	1803.1	1948.5	1961.7
Mean	1680.1	1855.8	2069.4	2057.5	1962.6
SEM	30.4	32.7	43.6	39.8	29.4
REE			NORMOXIA POST		
(kcal·day^{-1})	Fasted state	Postprandially			
Subject/Time (min)	0	15 - 30	45 - 60	75 - 90	105 - 120
S1	2429.5	2345.2	2605.7	2149.3	2166.8
S2	2136.4	2066.0	2358.1	1976.1	2222.7
S3	875.5	1723.0	1313.3	1710.9	1773.2
S4	1768.8	1850.0	2047.6	2144.1	2173.8
S5	1696.8	1814.7	2013.1	2286.9	2109.7
S6	1873.9	2228.9	2391.0	2485.8	2530.2
S7	1855.0	2036.7	2161.7	2254.6	2383.4
S8	1791.7	2191.5	2283.9	2178.5	2194.3
S9	1973.5	2181.0	2322.7	2360.3	2309.9
S10	1970.5	2166.4	2376.9	2273.1	2407.0
S11	1379.8	1681.7	1589.7	1802.9	1765.0
Mean	1795.6	2025.9	2133.1	2147.5	2185.1
SEM	36.59	20.37	34.60	21.24	21.84
REE			HYPOXIA PRE		
(kcal·day^{-1})	Fasted state	Postprandially			
Subject/Time (min)	0	15 - 30	45 - 60	75 - 90	105 - 120
S1	1236.7	1981.6	1965.2	1983.2	1903.6
S2	1738.2	2117.8	2240.6	2083.7	2137.8
S3	1494.2	1808.5	1680.8	1941.9	1865.4
S4	1713.9	1965.6	2122.6	1905.8	1956.2
S5	2258.9	1391.9	1717.7	2560.4	2252.3
S6	1656.1	1818.3	2263.5	2234.2	2317.9
S7	2023.1	2216.1	2400.8	2496.9	2256.3
S8	1811.9	2098.3	2202.9	2140.9	2024.0
S9	1947.8	2135.8	2147.8	2365.5	2271.1
S10	1755.4	2198.3	2309.1	2125.9	2340.6
S11	1669.4	1735.4	1867.2	2015.8	1796.7
Mean	1755.0	1951.6	2083.5	2168.6	2102.0
SEM	24.43	22.51	21.99	20.17	18.08
REE			HYPOXIA POST		
(kcal·day^{-1})	Fasted state	Postprandially			
Subject/Time (min)	0	15 - 30	45 - 60	75 - 90	105 - 120
S1	2004.7	3394.6	2361.5	2704.3	2523.4
S2	2136.4	2770.0	2977.7	2698.9	2767.0
S3	2320.5	2553.4	2637.6	3204.3	3442.0
S4	2888.8	3487.6	3032.2	2758.3	2706.6
S5	2764.7	1987.4	2975.8	3441.2	2234.1
S6	2546.9	2931.1	2792.9	2912.6	2847.3
S7	2860.6	3017.5	2666.9	2728.5	2501.7
S8	2266.5	2903.3	2919.9	2757.3	2606.1
S9	2651.7	2934.5	3375.7	3537.7	2745.2
S10	2676.6	3214.8	2658.5	3242.9	2956.0
S11	2674.9	2634.6	2830.1	2960.6	2902.6
Mean	2526.6	2893.5	2839.0	2995.1	2748.4
SEM	27.19	37.97	24.10	28.21	28.11

Study I. Resting minute ventilation ($\dot{V}$E) measured in sitting position before and after (PRE, POST) the 10-day normobaric normoxic confinemnet (NORMOXIA) and the 10-day normobaric hypoxic confinemnet (HYPOXIA).

$\dot{V}$E				
Subject/Condition	NORMOXIA PRE	NORMOXIA POST	HYPOXIA PRE	HYPOXIA POST
S1	14.9	13.4	13.3	15.0
S2	13.7	13.3	12.7	16.3
S3	16.1	18.8	18.4	20.2
S4	16.3	16.3	16.8	18.2
S5	14.4	16.4	13.7	15.9
S6	14.4	12.8	14.4	16.4
S7	16.2	15.3	15.8	18.3
S8	15.4	13.7	16.3	14.0
Mean	15.2	15.0	15.2	16.8
SEM	0.1	0.3	0.2	0.3

Study I. Noctural arterial oxygen saturation (SpO_2, %) during the 10-day normobaric normoxic confinemnet (NORMOXIA) and during the 10-day normobaric hypoxic confinemnet (HYPOXIA).

SpO_2 (%)	NORMOXIA									
Subject/Day	1	2	3	4	5	6	7	8	9	10
S1	97.6	98.3	98.4	98	99	98.7	98.4	98.6	98.1	98.8
S2	97.9	98.7	97.5	98.6	97.7	98.9	94.9	96.8	98	98
S3	96.3	97.7	96.9	98.7	93.8	96.6	95.9	97.6	97.8	96
S4	95.7	94.2	94.7	96.8	94.9	97.6	97	97	96.6	96.8
S5	94.9	92.2	93.3	93.6	95.2	96	97	97.7	96.1	96.5
S6	95.2	96.1	94	94.2	93	96.6	95.7	96.7	96.7	97
S7	97.4	98.7	99	97	98	99	99.4	99.4	97.9	98
S8	98	98.7	97.9	98	98.5	98.8	98.8	97.8	96.9	98.8
S9	93	92.5	94	98	98.8	98	97.9	98	96.6	95
S10	98.7	98.4	98	98	97.8	98.5	97.4	99	97.4	97.7
S11	98.8	98.4	98.6	98	98	99	98	97.9	98.8	98
Mean	96.7	96.7	96.6	97.2	96.8	98.0	97.3	97.9	97.4	97.3
SEM	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1
SpO_2 (%)	HYPOXIA									
Subject/Day	1	2	3	4	5	6	7	8	9	10
S1	86.6	85	87	88	90	89.6	89	89.5	90.7	90.5
S2	80.8	84.2	83.5	85	83.6	88.5	89.6	89.9	90.3	87.3
S3	96.5	82	81.6	83	86.9	88.3	88	86.4	86.7	89
S4	79.4	81.6	83.1	85	87.2	87.8	88.9	88.7	86.9	88
S5	85.8	85.8	86.3	88.2	87	92.1	87.8	86	84.7	85.2
S6	90.4	83	80.1	83	86.9	86	88.1	87.5	87.3	88.8
S7	81.1	85.8	87.2	88.3	89	86	87.8	88.5	91	90.6
S8	85.6	87.4	90	89.5	89.6	90.7	91.6	90.2	90	91.2
S9	83.8	87.8	90.4	89.1	89.8	90.4	93.2	90.8	93.8	92
S10	88.3	85.1	87.5	87.5	88.2	88.1	90	91	90	91
S11	88.1	90.3	90.3	89	90.2	92.3	89.9	88.7	90.2	91
Mean	86.0	85.3	86.1	86.9	88.0	89.1	89.4	88.8	89.2	89.5
SEM	0.4	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Study I. Noctural heart rate (HR) during the 10-day normobaric normoxic confinement (NORMOXIA) and during the 10-day normobaric hypoxic confinement (HYPOXIA).

HR (min^{-1})	NORMOXIA									
Subject/Day	1	2	3	4	5	6	7	8	9	10
S1	59.8	65	61	63.1	60.9	57.3	58.9	57.9	60	56.3
S2	60.9	65.4	63.3	62.3	60.2	63.9	60.7	64.4	65.6	63.9
S3	48.5	56.3	54.3	55	54	57	56.4	59.4	55.6	55.6
S4	75.6	82.8	73.5	70	68	67.3	67.4	65.3	64.5	66
S5	52.9	54	53	55	54	55	55.2	53.3	54	54
S6	64.4	65	67	63	61.2	60.2	59.3	57.2	55.9	59.3
S7	58	57	57.5	55	59.4	55	56.8	54.5	55	53.4
S8	60	60	65	60	58	57	58.3	55.9	60	57
S9	58	57.9	63	59	58.8	56	60.1	55.9	57.9	58
S10	60.7	61	59.9	65	63	63.8	62.1	59.7	60	61
S11	70	66	63.4	62.1	62.4	62.9	61	60	64	63.8
Mean	60.8	62.8	61.9	60.9	60.0	59.6	59.7	58.5	59.3	58.9
SEM	0.7	0.7	0.5	0.4	0.4	0.4	0.3	0.3	0.4	0.4
HR (min^{-1})	HYPOXIA									
Subject/Day	1	2	3	4	5	6	7	8	9	10
S1	63.6	63.5	65	64	67.2	59.8	60	63	68.9	57.3
S2	74.2	68.9	65	66	68.8	64	68.4	70	70	63.7
S3	54.8	57.2	54.4	56	58.7	55.2	60	63	59.1	63
S4	81.8	77	72.3	75	73	77.8	76	83.8	72.6	75.5
S5	62.4	61.4	62	61,3	68.1	76.3	69.6	68.8	70	64.7
S6	68.1	67	65.1	68	62.4	65	71.4	54.9	65.8	61.8
S7	63.7	57.4	53.5	55.4	59	55	52.1	56.2	96	90
S8	65.6	66.3	54.8	53.8	54.6	55.8	56	53.7	55	56.6
S9	68.6	67.5	65.6	68.6	66.4	68.4	66.3	69.4	65.7	64.3
S10	64.1	69	64	64.1	62.9	68.2	65.4	62.1	63.8	65
S11	68.2	69.1	50.6	57.6	58	57.6	60	62.3	61.5	63.2
Mean	66.8	65.8	61.1	62.9	63.6	63.9	64.1	64.3	68.0	65.9
SEM	0.6	0.5	0.6	0.6	0.5	0.7	0.6	0.8	1.0	0.9

