The Maastricht Study:
The Effect of Nocturnal Hypoxia on Metabolism and Satiety in Obesity

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Introduction:

Americans are gaining weight at an alarming rate. In 1999, 61% of the US population was classified as being overweight (BMI of 25 kg/m^2 or higher) [1], and recent data suggest that this trend still persists [2]. Also, in all regions of Europe obesity, overweight and obesity related clinical problems such as diabetes mellitus, are rising[3]. At least 200 million EU citizens are affected. In many countries now significantly more than half of the population is overweight and up to 30% of adults are clinically obese [4]. Therefore, effective weight loss and/or weight maintenance therapies are urgently needed.

Weight loss is a well-known and well-documented effect of high altitude, hypoxic exposures. An easy method to create a hypoxic environment is the use of a MountainAir^{TM} hypoxic tent system. Since the tent is relatively inexpensive, portable and safe, it is well accepted by competitive athletes to gain hypoxia induced competitive advantages.

The goal of the performed study was to explore the feasibility of using the MountainAir^{TM} hypoxic tent system to stimulate weight loss by nocturnal normobaric-hypoxia in moderately obese subjects. Outcome variables are changes in energy metabolism, thermoregulation, and anorexigenic factors that are indicative for promoting weight loss on the long term.

If exposure to normobaric hypoxia shows an increase in basal metabolic rate and/or anorexigenic factors in the blood, then the MountainAir^{TM} hypoxic tent system can become a non-invasive, portable and relatively inexpensive way to promote weight loss in the moderately obese. Additionally, this study can create a deeper understanding in mechanisms responsible for hypoxia induced weight loss.

Overview of the Study:

Maastricht University, in partnership with Altitude Control Technologies *(formerly known as Colorado Altitude Training)*, performed a study to explore the feasibility of using the MountainAir^{TM} hypoxic tent systems to stimulate weight loss through nocturnal normobaric-hypoxia in moderately obese subjects. Investigators were specifically looking for changes in energy metabolism (metabolic rate), thermoregulation, and anorexigenic factors that are indicative for promoting weight loss in the long term.

Data was collected from 11 subjects during a baseline test, during a 14 day stay in the tent at normoxic conditions, and then finally after a 14-day stint of nocturnal exposure to hypoxic conditions. Subjects were properly acclimatized by following a five-day stair-step process

wherein they increased simulated altitude by 300m per day until reaching 4,200m. Maastricht University doctors directed subjects to attempt to maintain a nocturnal exposure dosage of about 7 hours per night.

This study has been the first known well-controlled nocturnal hypoxia trial in obese subjects with the aim to lose body weight using a commercially available normobaric hypoxic tent system. The results demonstrate weight and fat mass loss as described in several high-altitude hypoxia studies [5,6,7,8]. Most of these published studies have been carried out in healthy, lean persons while this study focuses on the overweight to moderately obese.

The results reveal a significant weight loss of 1.2 kg, fat mass loss of 1.0 kg, and no reduction in fat free mass. In addition, 6-week nocturnal exposure in 6 subjects showed a mean weight loss of 2.3 kg.

Further, the acute exposure to hypoxia did not lead to any sign of heart failure in the obese participants. As far as could be judged from this study, there are no signs that adverse cardiac events are to be expected in this population. In conclusion, there are no contra-indications for the use of hypoxia for longer periods in healthy obese subjects.

Subjects:

After screening 14 healthy, non-smoking individuals enrolled. Three subjects discontinued the study. Two subjects dropped out during the normoxic period. One stopped because of the noise of the air system. The other subject had to be excluded as result of an important mitral regurgitation seen on the normoxic echocardiogram. The subject was aware of having a heart murmur, but after evaluating the screening ECG it was decided not to exclude him. The third subject stopped during the hypoxic period because of sleep disturbances. Baseline characteristics of the remaining 11 subjects are displayed in table 1.

Table 1: Subject Characteristics (n=11)

	Mean ± SD	Range
Age (years)	44 ± 7	35 - 55
Length (meters)	1.80 ± 0.07	1.69 - 1.96
Body Mass (kilograms)	105.1 ± 16.3	85.9 - 140.8
BMI (kg/m²)	32.3 ± 3.1	28.0 - 37.1

Study Design:

The study had a crossover design with a normoxic and a hypoxic period. It consisted of a 3-day familiarization period in the tent followed by a 14-day normoxic and a 19-day hypoxic exposure. Subjects had MountainAir™ hypoxic tent systems installed at their homes and were instructed how to operate the systems. The investigation team was available 24 hours by telephone in case of an emergency or questions. Throughout the familiarization and the normoxic period, subjects were exposed to normal room air (20.9% O_2). During the hypoxic period hypoxic air with an

oxygen partial pressure corresponding to an altitude of 4,200m (13,900ft) above sea level was blown into the tent.

