An Investigation into the Effects of Intermittent Hypoxia on Patients with Essential Hypertension.

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Mr. Grant Kemlo B.Sci. (Clin.Sci.) s3519927

Dr. Jim Kiatos M.B.B.S., Dip. App. Sc.(Naturopathy), Fellow ANTA

Mr. Cameron Gosling B.App.Sci. (HM), Grad Dip (Ex Rehab), M.Sc.

School of Health Science

Victoria University

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This thesis is a preliminary report of a study which is currently ongoing.

Abstract:

Background:

While physiological effects of chronic inhalation of hypoxic air may be detrimental, studies have shown that intermittently breathing hypoxic air can be beneficial. Some of these benefits include increased red blood cell count, haemoglobin concentration, tissue capillarisation, and decreased heart rate. An interesting effect observed following intermittent exposure to hypoxia is a noticeable decrease in blood pressure (BP) in people with essential hypertension. This study aimed to repeat these results using a small, inexpensive, easy-to-use, portable Hypoxicator rather than the bulky, expensive, fixed Hypoxicators used in past studies.

Methods:

This randomised blinded study of 40 people aged 18-65 with diagnosed essential hypertension employed both control and intervention groups. Participants were instructed to take their BP and heart rate (HR) using an electric sphygmomanometer each morning upon waking for 8 weeks. Participants were also instructed to breath through the Hypoxicator for 5 minutes, followed by breathing normal air for five minutes, before returning to the Hypoxicator, totalling one hour each evening, five days a week over the first four weeks.

Results:

To date data has been collected from 6 people (4 intervention; 2 control with mean age 39.2±19.3) for a total of 2 weeks. No effect was observed between intervention or control groups for systolic BP (SBP) ($p=0.944$), diastolic BP (DBP) ($p=0.225$) or HR

(p=0.353). Also no effect was observed within groups between baseline and week 1 or week 2 for SBP (p= 0.285), DBP (p=0.356) or HR (p=0.976)

Conclusion:

At this stage, the researchers do not have sufficient data to gain statistically significant results nor see any trends, as IH (Intermittent Hypoxia) has shown to have no significant impact until at least two weeks of intervention. Further analyses will be undertaken at the completion of data collection.

Introduction:

Inhaling hypoxic air is known to have a number of physiological effects on the human body, some of which are detrimental when the hypoxia is chronic [1]. However during intermittent hypoxia (IH), where hypoxic breathing is only for short periods of time, adaptation / acclimatisation to the low oxygen air can be triggered without the repercussions of chronic hypoxia in the form of altitude sickness [2,3,4]

Many studies [5,6] on people permanently living at high altitude (chronic hypoxia) have shown, a number of differing physiological responses compared to those living at sea-level. Some of these adaptations include, increased red blood cell count, increased haemoglobin concentration, decreased heart rate (HR) and increased tissue capillarisation [7]. These physiological adaptations to the environment occur in humans, over the generations [7], in response to low levels of atmospheric oxygen and reflect the body's attempt to increase the amount of oxygen available to the tissues. However in people who normally live at low altitudes, extended periods of time at high altitudes can lead to altitude sickness if their ascent occurs too quickly [7], and subsequently their ascent to these higher altitudes must be very slow in order for acclimatisation to take place.

An interesting effect observed following intermittent exposure to hypoxia is a noticeable decrease in blood pressure in people with essential hypertension (EH)[2,3,4]. With 20% of the world's population having increased blood pressure (BP)(both essential and non-essential hypertension)[8], from these past studies it seems that IH could play a role in the treatment of hypertension.

Essential hypertension (EH) is defined as a systolic blood pressure consistently over 140 mm Hg and a diastolic pressure consistently over 90 mm Hg with no identifiable cause [9]. Non-essential hypertension is defined as the same measurements above however, it has many different identifiable causes.

The Australian National Health Survey (2001, 1995)* reported that hypertension affects 10% of the entire Australian population (14% of 45-54 y.o. to 42% of those aged 75 years and over). Over a period of time, many complications can arise from EH such as ischaemic heart disease, cerebrovascular accidents, renal and retinal damage, however, there are rarely any symptoms or signs as a direct result of an increased blood pressure per se [10]. Although largely concurring with this data, other researchers add that EH patients may also experience a mild headache, tiredness, nausea, vomiting [9] as well as dizziness and sleep disturbances [3,4]. An important point is that EH patients have major risk of developing myocardial infarction or heart failure as a direct result of their hypertension or associated atheroma [11]. EH adds significantly to society's health costs due to this array of complications. In economic terms EH costs the Australian economy an average of $14.5 million annually (2003/2004) merely for antihypertensive medication [12]. Including health and societal cost benefits, if it can be demonstrated that IH can decrease BP, this may prove to be a safer and more efficient form of anti-hypertensive therapy.