Study I. Blood glucose in fasted state and postprandially during the meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Glucose (mmol·L^{-1})	NORMOXIA PRE												
Condition	Fasted state	Postprandially											
Subject/Time (min)	0	10	15	20	30	40	45	50	60	75	90	105	120
S1	5.40	5.40	6.40	6.80	8.20	8.00	7.60	7.10	6.50	6.40	6.60	6.40	6.40
S2	4.60	5.20	6.40	6.40	5.40	4.60	4.70	4.90	4.80	3.80	4.50	5.20	4.80
S3	4.85	6.00	7.10	7.60	7.00	5.90	5.40	5.40	5.70	5.90	5.00	4.70	4.70
S4	4.35	5.80	6.40	7.20	8.70	8.70	8.60	8.70	9.00	8.70	8.80	8.80	7.90
S5	5.25	5.30	6.40	7.50	8.90	9.30	9.10	8.80	8.10	5.50	7.00	6.20	4.20
S6	5.00	5.00	7.30	8.10	9.10	8.40	8.40	8.00	6.90	5.50	6.10	5.40	7.30
S7	4.90	5.70	6.30	6.50	7.20	5.40	5.10	5.30	6.20	6.30	6.30	5.20	4.70
S8	4.30	5.10	6.50	6.90	6.70	5.60	5.30	5.00	4.30	3.90	4.60	5.60	5.40
S9	5.45	5.50	6.50	6.50	6.00	5.80	6.70	7.10	7.30	6.20	5.60	4.10	4.70
S10	5.05	5.30	6.80	6.80	8.10	7.60	7.90	8.20	5.60	6.90	6.90	5.30	6.40
S11	4.15	5.10	6.30	6.70	7.00	5.90	5.40	5.70	4.80	4.90	5.80	5.50	4.50
Mean	4.85	5.40	6.58	7.00	7.48	6.84	6.75	6.75	6.29	5.82	6.11	5.67	5.55
SD	0.04	0.03	0.03	0.05	0.11	0.14	0.15	0.14	0.13	0.13	0.11	0.11	0.11
Glucose (mmol·L^{-1})	NORMOXIA POST												
Condition	Fasted state	Postprandially											
Subject/Time (min)	0	10	15	20	30	40	45	50	60	75	90	105	120
S1	4.90	5.70	6.30	7.00	8.20	8.00	8.70	8.20	7.50	5.80	5.40	5.50	5.90
S2	4.60	4.90	5.70	5.90	7.20	5.50	5.30	5.20	4.90	4.00	4.50	4.60	5.30
S3	4.80	6.10	7.50	8.10	7.70	6.10	5.20	5.00	5.40	6.00	5.30	5.80	6.00
S4	5.00	5.20	6.90	7.30	8.70	8.90	8.80	8.40	8.90	9.10	9.70	10.20	9.70
S5	5.75	6.90	7.60	7.40	8.20	8.50	8.50	8.30	8.50	7.50	7.00	7.00	7.90
S6	4.20	5.10	6.10	7.00	8.50	8.10	8.30	7.90	7.00	5.60	5.10	5.00	6.20
S7	5.80	6.40	7.00	7.50	7.70	6.90	6.60	6.10	5.50	5.70	6.50	6.70	5.20
S8	4.35	5.40	6.50	6.90	7.60	6.60	6.00	6.10	5.50	5.40	4.60	4.70	4.50
S9	5.25	4.90	5.90	6.20	7.40	8.10	7.70	8.30	8.10	8.00	7.00	6.50	6.30
S10	4.10	4.90	6.10	7.00	7.50	7.40	7.30	7.70	7.30	7.50	7.90	7.60	7.70
S11	4.05	4.40	5.40	5.80	6.70	6.50	6.00	5.80	5.10	5.10	6.20	6.30	6.10
Mean	4.80	5.45	6.45	6.92	7.76	7.33	7.13	7.00	6.70	6.34	6.29	6.35	6.44
SEM	0.06	0.07	0.07	0.06	0.05	0.10	0.12	0.12	0.13	0.14	0.14	0.15	0.13

Glucose (mmol·L^{-1})													
Condition	HYPOXIA PRE												
	Fasted state	Postprandially											
Subject/Time (min)	0	10	15	20	30	40	45	50	60	75	90	105	120
S1	5.40	5.40	6.00	6.20	8.40	7.90	7.30	6.80	6.60	5.40	5.20	5.80	5.80
S2	4.55	5.00	6.00	7.20	6.60	5.10	4.60	4.50	4.30	4.50	4.50	5.00	5.40
S3	4.90	6.50	8.10	7.60	5.60	4.30	4.40	4.80	5.80	6.10	5.30	5.40	5.10
S4	4.25	4.50	5.20	5.90	7.80	8.40	8.70	8.30	7.60	7.50	6.20	6.30	6.30
S5	6.40	6.70	8.00	8.60	9.50	8.60	7.40	6.60	6.10	5.30	5.80	5.70	3.80
S6	4.95	5.40	6.50	7.50	7.70	7.50	7.00	6.80	6.50	5.90	5.40	5.10	5.20
S7	4.55	5.10	5.50	6.40	7.50	6.40	5.90	5.60	5.30	5.90	6.20	5.00	6.00
S8	3.95	4.50	5.70	6.60	6.20	4.40	4.30	4.10	3.60	3.80	3.90	4.10	4.00
S9	4.55	5.00	6.70	7.00	8.30	8.70	9.40	9.50	9.80	8.70	8.10	6.10	6.30
S10	4.95	6.40	6.90	7.40	7.70	7.70	8.40	8.10	7.40	6.90	7.30	6.90	7.00
S11	4.45	5.00	6.40	6.50	6.70	5.30	5.40	5.70	6.00	5.30	5.00	4.20	4.50
Mean	4.81	5.41	6.45	6.99	7.45	6.75	6.62	6.44	6.27	5.94	5.72	5.42	5.40
SEM	0.06	0.07	0.09	0.07	0.10	0.16	0.16	0.15	0.15	0.12	0.11	0.08	0.09
Glucose (mmol·L^{-1})													
Condition	HYPOXIA POST												
	Fasted state	Postprandially											
Subject/Time (min)	0	10	15	20	30	40	45	50	60	75	90	105	120
S1	4.45	4.60	5.50	5.90	7.20	7.70	8.40	8.20	8.60	8.40	7.50	6.90	6.50
S2	4.05	5.10	5.60	6.20	6.30	5.50	5.30	4.60	4.70	5.70	5.20	5.60	4.90
S3	4.40	6.10	7.30	7.40	6.90	4.50	4.70	5.50	5.20	6.00	5.40	5.50	5.80
S4	4.65	5.80	7.10	7.80	9.00	9.10	9.20	8.60	8.50	7.60	8.00	8.10	7.70
S5	5.45	6.00	7.50	8.40	9.70	10.00	10.20	9.90	9.30	8.90	8.30	7.80	6.10
S6	4.75	4.70	5.00	5.50	7.40	7.80	7.80	8.30	7.60	6.30	5.60	6.10	6.00
S7	4.35	5.00	6.60	7.10	8.40	7.30	6.70	6.30	5.30	6.00	5.70	5.80	5.60
S8	4.10	5.10	6.60	7.00	8.40	7.80	7.50	6.90	6.50	6.50	5.50	5.00	5.40
S9	4.40	5.50	6.40	7.10	7.80	8.30	8.20	8.00	7.60	6.80	6.30	5.20	5.80
S10	4.40	5.60	6.60	7.00	8.10	7.60	7.30	7.30	6.80	6.60	6.80	6.80	5.90
S11	3.65	3.90	5.00	5.40	5.60	5.00	4.80	4.40	4.40	4.00	5.10	5.40	5.10
Mean	4.42	5.22	6.29	6.80	7.71	7.33	7.28	7.09	6.77	6.62	6.31	6.20	5.89
SEM	0.04	0.06	0.08	0.09	0.11	0.15	0.16	0.16	0.15	0.12	0.11	0.10	0.07

Study I. Serum insulin in fasted state and postprandially during the meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Insulin (mmol·L^{-1})	NORMOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1.64	21.56	49.96	56.50	28.38	29.07	20.26	16.21	18.07
S2	1.01	61.52	40.19	10.00	11.61	4.95	5.10	19.30	2.56
S3	1.67	45.97	37.67	19.26	15.74	42.84	13.11	24.27	8.06
S5	0.81	9.01	24.78	36.57	37.39	31.81	19.64	14.46	5.27
S7	2.68	17.22	43.70	10.01	21.21	21.66	14.49	11.12	4.41
S8	2.57	47.14	57.67	34.81	9.04	7.48	4.76	14.00	8.92
S9	3.13	25.72	15.85	39.10	56.46	25.77	22.72	9.51	5.89
S10	4.14	31.20	86.55	98.95	54.43	47.66	47.07	37.59	53.54
S11	3.14	40.95	68.69	63.53	27.89	21.38	36.99	36.24	15.78
Mean	2.3	33.4	47.2	41.0	29.1	25.8	20.5	20.3	13.6
SEM	0.1	1.4	2.1	2.8	2.2	1.9	2.3	1.6	2.1
Insulin (mmol·L^{-1})	NORMOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	3.73	24.87	76.88	104.43	68.41	43.86	28.59	31.89	36.83
S2	3.86	54.04	154.83	57.91	44.76	17.87	18.17	11.71	36.44
S3	1.15	67.90	50.62	22.73	17.14	21.26	13.95	26.40	12.72
S5	3.10	34.89	42.43	47.67	65.90	50.08	33.52	35.12	31.83
S7	4.61	44.43	59.20	75.38	22.58	33.20	37.39	40.26	13.40
S8	4.61	96.68	116.35	52.19	37.51	33.82	11.17	29.77	9.17
S9	4.42	21.35	50.02	71.61	58.16	69.53	57.97	49.38	36.68
S10	4.72	40.40	96.51	71.36	85.04	74.39	75.23	70.57	83.16
S11	3.48	42.81	102.77	67.75	45.98	62.02	64.83	62.50	51.88
Mean	3.7	47.5	83.3	63.4	49.5	45.1	37.9	39.7	34.7
SEM	0.1	2.0	3.4	2.5	2.4	3.4	3.5	4.3	3.4

Insulin (mmol·L^{-1})	HYPOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1.25	11.26	58.05	57.54	40.55	14.89	8.25	13.34	5.34
S2	1.47	50.97	93.61	41.36	8.29	6.34	3.18	2.70	4.76
S3	0.51	85.40	23.49	8.79	16.76	23.70	7.00	10.83	6.72
S5	1.95	17.08	31.29	36.29	22.03	15.45	19.39	8.82	4.96
S7	3.72	14.33	60.13	30.84	17.03	15.47	29.19	8.46	16.63
S8	3.85	60.29	47.62	29.26	8.56	8.22	5.11	5.89	3.46
S9	3.11	22.87	51.58	72.98	98.83	104.64	87.73	47.02	36.22
S10	2.16	38.94	42.52	68.66	35.54	38.68	41.96	33.83	38.30
S11	3.03	31.03	62.38	88.14	82.23	67.21	32.51	25.19	12.21
Mean	2.3	36.9	52.3	48.2	36.6	32.7	26.0	17.3	14.3
SEM	0.1	2.1	2.0	2.4	2.9	3.2	2.7	1.5	1.4

Insulin (mmol·L^{-1})	HYPOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1.4	13.3	60.1	75.4	79.8	82.0	51.1	35.2	25.9
S2	0.8	50.4	86.9	48.5	34.6	54.9	24.6	64.9	11.9
S3	1.0	58.9	50.1	22.7	13.7	28.8	17.5	22.4	20.7
S5	1.7	28.0	41.1	56.4	48.6	35.4	31.3	40.1	19.5
S6	3.3	10.3	147.6	201.2	162.2	68.5	37.7	67.9	49.5
S7	3.6	50.6	104.6	57.9	26.1	35.1	27.1	32.7	20.5
S8	2.8	59.8	116.5	70.5	34.4	46.7	18.2	17.2	16.6
S9	4.1	71.9	114.7	94.9	79.1	67.5	54.5	67.8	41.1
S10	2.7	40.2	65.2	86.4	93.8	73.8	83.6	29.9	25.9
S11	1.7	67.5	78.0	75.1	28.0	26.4	54.3	56.3	38.1
Mean	2.3	45.1	86.5	78.9	60.0	51.9	40.0	43.4	27.0
SEM	0.2	2.1	3.7	4.4	4.6	2.8	3.2	3.2	3.4