To avoid symptoms of acute mountain sickness, and other altitude related illnesses, subjects were acclimatized in a stair step fashion. Over 5 days subjects followed the so-called 300-meter rule, gradually ascending from about 2,700m (9,000ft) until they reached the desired altitude. In total two subjects did not reach the required 4200m in altitude but fulfilled their nocturnal stay at 3,300m and 4,000m. To exclude any safety issues nocturnal arterial oxygen saturation and heart rate were registered every night. Furthermore, throughout the study subjects completed daily recordings of the stay in the MountainAir™ hypoxic tent, physical activity, and sleepiness. Subjects were instructed to spend at least 7 hours a night in the tent during all conditions.

Study Protocol and Data Collection:

All measurements took place at Maastricht University. The primary study consisted of a 3-day familiarization period (tent open, air units off), a 14-day normoxic period (tent closed, air units pumping fresh air) and a 19-day hypoxic period (tent closed, air units pumping hypoxic air). Four subjects followed a second protocol. They went from the familiarization period directly to the hypoxic period. They then had a wash out period at least 25 days that was followed by the normoxic period.

Prior to baseline measurements participants came to the institute at 21:30hr for baseline blood sampling and thermoregulatory threshold tests, reaction time and vigilance tests. The next two measurement periods (normoxic, hypoxic) started at 22:00hr for blood sampling only. After finishing all tests, blood sampling, and preparations to obtain a complete nocturnal body temperature profile (normoxic and hypoxic conditions only) subjects entered the tent around 23:00hr.

All baseline, normoxic and hypoxic measurements were performed in the early morning, directly after waking up. First BMR measurement (30 minutes) and thermoregulatory thresholds for warm and cold sensation were performed in the tent under baseline, normoxic and hypoxic conditions. Hemodynamic information was acquired by means of echocardiography under normoxic and hypoxic conditions only. Underwater weighing to determine body composition followed. In case of a hypoxic measurement an additional post hypoxia BMR measurement was done approximately 30 minutes after leaving the tent, and approximately 90 minutes after the initial BMR. This measurement was done under normoxic conditions.

Results and Statistical Analysis:

The main findings of this study are a drop in body mass and fat mass during the nocturnal hypoxia of only 2 weeks. In contrast to most other altitude studies body composition has been determined with very acute techniques, combining underwater weighing and deuterium dilution. There was no significant relation between the initial body mass and the change in body mass. The change in body mass was also not related to the time spend in the hypoxic tent. Total Body Water did not change significantly under hypoxic conditions, nor was the hydration of the Fat Free Mass significantly affected by hypoxia compared to baseline. This shows that no

dehydration occurred, in contrast to studies under hypobaric conditions. Results from both protocols are summarized in tables 2 and 3.

The observed body weight loss in combination with a reduction of BMR indicates that energy intake was reduced during the two weeks of nocturnal hypoxia. Therefore, it is likely that the 2-week hypoxia caused a decrease in food intake, possibly by an increase in anorexigenic factors. Hypoxia could possibly deregulate leptin release and thereby diminish appetite. However, our study cannot confirm this statement, since leptin levels did not change significantly after two weeks nocturnal hypoxia. With respect to the anorexigenic factors in future studies it would be informative to include these blood parameters in a long-term study and follow the changes throughout the course of the experiment.

The results demonstrate weight and fat mass loss as described in several high-altitude continuous hypoxia studies. Most of these published studies have been carried out in healthy, lean persons while this study focuses on the overweight to moderately obese. Although the present study had only been performed in 11 subjects, the results reveal a significant weight loss of 1.2 kg, fat mass loss of 1.0 kg, and no reduction in fat free mass. In this study, no significant changes were seen in total body water and hydration of fat free mass, indicating that no dehydration occurred. To be more conclusive about the hypoxia induced weight loss in this study more detailed information on energy intake, appetite suppression and/or energy expenditure during the hypoxic period is needed.

Table 2: Protocol 1 Subjects Only (Baseline to Hypoxia)

Factor	N	Baseline ± SD	Normoxia ± SD	Hypoxia + SD	T-Test Base - Norm	T-Test Norm - Hypox
Body mass (kg)	7	106.7 ± 18.9	106.7 ± 18.3	105.4 ± 18.0	0.94	0.04*
BMI (kg/m²)	7	32.7 ± 3.5	32.7 ± 3.4	32.3 ± 3.5	0.98	0.04*
Fat mass water (kg)	7	38.4 ± 8.2	38.7 ± 8.7	37.6 ± 9.2	0.57	0.06*
Fat mass 3C (kg)	7	37.1 ± 8.5	36.8 ± 8.2	36.3 ± 8.2	0.37	0.11

*Significant

Table 3: Protocol 1 & 2 (assumes baseline as reference for normoxia among protocol 2 subjects)