However, some recent studies have shown that IH has not significantly decreased BP in hypertensive patients, and paradoxically it has caused an occasional increase in BP

* Internet site (accessed 25-6-05) http://www.abs.gov.au/Ausstats/abs@.nsf/0/cac1a34167e36be3ca2568a900139364?OpenDocument

[1]. In 2002, a study on 18 male volunteers found that IH did not result in a significant change in BP [13], however this study ran for 14 days, with only a total of 3 or 4 hypoxic sessions lasting 7 mins per day. At the other extreme a 1997 study claimed, “30 days of intermittent hypoxia sufficed for the development of a significant elevation of blood pressure” [1]. However, the rats used in this study were exposed to 7 hours of hypoxic air per day. This has been taken into account in the present study as one of the protocols used states that human exposure to hypoxic therapy should not exceed 1hour per day. Additionally the oxygen concentration of the hypoxic air used in their study was 2-3%, a level found only at extreme altitudes and causing a SaO2 (arterial blood oxyegn saturation) well below 80.

Early Russian studies into the hypotensive effects of IH in patients with EH showed very positive results. Approximately 80% of patients experienced blood pressure reductions of an average of 20 mm Hg [2,3,4]. However, the equipment used to provide hypoxic air in these studies was very large and participants were required to come in to the clinic for their daily hypoxic sessions and consequently this technique has not been seen as practical for use as an anti-hypertensive treatment.

The Altipower Hypoxicator used in this study is a small, lightweight, easy to use device that people can administer in the privacy of their own homes. The Altipower does not require the expertise of a technician, as has been required in the previous studies [2,3,4], and does not require electricity nor does it have any moving / motorised parts. The Altipower works as a rebreather and contains a soda-lime cartridge that absorbs carbon-dioxide from the expired air, thus avoiding hypercapnia (increased carbon dioxide inhalation). The action of breathing through the closed

circuit, lowers the available oxygen to be rebreathed. As such the Altipower Hypoxicator does not require expensive, semi-permeable membranes that have been employed in other, larger, powered Hypoxicators, making it a cheaper and easier way to administer hypoxic air.

There are several proposed mechanisms by which IH reduces blood pressure. One of the physiological effects of IH is the stimulation of erythropoiesis [5], which increases red blood cell (RBC) production, in turn increasing the blood's ability to transport oxygen [14,15,16]. As the main determinants of blood pressure are cardiac output and peripheral vascular resistance [17], if either of these can be lowered, the blood pressure (BP) must subsequently decrease. Improvement in oxygen transportation means less blood needs to circulate to transport the same amount of oxygen to the tissue and subsequently results in a decrease in cardiac output [14].

Intermittent hypoxia is also known to cause alterations in the functions of the autonomic nervous system [15], particularly a systemic decrease in sympathetic tone [2,3,4]. This decrease in sympathetic tone, as seen in acute systemic hypoxia in humans, results in limb vasodilation, also resulting in reduced BP.

Another mechanism by which IH acts to decrease BP is via an increase in vascular endothelial growth factor (VEGF), which is stimulated by the hypoxic tissues [18] and subsequently acts to increase the formation of micro-circulation vessels [2,3,4]. By increasing the micro-circulation, the blood subsequently has more paths by which to travel, allowing greater and easier oxygenation of the tissues and hence decreases the BP.

Also reported to decrease BP are the vasodilatory substances such as adenosine, adenosine monophosphate and E prostaglandins, whose production is stimulated by hypoxia [2,3,4]. These vasodilators act to expand the blood vessels, subsequently decreasing the peripheral vascular resistance, allowing a larger flow of blood to occur and acting to decrease the BP of the individual.