Study I. GLP-1 level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

GLP-1 (pM)	NORMOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1.18	2.02	1.24	1.38	0.84	1.59	1.50	1.49	1.57
S2	1.01	2.65	1.10	0.96	1.52	1.76	2.16	3.36	1.90
S3	1.54	2.52	2.81	1.46	1.68	2.19	1.46	3.19	2.09
S4	0.80	0.98	1.32	1.03	0.72	0.80	0.04	1.17	0.87
S5	3.03	0.99	5.35	4.78	4.92	4.14	2.96	4.31	4.59
S6	0.66	1.06	1.23	1.37	0.73	1.29	0.73	1.17	1.03
S7	1.21	1.23	1.20	1.20	1.27	1.41	1.24	1.40	1.15
S8	1.14	2.66	2.50	3.63	2.12	2.89	2.86	2.66	2.43
S9	4.42	9.36	5.52	5.48	6.93	5.37	7.72	6.78	5.26
S10	0.05	1.17	1.54	1.68	0.49	0.09	0.28	1.02	1.33
S11	3.07	5.55	3.97	4.96	3.55	4.21	5.25	4.96	4.36
Mean	1.6	2.7	2.5	2.5	2.3	2.3	2.4	2.9	2.4
SEM	0.1	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.1
GLP-1 (pM)	NORMOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.95	1.87	1.49	1.22	0.72	1.53	1.19	2.21	1.77
S2	1.02	2.72	1.59	0.82	1.12	1.91	1.69	1.77	1.93
S3	1.73	4.07	2.04	1.93	1.33	2.15	1.93	2.06	1.64
S4	0.89	1.32	1.68	1.13	1.62	1.51	1.10	1.25	1.09
S5	3.39	6.20	4.31	3.32	0.64	2.98	2.45	3.81	1.59
S6	0.37	1.08	3.37	2.97	1.08	0.64	0.54	1.07	0.76
S7	1.42	1.58	1.46	1.53	1.39	1.49	1.22	1.33	1.34
S8	2.05	4.82	3.18	2.92	2.53	3.48	3.21	3.01	3.68
S9	4.87	6.51	6.52	6.35	5.64	6.21	5.89	5.34	6.27
S10	0.83	3.90	3.27	2.53	1.89	2.04	1.43	1.86	0.92
S11	3.63	4.93	4.90	3.73	3.87	4.29	3.61	4.43	4.81
Mean	1.9	3.5	3.1	2.6	2.0	2.6	2.2	2.6	2.3
SEM	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.2

GLP-1 (pM)	HYPOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.57	1.58	2.19	1.83	1.18	1.51	0.90	2.03	1.99
S2	0.67	3.48	1.43	0.74	1.24	2.28	1.52	1.51	1.47
S3	1.77	7.92	3.30	3.07	2.09	2.00	2.39	2.43	1.40
S4	0.66	0.79	1.44	0.54	0.72	1.09	0.99	0.69	0.13
S5	1.51	3.84	2.35	2.84	2.17	2.22	1.21	0.94	1.74
S6	0.45	1.88	2.70	0.40	0.12	0.28	0.70	0.52	0.49
S7	1.15	1.27	1.24	1.15	1.21	1.26	1.21	1.21	1.17
S8	2.17	2.93	2.18	1.91	1.91	3.03	2.54	3.56	3.28
S9	4.61	5.46	5.38	5.88	5.08	4.81	6.90	5.71	5.05
S10	0.21	1.43	1.26	0.99	0.43	0.45	0.01	1.05	0.53
S11	0.33	2.29	1.02	1.39	0.93	1.58	1.79	1.79	0.69
Mean	1.3	3.0	2.2	1.9	1.6	1.9	1.8	1.9	1.6
SEM	0.1	0.2	0.1	0.1	0.1	0.1	0.2	0.1	0.1

GLP-1 (pM)	HYPOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1.1	1.8	1.8	1.9	1.3	1.3	1.5	1.5	2.2
S2	1.1	4.5	2.8	1.9	1.6	1.6	0.8	1.6	1.5
S3	1.7	4.1	2.1	2.1	1.7	2.0	2.2	2.0	2.1
S4	1.0	1.2	2.4	1.7	1.5	1.2	0.7	1.3	1.1
S5	2.3	4.1	4.7	4.1	2.5	2.9	2.7	3.6	4.6
S6	0.7	0.3	0.6	0.3	0.2	0.0	0.3	0.5	0.5
S7	1.1	1.6	1.3	1.2	1.5	1.4	1.2	1.3	1.2
S8	1.7	2.6	3.4	1.9	1.8	2.9	2.7	2.5	2.4
S9	0.2	3.6	2.6	2.2	1.1	1.5	0.8	1.1	1.0
S10	6.2	7.4	6.5	7.0	6.6	6.2	6.0	8.0	6.5
S11	3.5	6.0	5.1	4.6	3.9	4.4	4.5	4.6	4.3
Mean	1.9	3.4	3.0	2.6	2.2	2.3	2.1	2.6	2.5
SEM	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Study I. Adrenaline level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Adrenaline (nmol·L^{-1})	NORMOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.035	0.030	0.020	0.020	0.010	0.010	0.020	0.010	0.010
S2	0.100	0.080	0.090	0.110	0.140	0.090	0.100	0.100	0.120
S3	0.439	0.288	0.281	0.225	0.230	0.285	0.384	0.256	0.288
S4	0.209	0.148	0.169	0.142	0.112	0.141	0.116	0.187	0.236
S5	0.529	0.248	0.164	0.190	0.154	0.130	0.200	0.286	0.325
S6	0.326	0.314	0.069	0.320	0.072	0.093	0.112	0.105	0.074
S7	0.404	0.315	0.238	0.317	0.279	0.251	0.295	0.346	0.408
S8	0.309	0.246	0.219	0.274	0.305	0.274	0.401	0.304	0.365
S9	0.403	0.311	0.338	0.282	0.298	0.263	0.240	0.261	0.301
S10	0.394	0.275	0.203	0.405	0.358	0.433	0.335	0.393	0.498
S11	0.244	0.368	0.249	0.213	0.332	0.313	0.233	0.240	0.255
Mean	0.308	0.238	0.186	0.227	0.208	0.207	0.221	0.226	0.262
SEM	0.014	0.010	0.009	0.010	0.011	0.011	0.011	0.010	0.013
Adrenaline (nmol·L^{-1})	NORMOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.050	0.040	0.020	0.020	0.020	0.020	0.020	0.020	0.020
S2	0.110	0.120	0.090	0.100	0.080	0.080	0.080	0.120	0.110
S3	0.355	0.096	0.113	0.182	0.144	0.179	0.306	0.269	0.312
S4	0.431	0.164	0.107	0.118	0.141	0.129	0.165	0.112	0.157
S5	0.182	0.120	0.085	0.150	0.160	0.088	0.084	0.054	0.091
S6	0.086	0.080	0.058	0.060	0.090	0.061	0.060	0.059	0.061
S7	0.272	0.237	0.259	0.254	0.246	0.228	0.248	0.297	0.374
S8	0.318	0.281	0.279	0.319	0.379	0.402	0.357	0.335	0.365
S9	0.242	0.259	0.190	0.166	0.202	0.209	0.190	0.168	0.199
S10	0.580	0.400	0.296	0.390	0.330	0.525	0.423	0.444	0.393
S11	0.329	0.251	0.182	0.296	0.251	0.309	0.376	0.225	0.359
Mean	0.269	0.186	0.153	0.187	0.186	0.203	0.210	0.191	0.222
SEM	0.238	0.233	0.238	0.195	0.203	0.193	0.179	0.187	0.201

Adrenaline (nmol·L^{-1})	HYPOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.050	0.070	0.020	0.020	0.020	0.020	0.020	0.020	0.020
S2	0.096	0.103	0.081	0.093	0.112	0.099	0.120	0.111	0.161
S3	0.508	0.297	0.210	0.167	0.246	0.114	0.212	0.268	0.323
S4	0.195	0.244	0.207	0.183	0.070	0.175	0.190	1.617	0.225
S5	0.580	0.392	0.311	0.289	0.367	0.339	0.271	0.582	0.420
S6	0.247	0.216	0.188	0.196	0.172	0.199	0.154	0.180	0.220
S7	0.175	0.146	0.066	0.100	0.106	0.107	0.116	0.160	0.189
S8	0.248	0.223	0.164	0.171	0.216	0.185	0.219	0.274	0.228
S9	0.442	0.391	0.117	0.102	0.140	0.098	0.121	0.203	0.245
S10	0.555	0.740	0.682	0.266	0.412	0.292	0.296	0.202	0.431
S11	0.186	0.102	0.114	0.062	0.066	0.122	0.090	0.120	0.159
Mean	0.298	0.266	0.196	0.150	0.175	0.159	0.164	0.340	0.238
SEM	0.225	0.364	0.343	0.332	0.294	0.277	0.279	0.288	0.279
Adrenaline (nmol·L^{-1})	HYPOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.105	0.120	0.110	0.150	0.140	0.120	0.110	0.130	0.130
S2	0.211	0.185	0.192	0.189	0.168	0.191	0.188	0.171	0.240
S3	0.395	0.186	0.000	0.225	0.190	0.187	0.255	0.276	0.277
S4	0.174	0.145	0.080	0.140	0.129	0.115	0.144	0.207	0.172
S5	0.252	0.568	0.181	0.175	0.241	0.285	0.243	0.588	0.292
S6	0.119	0.143	0.293	0.316	0.251	0.225	0.110	0.078	0.130
S7	0.315	0.169	0.269	0.094	0.185	0.000	0.142	0.273	0.210
S8	0.308	0.313	0.173	0.144	0.211	0.252	0.230	0.288	0.307
S9	0.392	0.307	0.286	0.300	0.187	0.253	0.212	0.314	0.258
S10	0.508	0.226	0.067	0.108	0.087	0.057	0.089	0.075	0.071
S11	0.123	0.113	0.105	0.091	0.147	0.149	0.095	0.121	0.231
Mean	0.264	0.225	0.160	0.176	0.176	0.167	0.165	0.229	0.211
SEM	0.225	0.364	0.343	0.332	0.294	0.277	0.279	0.288	0.279

Study I. Noradrenaline level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Noradrenaline (nmol·L^{-1})	NORMOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.525	0.025	0.015	0.025	0.105	0.065	0.135	0.015	0.015
S2	0.515	0.125	0.115	0.115	0.095	0.105	0.215	0.135	0.015
S3	1.157	0.085	0.204	0.162	0.236	0.157	0.172	0.077	0.045
S4	0.916	0.103	0.323	0.299	0.112	0.089	0.052	0.449	0.349
S5	1.158	0.263	0.144	0.432	0.496	0.252	0.070	0.274	0.069
S6	0.774	0.774	0.153	0.369	0.321	0.245	0.050	0.140	0.078
S7	1.247	0.007	0.065	0.128	0.060	0.029	0.042	0.075	0.073
S8	0.771	0.326	0.160	0.227	0.064	0.227	0.116	0.042	0.062
S9	1.266	0.117	0.208	0.063	0.120	0.049	0.036	0.042	0.043
S10	0.739	0.164	0.277	0.443	0.243	0.531	0.684	0.386	0.381
S11	0.772	0.155	0.125	0.063	0.065	0.028	0.062	0.125	0.066
Mean	0.894	0.038	0.126	0.171	0.100	0.133	0.089	0.121	0.048
SEM	0.025	0.027	0.013	0.018	0.018	0.016	0.020	0.017	0.015
Noradrenaline (nmol·L^{-1})	NORMOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.450	0.120	0.360	0.030	0.040	0.150	0.220	0.030	0.120
S2	0.605	0.135	0.255	0.085	0.095	0.085	0.245	0.215	0.115
S3	0.669	0.084	0.003	0.115	0.052	0.001	0.116	0.087	0.032
S4	1.283	0.212	0.228	0.158	0.145	0.095	0.106	0.228	0.127
S5	0.622	0.392	0.389	0.398	0.258	0.501	0.026	0.533	0.411
S6	0.877	0.019	0.045	0.033	0.159	0.060	0.013	0.081	0.080
S7	0.602	0.114	0.106	0.255	0.190	0.278	0.021	0.095	0.005
S8	0.625	0.287	0.053	0.005	0.011	0.027	0.104	0.027	0.085
S9	0.881	0.243	0.279	0.310	0.209	0.162	0.258	0.128	0.115
S10	1.239	0.019	0.137	0.339	0.058	0.461	0.139	0.509	0.371
S11	0.626	0.010	0.116	0.067	0.069	0.016	0.035	0.021	0.061
Mean	0.771	0.086	0.137	0.128	0.043	0.139	0.066	0.132	0.090
SEM	0.025	0.016	0.016	0.016	0.013	0.018	0.012	0.020	0.016