Factor	N	Normoxia		Hypoxia		T-Test Base - Norm	T-Test Norm-Hypox
		Pre ± SD	Post ± SD	Pre ± SD	Post ± SD		
Body mass (kg)	11	105.1 ± 16.3	104.8 ± 16	105 ± 15.9	103.9 ± 15.8	0.56	0.01*
BMI (kg/m²)	11	32.3 ± 3.1	32.2 ± 3.1	32.2 ± 3.1	31.9 ± 3.2	0.59	0.009*
Fat mass water (kg)	11	35.3 ± 7.4	34.9 ± 7.3	35.0 ± 7.2	34.3 ± 7.4	0.39	0,05*
Fat mass 3C (kg)	11	36.5 ± 7.1	36.2 ± 7.9	36.7 ± 7.6	35.4 ± 8.3	0.62	0.04*

*Significant

Post Study: An Additional 6 Weeks

Four male and 2 female subjects were willing to participate in an expanded 6-week hypoxia study. This trial consisted of 4 male subjects who continued the original 2-week hypoxic exposure with 4 additional weeks. The participating female subjects were partners of 2 male subjects and shared a tent. The subject characteristics are displayed in tables 4 and 5.

Table 4: Subject Characteristics (n=4 males)

	Mean ± SD	Range
Age (years)	45 ± 6	38 - 52
Length (meters)	1.82 ± 0.11	1.69 - 1.96
Body Mass (kilograms)	107.3 ± 22.0	87.4 - 138.7
BMI (kg/m²)	32.2 ± 2.7	30.5 - 36.3

Table 5: Subject Characteristics (n=2 females)

	Mean ± SD	Range
Age (years)	37 ± 5	33 - 40
Length (meters)	1.69 ± 0.02	1.67 - 1.70
Body Mass (kilograms)	94.0 ± 14.5	83.8 - 104.3
BMI (kg/m²)	33.2 ± 5.9	29.0 - 37.4

Friedman non-parametric testing revealed significant changes in body mass and BMI between baseline, 4 week hypoxia and 6 week hypoxia in male subjects. One-tailed paired t-tests are significant ($p<0.05$) for body mass after 4 weeks and for fat free mass for the whole 6 week hypoxic study (table 6). In the female subjects the mean weight loss was 2.7 kg during the 6-week period (table 6) and in the males 2.3 kg (table 7).

Table 6: Body Composition During 6 Week Study (All Subjects)

Factor	Gender	N	Baseline ± SD (Normoxia)	Hypoxia ± SD	Hypoxia ± SD (6 weeks)	Friedman
Body Mass (kg)	m	4	107.3 ± 22.0	106.9 ± 20.5	105.0 ± 19.9	<0.05
BMI (kg/m²)	m	4	32.2 ± 2.7	32.2 ± 2.3	31.6 ± 2.3	<0.05
Body Fat %	m	4	32.8 ± 3.2	32.5 ± 3.7	32.5 ± 2.8	NS
FFM %	m	4	71.9 ± 13.3	72.0 ± 13.0	70.8 ± 12.9	NS
Fat Mass (kg)	m	4	35.4 ± 9.5	34.9 ± 8.8	34.2 ± 7.8	NS
Body Mass (kg)	f	2	94.0 ± 14.5		91.3 ± 16.3	ND

NS - not significant
ND - not determined

Table 7: Weight Loss After 2, 4, and 6 Weeks (Male Subjects)

Time Span	0 - 2 weeks		2 - 4 weeks		0 - 6 weeks	
Factor	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
Weight Loss (kg)	-0.4 ± 1.7	-2.84 - 0.90	-1.9 ± 1.4	-3.59 - -0.26	-2.3 ± 2.3	-5.19 - -0.29

*Although this study is carried out with only 6 subjects the tests are of importance since all subjects significantly lost weight during the six-week nocturnal hypoxia. The results in weight loss are similar to some of the high altitude studies.

Conclusion:

This study has been the first known well-controlled nocturnal hypoxia trial in obese subjects with the aim to lose body weight using a commercially available normobaric hypoxic tent system. The results demonstrate weight and fat mass loss as described in several high altitude, hypoxia studies [5,6,7,8].

Although the present study had only been performed in 11 subjects, the results reveal a significant weight loss of 1.2 kg, fat mass loss of 1.0 kg, and no reduction in fat free mass. In addition, a 6 week nocturnal exposure in 6 subjects showed a mean weight loss of 2.3 kg.

Initial body weight loss under hypobaric, continuous hypoxia has been attributed to a reduction in energy intake, [7,8] increase in energy expenditure, dehydration[6], and intestinal malabsorption[5]. In this study, no significant changes were seen in total body water and hydration of fat free mass, indicating that no dehydration occurred. However, a decrease in energy expenditure during hypoxia was noticed. This indicates that in particular energy intake must have been reduced during the hypoxic period due to a decreased appetite. To be more conclusive about the hypoxia induced weight loss in this study more detailed information on energy intake, appetite suppression and/or energy expenditure during the hypoxic period is needed.

Safety and Health Concerns:

The acute exposure to hypoxia did not lead to any sign of heart failure in the obese participants. As far as could be judged from this study, there are no signs that adverse cardiac events are to be expected in this population. In conclusion, there are no contra-indications for the use of hypoxia for longer periods in healthy obese subjects.

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Editor's Note: MountainAir was formally known as the Colorado Altitude Training (CAT) hypoxic tent.