Noradrenaline (nmol·L^{-1})	HYPOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.740	0.020	0.100	0.150	0.060	0.460	0.170	0.020	0.000
S2	0.810	0.343	0.364	0.507	0.128	0.182	0.240	0.100	0.038
S3	0.780	0.099	0.103	0.251	0.081	0.147	0.125	0.036	0.217
S4	0.527	0.368	0.085	0.148	0.230	0.046	0.163	0.035	0.049
S5	0.572	0.437	0.516	0.574	0.341	0.267	0.188	0.680	0.488
S6	1.026	0.044	0.174	0.221	0.121	0.059	0.096	0.042	0.092
S7	1.318	0.279	0.042	0.003	0.355	0.378	0.433	0.154	0.152
S8	0.882	0.026	0.006	0.040	0.218	0.201	0.073	0.208	0.181
S9	1.423	0.106	0.436	0.147	0.018	0.016	0.137	0.003	0.153
S10	1.652	0.232	0.379	0.198	0.135	0.143	0.284	0.246	0.090
S11	1.427	0.672	0.037	0.022	0.149	0.001	0.330	0.230	0.260
Mean	1.014	0.062	0.177	0.166	0.003	0.019	0.025	0.003	0.015
SEM	0.035	0.029	0.019	0.020	0.019	0.021	0.022	0.023	0.019

Noradrenaline (nmol·L^{-1})	HYPOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.745	0.045	0.255	0.235	0.115	0.095	0.015	0.115	0.125
S2	1.186	0.100	0.234	0.426	0.228	0.339	0.283	0.345	0.320
S3	0.952	0.130	0.952	0.226	0.268	0.153	0.232	0.031	0.284
S4	1.490	0.367	0.633	0.550	0.686	0.639	1.172	0.592	0.758
S5	1.270	0.354	0.041	0.219	0.274	0.047	0.142	0.381	0.145
S6	1.557	0.268	0.312	0.385	0.203	0.187	0.437	0.226	1.557
S7	0.853	0.212	0.244	0.085	0.033	0.088	0.057	0.234	0.029
S8	1.493	0.187	0.469	0.434	0.260	0.303	0.014	0.259	0.204
S9	1.371	0.546	0.084	0.141	0.189	0.208	0.139	0.390	0.205
S10	2.383	0.641	0.641	0.396	0.185	0.116	0.028	0.095	0.057
S11	0.994	0.136	0.491	0.525	0.153	0.136	0.067	0.154	0.248
Mean	1.299	0.271	0.223	0.304	0.186	0.174	0.222	0.257	0.032
SEM	0.041	0.017	0.040	0.019	0.020	0.019	0.032	0.015	0.053

Study I. PYY level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

PYY (pg·mL^{-1})	NORMOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	102.86	132.66	138.05	135.30	123.06	121.02	121.94	136.41	143.31
S2	99.93	139.01	154.88	141.23	133.70	129.19	145.78	181.96	170.33
S3	149.30	157.36	173.54	160.36	150.62	122.64	128.97	165.08	148.18
S4	90.27	125.28	126.34	123.35	124.99	124.95	124.06	114.80	130.30
S5	67.87	86.18	99.62	92.79	99.38	100.83	93.47	130.48	129.97
S6	186.79	132.60	182.76	126.50	152.52	133.84	83.38	134.07	141.31
S7	103.99	125.69	114.21	132.35	116.57	119.17	116.81	118.99	116.61
S8	89.23	123.35	130.56	136.27	123.28	142.73	119.61	136.84	149.28
S9	62.51	100.05	91.65	85.63	104.62	97.93	109.86	138.63	126.90
S10	77.63	85.63	99.42	85.20	78.29	76.34	73.23	82.30	86.23
S11	69.17	130.99	103.13	94.32	92.33	97.29	109.35	109.89	108.57
Mean	100.0	121.7	128.6	119.4	118.1	115.1	111.5	131.8	131.9
SEM	3.4	2.0	2.8	2.3	2.1	1.8	1.9	2.4	2.1
PYY (pg·mL^{-1})	NORMOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	116.00	126.72	128.44	129.69	134.13	113.54	118.93	136.07	128.84
S2	114.22	135.12	133.18	123.43	124.33	133.91	137.12	140.25	137.41
S3	119.58	172.81	157.91	146.23	152.21	146.52	156.44	171.96	142.20
S4	106.86	110.28	161.45	147.50	149.33	138.60	149.00	130.57	116.01
S5	124.73	161.62	193.92	163.81	133.29	138.11	117.49	126.60	121.52
S6	91.32	111.33	131.97	118.98	104.35	112.20	113.88	117.80	109.25
S7	195.23	191.27	189.28	167.36	169.25	185.20	160.78	160.16	152.00
S8	97.18	145.62	150.17	129.57	115.41	147.98	149.26	142.79	181.77
S9	94.91	113.89	112.72	87.10	89.71	104.48	97.38	95.78	107.61
S10	107.39	125.43	123.07	121.68	118.75	117.79	111.89	106.59	95.08
S11	96.32	106.99	108.42	110.12	96.36	112.77	112.23	113.84	118.03
Mean	114.9	136.5	144.6	131.4	126.1	131.9	129.5	131.1	128.2
SEM	2.6	2.6	2.6	2.1	2.2	2.1	2.0	2.1	2.2

PYY (pg·mL^{-1})	HYPOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	110.22	136.79	157.20	165.26	149.23	145.62	164.46	168.94	167.64
S2	92.56	126.79	128.28	126.08	131.05	140.98	148.68	159.93	152.02
S3	110.80	215.17	197.01	195.86	178.59	171.27	173.74	176.37	158.78
S4	101.34	119.00	125.13	129.59	123.12	134.89	132.08	145.93	122.65
S5	130.70	134.80	145.75	160.00	139.29	137.18	116.59	123.24	130.23
S6	124.61	157.56	175.45	152.24	141.53	129.76	145.38	142.65	145.88
S7	132.47	162.79	154.70	141.39	124.06	135.51	133.91	126.47	117.59
S8	86.17	88.17	97.63	96.45	91.18	120.86	110.65	109.40	114.62
S9	61.80	73.96	81.43	91.72	81.03	80.23	117.62	109.57	94.93
S10	68.70	75.83	77.17	71.72	69.45	64.70	67.13	69.38	66.02
S11	55.83	78.42	76.64	74.21	69.75	74.56	73.40	79.04	72.44
Mean	97.7	124.5	128.8	127.7	118.0	121.4	125.8	128.3	122.1
SEM	2.5	4.0	3.8	3.7	3.2	3.1	3.1	3.2	3.1

PYY (pg·mL^{-1})	HYPOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	102.5	134.1	132.3	120.2	122.6	108.5	119.7	116.4	116.1
S2	117.9	175.0	180.1	158.3	154.2	165.4	161.6	189.4	174.8
S3	126.7	179.4	168.6	163.0	173.9	169.5	166.2	197.9	156.7
S4	103.4	122.1	166.7	164.6	165.0	156.1	163.1	167.0	159.0
S5	80.4	109.6	106.9	99.1	89.4	86.5	89.7	94.5	98.2
S6	94.7	111.7	120.9	113.6	101.5	96.5	93.1	119.6	116.7
S7	141.3	201.0	167.0	147.1	157.7	162.2	165.9	156.4	181.9
S8	86.3	102.9	104.5	97.4	106.2	134.6	149.3	160.3	144.4
S9	106.2	140.4	135.3	135.1	114.9	90.6	103.2	95.6	94.6
S10	90.5	122.1	109.4	99.3	113.3	110.7	131.1	140.6	118.3
S11	128.8	162.6	179.2	175.1	174.1	171.7	165.3	174.4	154.7
Mean	107.2	141.9	142.8	133.9	133.9	132.0	137.1	146.6	137.8
SEM	1.8	3.0	2.7	2.7	2.9	3.1	2.8	3.3	2.8

Study I. Leptin level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Leptin ($ng \cdot mL^{-1}$)	NORMOXIA		HYPOXIA	
Subject/Condition	PRE	POST	PRE	POST
S1	4.57	4.45	1.86	4.85
S2	1.20	1.64	1.43	1.36
S3	2.32	3.28	1.93	2.69
S4	7.71	8.59	8.67	10.28
S5	1.21	1.34	1.02	1.43
S6	3.34	5.91	5.15	5.99
S7	1.34	1.22	1.27	1.06
S8	1.63	2.35	1.41	1.81
S9	1.47	1.72	1.45	2.91
S10	2.83	2.74	2.19	1.80
S11	5.58	5.92	2.17	5.70
Mean	3.02	3.56	2.60	3.63
SEM	0.19	0.22	0.21	0.26

Study I. Ghrelin level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Ghrelin (pg·mL^{-1})	NORMOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	999.52	1044.30	1043.80	915.76	889.39	1032.60	980.66	842.49	838.87
S2	1460.80	1562.10	1194.00	1288.50	1160.70	1175.90	1314.00	1463.90	1418.60
S3	1146.75	1001.90	1055.00	1040.40	939.55	1037.60	984.71	961.96	1036.00
S4	803.54	850.69	753.87	814.30	760.57	787.83	739.60	806.44	717.12
S5	1058.75	1029.40	941.80	775.96	699.41	754.34	692.98	779.19	681.24
S6	845.51	739.42	872.79	853.04	811.05	773.03	822.57	673.99	896.72
S7	1091.20	1067.00	1074.80	1075.60	955.72	955.72	1004.90	932.43	958.84
S8	1146.40	1146.30	1141.30	1092.30	1173.90	1167.20	1127.20	1122.70	1052.40
S9	1298.60	1278.00	1053.70	1061.60	953.15	935.12	817.76	1014.50	901.81
S10	1046.55	948.71	827.29	741.57	690.40	754.25	731.84	622.77	642.94
S11	2197.20	1865.60	1672.90	1592.50	1525.00	1584.60	1470.80	1338.10	1438.90
Mean	1190.4	1139.4	1057.4	1022.9	959.9	996.2	971.5	959.9	962.1
SEM	34.7	29.5	22.2	22.8	22.5	22.8	22.8	23.9	24.3
Ghrelin (pg·mL^{-1})	NORMOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1032.83	1007.70	894.50	788.61	908.52	916.08	884.34	860.47	924.39
S2	1533.40	1408.00	1269.10	1119.90	1126.00	1182.60	1232.60	1107.50	1171.60
S3	1289.95	1232.30	1041.20	1073.10	1015.00	980.12	952.13	957.47	881.32
S4	815.51	759.57	834.34	787.99	725.31	689.66	484.40	731.92	744.19
S5	989.03	795.44	754.72	655.44	706.35	780.18	677.13	604.76	510.51
S6	1080.40	980.69	1022.40	827.97	932.11	871.02	822.32	943.07	753.19
S7	1003.47	1047.10	956.43	888.15	942.66	893.55	805.28	884.67	829.61
S8	882.46	874.25	857.44	923.80	972.73	625.65	613.78	613.20	648.44
S9	1324.05	1314.30	1181.20	1088.50	980.65	979.79	897.18	927.80	962.37
S10	763.96	686.04	608.12	436.76	580.26	611.50	506.43	484.31	418.08
S11	2081.70	1863.90	1698.20	1649.40	1563.10	1498.70	1396.60	1402.70	1347.50
Mean	1163.3	1088.1	1010.7	930.9	950.2	911.7	842.9	865.3	835.6
SEM	34.8	31.4	26.8	28.3	23.4	23.5	25.7	23.4	24.6

Ghrelin (pg·mL^{-1})	HYPOXIA PRE								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1069.25	1093.10	986.61	979.71	928.34	900.94	1062.30	979.87	926.81
S2	1625.70	1598.30	1361.20	1537.60	1286.40	1427.60	1304.10	1305.30	1215.60
S3	1205.95	1015.40	1021.30	986.36	1040.80	964.38	1026.90	896.48	1019.50
S4	679.59	729.51	741.45	709.20	723.29	778.08	573.90	645.61	655.58
S5	729.13	755.32	635.11	669.15	587.63	658.63	672.58	630.93	689.45
S6	902.92	901.45	741.89	880.15	727.22	748.82	513.31	820.95	654.47
S7	916.81	909.35	864.58	831.63	1016.80	897.66	845.23	884.09	978.24
S8	1011.09	933.73	1061.80	905.05	980.93	924.52	994.41	908.13	940.08
S9	1310.80	1199.20	1092.50	984.21	869.19	839.02	776.21	783.71	819.63
S10	949.76	899.41	725.99	640.51	556.59	616.68	472.07	552.60	452.45
S11	933.44	993.21	900.92	714.39	793.72	822.62	890.52	806.77	779.90
Mean	1030.4	1002.5	921.2	894.4	864.6	870.8	830.1	837.7	830.2
SEM	24.5	21.7	19.2	22.7	19.6	19.5	23.5	18.5	19.4

Ghrelin (pg·mL^{-1})	HYPOXIA POST								
Condition	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1088.8	1078.4	1033.0	931.2	984.9	1016.0	935.7	940.4	1014.7
S2	1649.0	1518.9	1215.7	1450.1	1325.1	628.0	1323.3	1172.5	1081.0
S3	1164.0	1104.2	1045.1	997.0	1057.0	1030.8	991.0	932.4	986.3
S4	763.9	833.2	777.3	850.9	830.7	790.6	616.1	634.5	642.5
S5	1066.8	909.2	885.0	777.5	729.3	725.7	738.6	669.1	633.1
S6	1193.1	1277.1	1136.5	860.0	791.4	645.1	1098.2	820.1	1646.1
S7	984.7	974.7	934.4	760.8	863.1	800.0	785.4	714.9	923.1
S8	1058.6	1092.4	947.5	928.9	879.9	1002.0	868.7	881.7	877.0
S9	753.3	640.9	525.7	485.8	508.4	332.3	577.2	485.7	345.2
S10	1276.0	1272.5	1092.2	932.2	926.0	651.3	839.3	757.3	752.8
S11	1946.7	1731.6	1572.1	1465.6	1396.3	1393.3	1251.5	1314.0	1213.6
Mean	1176.8	1130.3	1015.0	949.1	935.6	819.6	911.4	847.5	919.6
SEM	32.1	28.2	24.0	26.0	23.1	25.5	21.9	21.8	31.1

Study II. Descriptive characteristics (body mass, body mass index, body fat) of the present study participants before and after (PRE, POST) the 10-day normobaric normoxic confinemnet (NORMOXIA) and the 10-day normobaric hypoxic confinemnet (HYPOXIA).

Condition				NORMOXIA		
		PRE			POST	
Subject/variable	Body mass (kg)	BMI (kg·m^{-2})	Body fat (%)	Body mass (kg)	BMI (kg·m^{-2})	Body fat (%)
S1	103.60	31.87	24.4	103.90	31.96	26.1
S2	134.10	35.93	26.9	135.70	36.36	27.1
S3	123.30	34.52	28.4	123.30	34.52	32
S4	120.80	36.91	29.6	119.60	36.55	30.2
S5	150.50	45.19	41	153.70	46.15	39.9
S6	143.60	46.04	38.1	148.10	47.49	36.9
S7	124.50	41.69	32.9	124.50	41.69	34.7
S8	99.70	28.73	24.9	99.40	28.64	25.7
Mean	125.01	37.61	30.78	126.03	37.92	31.58
SEM		0.22	0.53	0.63	0.24	0.55
Condition				HYPOXIA		
		PRE			POST	
Subject/variable	Body mass (kg)	BMI (kg·m^{-2})	Body fat (%)	Body mass (kg)	BMI (kg·m^{-2})	Body fat (%)
S1	102.90	31.65	25.9	101.10	31.10	26.7
S2	134.20	35.95	27.3	132.50	35.50	28.1
S3	121.00	33.87	29.8	120.00	33.59	28.5
S4	118.90	36.33	30.4	117.20	35.81	32.2
S5	148.20	44.50	43	151.00	45.34	42.2
S6	144.20	46.24	39.8	143.60	46.04	38.1
S7	123.80	41.46	35.8	123.40	41.33	34.3
S8	97.60	28.12	24.6	96.30	27.75	24.5
Mean	123.85	37.27	32.08	123.14	37.06	31.83
SEM	0.53	0.17	0.55	0.57	0.18	0.50

Study II. Noctural arterial oxygen saturation (SpO_2, %) during the 10-day normobaric normoxic confinement (NORMOXIA) and during the 10-day normobaric hypoxic confinement (HYPOXIA).

SpO_2 (%)	NORMOXIA									
Subject/Day	1	2	3	4	5	6	7	8	9	10
S1	98	98.8	99	98.5	98.6	98.5	98	98.2	98.1	98.8
S2	97.9	97.6	97.5	98	98	98	98	98	98	98
S3	98.7	98	97.8	99	93.8	93.8	93.8	93.8	97.8	96
S4	95.4	94.2	94.7	95.6	96.2	96	97	97.4	96.6	96.8
S5	94.9	92.2	93.3	93.6	95	96.1	94.7	95.9	96.1	96.5
S6	95.2	96.1	94	94.2	94.9	98.3	97.3	98	96.7	97
S7	93	92.5	94.4	94.5	93.3	94.3	95.4	95.2	96.6	95
S8	98.8	98.2	98	97.9	99	98.2	98.1	98	98.8	98
Mean	96.5	96.0	96.1	96.4	96.1	96.7	96.5	96.8	97.3	97.0
SEM	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.1	0.2
SpO_2 (%)	HYPOXIA									
Subject/Day	1	2	3	4	5	6	7	8	9	10
S1	91.2	88.1	90	91.2	89.2	90.6	89	90	89	90.1
S2	89.5	88	87	91	90.5	90.5	90.9	89.9	90.2	92.1
S3	90.9	84	91.1	90	90	89.7	90.9	88.8	89.2	91.6
S4	91	89.9	88.7	89.9	90.5	88.3	92.1	92.1	89.1	93
S5	90.9	86	88	88.2	86.3	88.9	90.7	90.5	90.6	91
S6	90.4	80	88.3	89.7	88	89.9	85.6	87.6	89	88.5
S7	88.8	86	85	88	90.1	89.7	89.7	90.7	91	90.6
S8	87.6	85	91.2	91.1	89.1	90.7	89.7	90.2	90	91.2
Mean	90.0	85.9	88.7	89.9	89.2	89.8	89.8	90.0	89.8	91.0
SEM	0.2	0.4	0.3	0.2	0.2	0.1	0.2	0.2	0.1	0.2

HR (min^{-1})	NORMOXIA									
Subject/Day	1	2	3	4	5	6	7	8	9	10
S1	60	67	67	67	67	67	67	67	65.5	65
S2	84	70	70	70	70	70	70	70	82	82
S3	70	70	70	70	69.4	65	68	70	74.7	77
S4	97.2	82.8	73.5	75.6	70.1	70.2	76	77	79.8	80
S5	82	77	82.4	102.6	90.5	98	77	85.5	95	95
S6	82.9	77.6	90.7	78.7	80	90	77	70.5	75.7	70
S7	104.3	101.9	100.2	89	88	90	71	88	90.5	96
S8	60	65.5	66.2	65	71	69.8	66.7	67.2	70	85
Mean	80.1	76.5	77.5	77.2	75.8	77.5	71.6	74.4	79.2	81.3
SEM	2.0	1.5	1.6	1.6	1.1	1.6	0.6	1.0	1.2	1.4
HR (min^{-1})	HYPOXIA									
Subject/Day	1	2	3	4	5	6	7	8	9	10
S1	72	72	72.8	79	73.6	85.9	81.9	80.1	85	84.5
S2	76.9	75.5	76.6	81.5	88.3	78.9	80.5	79.8	76.6	82
S3	79.5	76.7	81.4	82.6	88.3	78	96.2	86.8	82.4	95.5
S4	88.9	81	75.9	94.4	96.3	77.3	96	88	87.9	88.6
S5	95.4	91.5	96.2	85.7	92.2	91.7	101.5	97.8	89.7	85.8
S6	93	87	89.6	105.6	81.2	85.6	75.4	80.9	90.6	88.7
S7	77.7	88.3	93.9	75.3	86	88	90.6	90	96	90
S8	65.6	63.9	65.2	62.1	64.8	76.2	64.4	78.2	70.1	80.4
Mean	81.1	79.5	81.5	83.3	83.8	82.7	85.8	85.2	84.8	86.9
SEM	1.3	1.2	1.4	1.6	1.3	0.7	1.6	0.8	1.0	0.6

Study II. Resting energy expenditure (REE) before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

REE		NORMOXIA PRE			
(kcal·day^{-1})	Fasted state	Postprandially			
Subject/Time (min)		15 - 30	45 - 60	75 - 90	105 - 120
S1	2285.6	2773.1	2655.4	2506.8	2555.2
S2	2820.8	2908.6	3057.2	3382.8	3217.3
S3	2481.3	2327.0	2491.9	2491.9	2522.5
S4	2889.9	3069.5	3172.1	2930.9	3047.3
S5	2987.3	2910.9	2836.9	3114.6	3029.9
S6	2959.0	3279.0	3281.4	3214.4	3028.0
S7	2391.6	2520.7	2526.8	2558.9	2463.6
S8	2227.5	2493.1	2661.9	2586.0	2490.5
Mean	2630.4	2785.2	2835.5	2848.3	2794.3
SEM	39.51	40.12	37.72	44.66	39.12
REE		NORMOXIA POST			
(kcal·day^{-1})	Fasted state	Postprandially			
Subject/Time (min)		15 - 30	45 - 60	75 - 90	105 - 120
S1	2304.5	2391.9	2688.1	2768.7	2964.7
S2	2936.9	3195.8	3155.3	3422.6	3342.1
S3	2503.2	2720.3	2767.7	2456.4	2700.0
S4	2682.1	3150.9	3185.2	3205.0	3118.5
S5	3096.3	3534.8	3472.1	3417.6	3353.6
S6	2699.9	3165.5	3126.6	2966.1	2916.8
S7	2429.0	2509.5	2855.7	2913.2	3020.3
S8	2126.5	2552.6	2720.0	2701.1	2519.1
Mean	2597.3	2902.6	2996.3	2981.3	2991.9
SEM	40.27	51.48	34.96	43.28	36.15
REE		HYPOXIA PRE			
(kcal·day^{-1})	Fasted state	Postprandially			
Subject/Time (min)		15 - 30	45 - 60	75 - 90	105 - 120
S1	1957.2	2324.2	2614.9	2664.8	2719.8
S2	2699.3	3003.3	2607.8	3120.7	3244.0
S3	2429.3	2527.8	2676.1	2609.1	2632.5
S4	2453.1	2510.1	2625.8	2403.1	2721.8
S5	2982.0	3266.0	2980.6	2965.6	2857.8
S6	2700.7	3649.9	3231.0	3216.2	3149.5
S7	2501.4	2518.6	2643.2	2643.3	2674.0
S8	2249.7	2674.0	2863.7	2861.6	2851.2
Mean	2496.6	2809.2	2780.4	2810.6	2856.3
SEM	38.87	57.08	28.38	34.82	28.20
REE		HYPOXIA POST			
(kcal·day^{-1})	Fasted state	Postprandially			
Subject/Time (min)		15 - 30	45 - 60	75 - 90	105 - 120
S1	2549.7	2353.0	3411.3	3089.421025	3956.6
S2	2725.4	3339.2	3735.6	3912.1	3912.1
S3	3529.7	3250.1	3741.6	3090.1	2589.6
S4	2357.7	2143.8	2421.1	2914.0	2007.3
S5	2978.0	3808.6	4069.6	3858.0	2847.8
S6	3188.6	3257.6	4136.0	3399.4	2948.7
S7	2781.2	3343.6	2930.6	3635.2	3732.2
S8	2726.6	3034.6	3689.1	3616.2	3172.2
Mean	2854.6	3066.3	3516.9	3439.3	3145.8
SEM	46.31	69.01	72.77	47.02	86.12

Study II. Blood glucose in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Glucose ($mmol \cdot L^{-1}$)		NORMOXIA PRE											
	Fasted state	Postprandially											
Subject/Time (min)		10	15	20	30	40	45	50	60	75	90	105	120
S1	4.7	5.7	6.7	7.7	8.3	8.1	7.4	7.4	7.2	6.5	6.3	6.7	6.6
S2	7.9	5.2	7	7.1	7.6	7.9	8.2	8.7	8.5	9.1	9	9.6	9.7
S3	4.2	5	5.2	4.8	7	7.4	7.7	7.3	7.9	6.9	7.7	7.3	6.3
S4	7.3	5.1	6.4	7.1	8	8.5	8.6	8.3	7.7	6.8	5.9	5.3	5.9
S5	4.7	6.6	7.9	8.4	8.3	8.7	9	8.9	8.2	7.5	6.7	6.9	6.4
S6	5.4	5.7	6.8	7.2	9.2	10.2	10.3	9.9	9.7	8.6	7.5	6.7	5.9
S7	4.7	4.6	4.8	5.2	7.9	8.34	8.3	8.3	8.6	9.9	10	9.6	9.2
S8	6.4	4.4	4.8	5.6	6.9	7.6	8.2	8.5	8.3	7.7	7.5	7.8	7.4
Mean	5.7	5.3	6.2	6.6	7.9	8.3	8.5	8.4	8.3	7.9	7.6	7.5	7.2
SEM	0.2	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2
Glucose ($mmol \cdot L^{-1}$)		NORMOXIA POST											
	Fasted state	Postprandially											
Subject/Time (min)		10	15	20	30	40	45	50	60	75	90	105	120
S1	5.9	5.4	5.9	6.7	7.8	8.5	8.1	7.9	7.6	7.1	8.1	7.9	7.6
S2	5.3	3.5	5.3	5.8	6	5.5	6.5	6.6	7.8	8.3	8.7	9.4	8.7
S3	6	4.8	5.7	6.5	7.5	8	8.1	7.4	7	7.5	6.3	6.7	6.1
S4	9.7	6.7	7.7	8.4	8.3	8.6	8.7	8.3	8	7.2	6.8	6.6	5.4
S5	7.9	6.7	7.5	8.1	8.3	9.6	9.8	10.4	10.6	9.7	9.5	8.7	9.6
S6	6.2	6	6.9	7.6	8.3	7.6	9.6	9.6	9.7	8.6	7.4	6.7	5.7
S7	5.2	4.5	5.4	5.4	5.8	7.2	8.1	7.4	9	9.2	9.7	9.9	10
S8	4.5	4.5	5.6	6.3	6.9	6.9	6.9	6.9	7	7.2	7.6	8.3	8
Mean	6.3	5.3	6.3	6.9	7.4	7.7	8.2	8.1	8.3	8.1	8.0	8.0	7.6
SD	0.2	0.1	0.1	0.1	0.1	0.2	0.1	0.2	0.2	0.1	0.2	0.2	0.2

Glucose ($mmol \cdot L^{-1}$)													
		HYPOXIA PRE											
	Fasted state	Postprandially											
Subject/Time (min)		10	15	20	30	40	45	50	60	75	90	105	120
S1	4.5	5.3	7.1	6.9	7.3	6.8	6.9	6	6.3	5.6	5.8	6.3	5.5
S2	3.45	4.6	5.2	5.2	6	6.9	6	7.4	7.6	8.2	8.2	9.1	7.5
S3	4.15	4.1	5.6	5.1	7.7	7.6	7.5	7.9	6.8	7	6	6.3	6.3
S4	4.1	4.7	5	6.7	8.1	7.3	7.4	6.7	5.8	4	4.4	7.1	7.7
S5	5.2	6.2	6.5	7.4	8.2	8.2	8.3	7.6	6.6	6.7	6.9	7.1	7.1
S6	5	6.3	7	8.2	9.5	10.3	10.5	9.9	9.9	9.2	8	7.5	6.1
S7	4.15	4.9	6.2	5.5	7.2	8	8.5	8.4	9	8.6	9.3	9.6	9.6
S8	4.8	6.4	7.6	6	8.3	7.7	8.5	7.1	8.1	7.9	7.1	6.5	6.4
Mean	4.4	5.3	6.3	6.4	7.8	7.9	8.0	7.6	7.5	7.2	7.0	7.4	7.0
SD	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.2	0.2	0.2	0.2	0.2
Glucose ($mmol \cdot L^{-1}$)													
		HYPOXIA POST											
	Fasted state	Postprandially											
Subject/Time (min)		10	15	20	30	40	45	50	60	75	90	105	120
S1	4.1	4.3	5.5	6.2	7.6	7.7	7.8	8.1	8.3	8.4	8.4	9.1	8.8
S2	3.9	4.4	5.3	6.2	7.7	7.9	8.8	9.0	9.9	10.4	11.1	12.4	12.3
S3	4.4	5.4	5.6	5.5	7.5	7.9	8.1	8.6	7.9	7.3	7.6	7.5	6.8
S4	4.1	4.4	5.3	6.4	6.8	7.5	7.5	8.3	5.6	4.3	6.8	8.4	8.3
S5	5.5	5.5	6.5	7.0	8.1	8.0	8.7	8.5	8.4	8.4	9.1	9.1	9.1
S6	4.9	6.3	7.1	6.8	7.6	9.6	10.2	10.1	8.4	9.2	8.3	7.4	5.7
S7	4.6	4.6	5.5	6.1	6.4	8.5	8.3	9.1	9.8	9.2	9.1	10.0	10.2
S8	4.2	5.2	5.9	6.5	7.9	7.8	7.8	7.9	7.8	8.2	7.2	6.5	6.4
Mean	4.4	5.0	5.8	6.3	7.5	8.1	8.4	8.7	8.3	8.2	8.5	8.8	8.5
SD	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.3

Study II. Insulin in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Insulin ($mmol \cdot L^{-1}$)	NORMOXIA PRE								
	Fasted state	Postprandially							
Subject/Time	0	15	30	45	60	75	90	105	120
S1	4.10	53.82	107.06	126.61	93.10	59.14	57.65	77.66	76.78
S2	8.20	40.78	94.81	146.96	137.34	84.28	142.64	158.52	83.34
S3	19.27	120.39	228.42	216.02	203.92	216.97	161.81	124.59	140.26
S4	57.29	193.23	234.67	335.69	246.82	247.97	198.41	270.46	147.15
S5	11.58	53.84	142.51	168.53	139.99	94.99	80.96	55.14	44.43
S7	28.15	60.24	143.00	175.94	174.61	271.48	297.83	266.25	323.95
Mean	21.4	87.1	158.4	195.0	166.0	162.5	156.5	158.8	136.0
SEM	2.8	8.4	8.5	10.7	7.8	13.3	12.4	13.2	14.3
Insulin ($mmol \cdot L^{-1}$)	NORMOXIA POST								
	Fasted state	Postprandially							
Subject/Time	0	15	30	45	60	75	90	105	120
S1	3.47	49.85	115.56	95.67	100.68	132.64	128.23	273.01	134.53
S2	11.58	68.77	167.45	213.95	141.33	164.92	95.50	168.63	109.53
S3	11.16	161.12	213.04	212.96	192.18	230.97	237.37	161.43	177.27
S4	31.58	147.51	215.54	301.68	302.52	321.52	317.33	244.73	339.47
S5	16.09	132.62	201.07	258.03	248.01	219.34	139.38	123.11	95.45
S7	41.54	181.53	268.51	280.00	360.58	273.92	282,04	295.00	300.00
Mean	19.2	123.6	196.9	227.0	224.2	223.9	183.6	211.0	192.7
SEM	2.1	7.5	7.4	10.5	14.1	9.9	13.1	9.9	14.7

Insulin	HYPOXIA PRE								
(mmol·L^{-1})	Fasted state	Postprandially							
Subject/Time	0	15	30	45	60	75	90	105	120
S1	2.86	114.84	239.70	149.39	102.95	72.09	87.61	85.69	101.82
S2	12.82	151.63	217.05	228.72	206.91	158.31	149.61	136.65	137.11
S3	11.24	62.91	158.84	147.62	104.52	37.40	25.41	129.62	139.76
S4	35.49	154.95	231.27	259.37	141.23	145.69	135.30	153.72	141.85
S5	9.00	97.35	164.57	236.59	282.26	295.07	282.44	254.44	194.37
S7	22.89	109.08	208.88	257.37	246.99	223.24	306.47	323.74	350.16
Mean	15.7	115.1	203.4	213.2	180.8	155.3	164.5	180.6	177.5
SEM	1.7	4.9	4.9	7.4	10.8	13.6	15.7	12.8	12.8
Insulin	HYPOXIA POST								
(mmol·L^{-1})	Fasted state	Postprandially							
Subject/Time	0	15	30	45	60	75	90	105	120
S1	3.3	49.2	121.8	142.1	166.4	200.4	153.5	257.1	227.1
S2	11.7	84.5	199.1	243.2	148.5	172.8	191.7	183.2	167.9
S3	10.0	92.8	163.7	204.0	200.1	86.2	65.8	159.2	170.4
S4	33.2	140.2	196.3	259.7	259.2	226.0	271.1	305.1	364.5
S5	16.2	140.3	199.3	260.5	246.0	179.0	151.7	134.8	79.4
S6	26.8	106.6	221.9	297.9	290.4	276.4	275.0	268.0	271.5
S7	7.2	116.3	184.8	208.9	270.9	137.3	182.9	114.9	123.7
Mean	15.5	104.3	183.8	230.9	225.9	182.6	184.5	203.2	200.7
SEM	1.5	4.6	4.6	7.2	7.8	8.7	10.4	10.5	13.7

Study II. GLP-1 level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

GLP-1 (pM)	NORMOXIA PRE								
	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.88	4.87	3.59	2.20	1.18	2.24	1.83	1.99	1.35
S2	4.25	6.49	4.12	4.18	4.06	4.14	3.55	3.68	4.23
S3	2.06	3.46	2.64	2.60	2.46	2.17	2.77	2.48	2.83
S4	2.06	3.38	4.09	2.51	1.85	2.89	2.71	2.95	2.81
S5	1.81	6.59	4.67	3.58	1.96	1.81	1.91	1.81	1.76
S6	2.47	13.74	11.16	6.75	4.54	3.07	2.61	2.68	2.57
S7	1.19	2.28	2.30	2.06	2.17	1.70	1.11	0.88	0.83
S8	1.81	3.87	2.98	2.59	3.13	2.49	2.49	2.31	2.25
Mean	2.1	5.6	4.4	3.3	2.7	2.6	2.4	2.3	2.3
SEM	0.1	0.5	0.4	0.2	0.1	0.1	0.1	0.1	0.1
GLP-1 (pM)	NORMOXIA POST								
	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.86	4.80	3.08	2.58	1.80	2.23	1.54	2.13	1.84
S2	3.53	4.77	4.99	5.41	4.50	4.69	4.39	3.89	4.00
S3	2.47	3.72	3.58	8.71	2.88	2.72	2.62	2.61	2.84
S4	1.46	2.63	2.55	2.44	1.28	1.64	2.02	3.17	2.82
S5	1.64	2.96	2.59	1.39	0.93	0.91	2.31	1.37	1.71
S6	2.36	11.25	14.57	11.59	7.93	6.54	5.58	4.82	3.59
S7	0.67	0.96	1.78	1.11	2.71	1.82	1.93	1.21	1.38
S8	2.14	2.90	2.59	2.40	2.30	3.15	2.80	3.13	3.56
Mean	1.9	4.2	4.5	4.5	3.0	3.0	2.9	2.8	2.7
SEM	0.1	0.4	0.5	0.5	0.3	0.2	0.2	0.2	0.1

GLP-1	HYPOXIA PRE								
(pM)	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.86	4.80	3.08	2.58	1.80	2.23	1.54	2.13	1.84
S2	3.53	4.77	4.99	5.41	4.50	4.69	4.39	3.89	4.00
S3	2.47	3.72	3.58	8.71	2.88	2.72	2.62	2.61	2.84
S4	1.46	2.63	2.55	2.44	1.28	1.64	2.02	3.17	2.82
S5	1.64	2.96	2.59	1.39	0.93	0.91	2.31	1.37	1.71
S6	2.36	11.25	14.57	11.59	7.93	6.54	5.58	4.82	3.59
S7	0.67	0.96	1.78	1.11	2.71	1.82	1.93	1.21	1.38
S8	2.14	2.90	2.59	2.40	2.30	3.15	2.80	3.13	3.56
Mean	1.9	4.2	4.5	4.5	3.0	3.0	2.9	2.8	2.7
SEM	0.1	0.4	0.5	0.5	0.3	0.2	0.2	0.2	0.1
GLP-1	HYPOXIA POST								
(pM)	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1.0	1.8	6.2	3.7	2.1	1.8	1.5	1.8	1.7
S2	4.0	5.2	5.4	5.8	5.4	4.8	4.6	4.3	4.0
S3	2.9	4.7	4.0	3.4	3.2	3.0	3.9	2.9	3.3
S4	1.6	2.8	3.3	3.1	2.4	2.0	2.4	3.0	2.8
S5	2.3	6.4	3.7	2.8	2.0	1.7	1.6	2.0	2.4
S6	2.2	10.4	11.6	5.5	3.8	3.5	3.0	2.7	2.6
S7	1.5	2.3	2.2	2.1	2.4	1.5	1.7	1.6	1.5
S8	1.9	3.3	3.2	2.3	2.3	2.4	2.8	3.2	3.3
Mean	2.2	4.6	4.9	3.6	2.9	2.6	2.7	2.7	2.7
SEM	0.1	0.4	0.4	0.2	0.1	0.1	0.1	0.1	0.1

Study II. Adrenaline level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Adrenaline ($nmol \cdot L^{-1}$)	NORMOXIA PRE								
	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.494	0.055	0.034	0.033	0.042	0.022	0.033	0.040	0.022
S2	0.133	0.291	0.265	0.215	0.228	0.313	0.261	0.332	0.255
S3	0.130	0.144	0.144	0.106	0.144	0.129	0.212	0.110	0.144
S4	0.169	0.121	0.108	0.081	0.104	0.105	0.122	0.105	0.125
S5	0.156	0.116	0.054	0.098	0.079	0.092	0.140	0.084	0.166
S6	0.054	0.112	0.102	0.124	0.154	0.154	0.115	0.199	0.163
S7	0.121	0.030	0.035	0.048	0.017	0.019	0.037	0.017	0.017
S8	0.168	0.051	0.054	0.028	0.028	0.080	0.053	0.025	0.056
Mean	0.178	0.115	0.109	0.091	0.100	0.114	0.122	0.114	0.118
SEM	0.017	0.010	0.010	0.008	0.009	0.012	0.010	0.013	0.010
Adrenaline ($nmol \cdot L^{-1}$)	NORMOXIA POST								
	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.468	0.058	0.138	0.176	0.110		0.100	0.104	0.093
S2	0.153	0.365	0.159	0.182	0.167	0.191	0.204	0.231	0.278
S3	0.154	0.115	0.072	0.058	0.113	0.115	0.060	0.096	0.119
S4	0.209	0.080	0.088	0.053	0.140	0.142	0.114	0.127	0.087
S5	0.065	0.118	0.133	0.122	0.094	0.113	0.150	0.086	0.141
S6	0.017	0.065	0.026	0.066	0.034	0.106	0.114	0.090	0.078
S7	0.096	0.017	0.018	0.017	0.017	0.042	0.016	0.017	0.026
S8	0.170	0.078	0.058	0.078	0.020	0.017	0.043	0.019	0.020
Mean	0.167	0.112	0.087	0.094	0.087	0.104	0.100	0.096	0.105
SEM	0.017	0.013	0.007	0.008	0.007	0.007	0.008	0.008	0.010

Adrenaline ($nmol \cdot L^{-1}$)	HYPOXIA PRE								
	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.162	0.106	0.114	0.098	0.098	0.230	0.178	0.141	0.217
S2	0.299	0.170	0.095	0.092	0.066	0.135	0.108	0.097	0.127
S3	0.190	0.118	0.039	0.112	0.107	0.117	0.128	0.110	0.152
S4	0.079	0.184	0.123	0.159	0.207	0.237	0.297	0.146	0.154
S5	0.053	0.098	0.104	0.069	0.102	0.091	0.137	0.129	0.130
S6	0.121	0.125	0.078	0.162	0.119	0.105	0.133	0.084	0.054
S7	0.152	0.069	0.020	0.021	0.021	0.022	0.043	0.010	0.021
S8	0.083	0.051	0.054	0.028	0.028	0.080	0.053	0.025	0.056
Mean	0.143	0.115	0.078	0.093	0.094	0.127	0.135	0.093	0.114
SEM	0.010	0.006	0.005	0.007	0.007	0.009	0.010	0.006	0.008
Adrenaline ($nmol \cdot L^{-1}$)	HYPOXIA POST								
	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.092	0.180	0.259	0.234	0.226	0.353	0.209	0.228	0.247
S2	0.147	0.129	0.043	0.104	0.076	0.213	0.138	0.155	0.161
S3	0.147	0.049	0.055	0.123	0.038	0.056	0.133	0.143	0.186
S4	0.067	0.149	0.054	0.085	0.091	0.445	0.130	0.110	0.186
S5	0.090	0.089	0.071	0.095	0.099	0.095	0.108	0.074	0.115
S6	0.026	0.058	0.044	0.038	0.068	0.060	0.058	0.097	0.058
S7	0.116	0.042	0.033	0.046	0.022	0.044	0.045	0.064	0.010
S8	0.066	0.051	0.021	0.039	0.032	0.040	0.082	0.041	0.082
Mean	0.094	0.093	0.072	0.095	0.081	0.163	0.113	0.114	0.131
SEM	0.005	0.007	0.010	0.008	0.008	0.020	0.007	0.008	0.010

Study II. Noradrenaline level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Noradrenaline	NORMOXIA PRE								
($nmol \cdot L^{-1}$)	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1.074	1.148	1.256	1.273	1.133	1.158	1.176	1.074	1.217
S2	1.116	1.326	1.206	1.222	1.201	1.187	1.322	1.133	1.340
S3	0.967	0.934	0.934	0.915	1.103	1.039	1.165	0.953	1.103
S4	1.028	1.336	1.626	1.281	1.165	1.298	1.252	1.298	1.306
S5	1.694	2.724	2.541	1.575	1.586	1.532	2.920	2.676	3.012
S6	1.577	2.596	3.299	3.170	2.755	2.135	1.980	1.813	1.558
S7	1.149	1.233	1.710	1.600	1.575	1.397	1.332	1.639	1.372
S8	1.067	1.025	1.102	1.245	1.231	1.237	1.124	1.245	1.240
Mean	1.209	1.540	1.709	1.535	1.469	1.373	1.534	1.479	1.519
SEM	0.034	0.088	0.102	0.087	0.069	0.043	0.078	0.070	0.077
Noradrenaline	NORMOXIA POST								
($nmol \cdot L^{-1}$)	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	0.953	1.061	1.316	1.088	1.053	1.540	1.137	1.144	1.075
S2	0.969	1.038	1.117	1.090	1.305	1.086	1.104	1.112	1.232
S3	0.708	0.677	0.891	0.913	0.840	0.858	0.943	0.903	1.003
S4	0.940	1.265	1.603	1.298	1.364	1.410	1.121	1.428	1.237
S5	2.976	1.667	1.908	2.060	2.082	3.102	3.265	3.102	3.677
S6	1.011	1.422	1.881	1.618	1.210	1.068	1.050	1.128	0.978
S7	1.715	1.821	1.925	2.111	1.900	2.174	2.042	2.131	2.015
S8	0.811	1.125	0.899	1.063	1.000	1.048	0.955	0.922	0.970
Mean	1.260	1.259	1.443	1.405	1.344	1.536	1.452	1.484	1.523
SEM	0.095	0.046	0.056	0.059	0.054	0.094	0.102	0.095	0.117

Noradrenaline ($nmol \cdot L^{-1}$)				HYPOXIA PRE					
	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1.277	1.193	1.566	1.234	1.326	1.451	1.198	1.141	1.272
S2	0.852	1.036	0.934	1.274	1.082	0.925	1.002	1.125	1.107
S3	0.860	0.990	1.024	0.940	1.026	1.030	0.992	1.005	1.047
S4	1.184	1.057	1.173	1.263	0.930	1.023	0.959	1.294	0.996
S5	1.373	1.698	1.508	1.591	1.673	1.701	1.678	1.713	1.788
S6	0.671	1.319	1.624	2.654	2.077	1.063	1.520	1.009	0.906
S7	1.517	1.246	1.475	1.549	1.438	1.359	1.438	1.437	1.541
S8	1.166	1.433	1.166	1.283	1.100	1.186	1.098	1.216	1.100
Mean	1.113	1.246	1.309	1.473	1.332	1.217	1.236	1.243	1.220
SEM	0.036	0.030	0.033	0.065	0.049	0.033	0.034	0.030	0.038
Noradrenaline ($nmol \cdot L^{-1}$)				HYPOXIA POST					
	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	1.690	1.732	1.862	1.794	1.630	1.550	1.804	1.691	1.626
S2	1.102	1.119	1.352	1.581	1.438	1.430	1.502	1.304	1.270
S3	0.984	1.114	1.214	1.248	1.209	1.239	1.221	1.149	1.324
S4	1.186	1.446	1.642	1.928	1.741	0.959	1.199	1.425	1.485
S5	1.547	1.335	1.669	1.781	1.649	1.830	1.809	2.104	2.043
S6	0.759	1.196	1.353	1.078	1.072	0.986	0.865	0.925	0.865
S7	2.408	2.829	3.109	2.682	2.269	2.092	2.165	2.260	2.309
S8	0.955	1.132	1.206	1.195	1.284	1.298	1.450	1.319	1.130
Mean	1.329	1.488	1.676	1.661	1.536	1.423	1.502	1.522	1.507
SEM	0.067	0.073	0.078	0.065	0.047	0.049	0.052	0.058	0.060

Study II. Leptin level in fasted state before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Leptin ($ng \cdot mL^{-1}$)	NORMOXIA		HYPOXIA	
Subject/Condition	PRE	POST	PRE	POST
S1	8.19	9.95	6.83	9.28
S2	15.58	15.06	11.14	16.26
S3	12.15	12.65	8.65	11.81
S4	21.57	22.71	18.63	13.66
S5	35.89	38.87	30.04	33.56
S6	21.25	29.06	31.77	30.94
S7	25.63	32.75	21.84	24.48
S8	8.55	7.47	7.99	7.92
Mean	18.60	21.07	17.11	18.49
SEM	0.86	1.05	0.91	0.90

Study II. Ghrelin level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

Ghrelin	NORMOXIA PRE								
($pg \cdot mL^{-1}$)	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	879.83	723.03	705.65	776.15	732.65	974.77	806.92	645.44	671.29
S2	834.57	607.00	707.09	674.04	1222.20	1093.80	663.15	662.22	762.29
S3	885.08	979.30	951.38	926.77	912.80	881.83	971.39	937.85	840.27
S4	777.08	702.20	673.49	616.61	616.62	574.97	681.44	627.94	609.36
S5	858.72	878.73	824.81	780.26	817.06	875.60	742.80	864.00	818.74
S6	829.91	794.73	770.43	844.06	843.49	627.41	821.89	691.35	776.25
S7	617.27	633.83	625.38	550.25	535.61	536.45	660.52	504.87	551.42
Mean	811.8	759.8	751.2	738.3	811.5	795.0	764.0	704.8	718.5
SEM	11.6	16.7	13.7	16.5	28.0	27.0	14.1	18.5	13.7
Ghrelin	NORMOXIA POST								
($pg \cdot mL^{-1}$)	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	811.4	841.1	633.4	690.8	522.3	800.8	714.3	638.2	742.3
S2	780.6	747.6	718.1	666.3	740.3	740.1	723.0	506.3	643.6
S3	1049.8	970.1	971.8	911.3	840.0	906.1	836.7	815.3	872.3
S4	804.7	767.8	748.4	678.6	568.8	620.9	708.1	683.2	707.9
S5	884.3	874.2	887.1	885.3	773.1	720.3	775.2	950.7	820.3
S6	831.3	892.8	816.3	806.0	821.1	839.2	875.5	763.7	754.1
S7	601.3	578.6	554.5	554.3	542.3	462.2	579.3	553.8	478.8
Mean	823.3	810.3	761.4	741.8	686.8	727.1	744.6	701.6	717.0
SEM	16.7	15.9	18.0	16.2	17.2	18.5	12.1	19.3	16.1

Ghrelin ($pg \cdot mL^{-1}$)	HYPOXIA PRE								
	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	963.83	1259.00	967.86	835.15	587.54	668.33	590.36	863.76	749.82
S2	855.29	1030.50	882.60	882.12	917.44	918.93	956.87	810.51	779.04
S3	945.23	1047.30	846.43	987.50	914.34	1049.90	912.96	988.40	889.20
S4	892.56	845.57	747.85	827.69	681.22	642.63	935.53	836.72	660.46
S5	804.95	742.44	695.81	730.23	766.28	684.92	771.96	796.36	726.81
S6	764.25	795.09	750.05	886.39	871.40	775.10	705.93	755.96	728.29
S7	597.25	564.56	590.40	509.05	449.44	505.47	594.43	559.99	576.14
Mean	831.9	897.8	783.0	808.3	741.1	749.3	781.1	801.7	730.0
SEM	15.7	28.8	15.7	19.1	22.3	22.9	19.7	16.2	12.1
Ghrelin ($pg \cdot mL^{-1}$)	HYPOXIA POST								
	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	883.6	884.9	494.0	662.8	688.0	595.7	562.3	582.8	595.4
S2	1023.8	961.3	977.1	914.0	884.9	923.0	913.0	848.5	865.4
S3	845.2	981.5	1022.0	953.6	983.4	963.8	858.0	814.6	848.5
S4	865.7	861.1	840.1	673.0	871.4	561.1	892.7	651.6	632.4
S5	879.0	897.4	918.6	874.9	789.5	837.1	989.6	949.6	937.3
S6	818.9	898.1	772.9	768.8	767.7	774.8	768.9	807.3	855.1
S7	759.9	856.0	717.2	636.2	536.7	572.7	618.2	570.1	583.1
Mean	868.0	905.7	820.3	783.3	788.8	746.9	800.4	746.3	759.6
SEM	10.1	6.0	22.5	16.4	18.3	21.3	19.8	18.2	18.7

Study II. PYY level in fasted state and postprandially during meal tolerance test before and after (PRE, POST) the 10-day normobaric normoxic confinement (NORMOXIA) and the 10-day normobaric hypoxic confinement (HYPOXIA).

PYY	NORMOXIA PRE								
($pg \cdot mL^{-1}$)	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	122.39	178.89	149.15	138.83	130.89	132.62	130.20	139.39	124.29
S2	93.10	199.42	159.24	148.66	133.35	136.43	138.32	119.34	126.40
S3	69.16	94.47	92.11	76.36	79.73	71.97	79.59	84.90	81.80
S4	134.57	159.42	207.06	202.51	193.70	185.90	188.62	177.02	205.12
S5	138.01	199.66	206.89	184.95	153.79	155.78	145.70	149.32	147.36
S6	90.46	153.74	176.47	187.05	169.28	148.74	130.54	125.17	139.42
S7	99.12	123.49		129.78	112.09	103.06	88.67	99.24	94.78
S8	100.53	108.07	106.44	90.84	103.96	99.60	101.06	102.49	103.28
Mean	105.9	152.1	156.8	144.9	134.6	129.3	125.3	124.6	127.8
SEM	3.0	5.0	5.6	5.7	4.6	4.5	4.4	3.8	4.8
PYY	NORMOXIA POST								
($pg \cdot mL^{-1}$)	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	105.37	118.98	138.50	111.21	114.19	112.29	111.32	104.32	100.72
S2	88.64	136.11	142.34	141.00	123.99	127.27	117.61	120.57	129.06
S3	72.08	115.48	142.86	154.04	137.51	138.23	151.40	153.63	155.27
S4	142.04	177.47	210.91	182.43	171.66	159.65	144.50	169.66	177.50
S5	119.22	154.48	162.28	163.97	129.72	121.84	109.03	119.01	110.32
S6	65.69	222.70	188.06	165.28	150.14	121.58	113.02	101.60	107.96
S7	92.60	109.95	99.43	103.62	98.74	89.32	92.88	92.27	90.88
S8	91.60	103.54	95.12	105.21	104.34	99.91	99.37	101.03	97.02
Mean	97.2	142.3	147.4	140.8	128.8	121.3	117.4	120.3	121.1
SEM	3.1	5.1	5.0	3.8	3.0	2.7	2.6	3.4	3.8

PYY	HYPOXIA PRE								
(pg·mL^{-1})	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	112.27	171.13	183.64	162.27	137.06	140.19	121.46	135.92	125.76
S2	94.61	109.29	137.09	144.54	124.44	125.21	120.54	138.26	129.23
S3	69.40	98.51	78.35	78.67	78.34	81.47	82.58	86.57	91.58
S4	145.19	161.62	170.45	170.10	162.23	207.85	193.55	201.09	189.16
S5	117.50	130.94	140.02	119.40	127.12	114.74	121.11	119.85	123.80
S6	85.35	220.28	264.36	263.67	237.85	245.68	216.35	217.24	202.98
S7	100.83	103.88	105.57	107.93	93.71	93.83	92.01	93.96	93.29
S8	98.99	112.32	100.73	99.87	102.01	85.11	92.27	101.58	113.57
Mean	103.0	138.5	147.5	143.3	132.8	136.8	130.0	136.8	133.7
SEM	2.8	5.3	7.4	7.2	6.2	7.5	6.1	6.1	5.1
PYY	HYPOXIA POST								
(pg·mL^{-1})	Fasted state	Postprandially							
Subject/Time (min)	0	15	30	45	60	75	90	105	120
S1	77.6	106.4	166.4	176.4	153.0	128.9	112.8	118.7	107.4
S2	83.1	111.7	100.9	110.8	101.5	103.3	89.0	115.2	99.1
S3	69.9	86.9	86.7	79.1	72.1	73.6	74.4	79.6	87.9
S4	102.8	114.9	151.4	147.1	148.9	128.4	144.0	151.1	146.7
S5	124.7	199.7	186.6	153.5	120.6	128.0	113.2	131.6	124.3
S6	79.6	278.3	361.2	262.8	207.5	202.3	186.3	201.7	170.0
S7	96.8	91.5	102.0	97.9	90.8	89.9	86.4	81.4	86.8
S8	100.5	118.7	109.6	113.5	117.4	103.1	100.6	107.7	109.7
Mean	91.9	138.5	158.1	142.6	126.5	119.7	113.3	123.4	116.5
SEM	2.2	8.3	11.2	7.3	5.3	4.9	4.5	5.0	3.6