Although many effective pharmaceutical treatments for hypertension exist, the side effects are often significant, with some pharmaceuticals having adverse effects in more than 10% of patients [19]. There are five main groups of anti-hypertensive drugs, four of which have adverse effects that are classified as very common and seen in more than 10% of patients. These anti-hypertensives (and their very common adverse effects) are: Vasodilators (causing tachycardia, palpitations and headache); Beta-adrenergic Blocking Agents (causing fatigue); Diuretics (causing hypokalemia, hyperuricaemia and a rise in blood lipids); and Angiotensin Converting Enzyme Inhibitor (causing a rash) [19]. The fifth group of anti-hypertensives are Calcium Ion Influx Inhibitors who along with the previous four groups have many common adverse reactions (seen in >1% - <10% of patients), however these are too numerous to discuss in detail [19]. Due to the widespread incidence of adverse reactions, it is imperative that the safest and most efficacious form of therapy to reduce blood pressure be sought.

Although IH has been shown in a number of studies to significantly reduce blood pressure via physiological mechanisms that do not result in appreciable negative side effects [2,3,4,20], the technology has hitherto required the use of large and expensive

devices that require a trained technician to operate them in specialised clinics. In this present study the researchers aimed to repeat these results using a small, relatively inexpensive device that participants take home to administer their own hypoxic sessions. The current research aims to explore the efficacy of a small, relatively inexpensive device that makes unsupervised home use a distinct reality. It is clear that further research on the efficacy of a portable IH device, is not only important, but long overdue.

The significance of the present study is that if this portable IH device is found to significantly reduce blood pressure in patients with EH, it will enable people to reduce their blood pressure at home by themselves, either without the need for drugs or with a reduction in the required dosage needed to control their hypertension. Accordingly IH could save both public and private health systems many millions of dollars that would otherwise be spent on anti-hypertensives, in addition to treating the consequences of chronic anti-hypertensive medication [19]. IH may either be used alone, or if necessary, in conjunction with other forms of antihypertensive therapy, without the added danger of drug interactions or side effects. [4]

In this study the researchers aimed: to see whether the Altipower Hypoxicator replicated similar results to the previous Hypoxicators used; to test whether IH significantly decreased BP in patients with diagnosed EH (on medication or not); to see whether effects lasted for one month; and to test whether IH can allow lower medication dosage and still control participants' EH.

Methodology:

Subjects:

The study was designed to include approximately 40 people between the ages of 18 and 65 with the following characteristics; all participants must have diagnosed essential hypertension (a blood pressure of at least 140/90 mm Hg and of unknown cause); may or may not be on medication; and had to be otherwise healthy. Power analysis (Cohen's D) from a previous study by Vorobyev (1994) [4] demonstrated effect sizes of 10.95 for systolic blood pressure, 10.98 for diastolic blood pressure and 3.35 for heart rate. Cohen's Power Tables determination of sample size, using an effect size of 1.4, indicated groups of 20 was sufficient to gain a Power of 99%.

Procedures:

Recruitment / Screening:

Volunteers were recruited via posters, global email and advertisements in newspapers. Once volunteers informed the researchers that they were interested in participating, the researchers screened all volunteers for exclusion criteria.

Volunteers were included in the study only if they satisfied all exclusion criteria (see Table 1). Any participants that had respiratory infections or any respiratory diseases were excluded due to the decreased capacity for pathological lungs to absorb oxygen [21]. Exposing them to further reductions in oxygen concentrations was deemed too risky and they were excluded as participants who had a potential known intolerance to hypoxia [21]. For obvious reasons the researchers excluded anyone who had conditions requiring intensive care or any severe / terminal stage diseases. Pregnancy was an exclusion criterion as a fetus relies on maternal respiration for its oxygen supply and, it has been shown that hypoxic conditions in the mother can have adverse effects on fetal development. Further exclusion criterion were kidney disease [22,23], diabetes [24] and endocrine disorders (especially thyroid related) [23] as all of these can be reasons for the participant's hypertension. The researchers established this list of exclusion criteria in order to obtain a very specific group of participants who were all truly “essential hypertensives” (high blood pressure of unknown cause) and who also would have no foreseeable adverse reactions to the breathing of lower oxygen air. All participants provided written informed consent to participate and the Victoria University Human Research Ethics Committee approved the study. Participants also visited their general practitioner prior to commencing the study and had their doctor sign a separate informed-consent document. This was so the researchers could ensure

that all participants had an informed physician in the event of a decrease in blood pressure, which may have required alteration of the participant's medication.

Randomisation:

Participants were to be separated into two groups: one to be the control group and the other the intervention group. This separation was initially envisaged to be made of randomised matched pairs, based on age, sex and approximate blood pressure, however as the study progressed it became very clear that some participants were technologically or scientifically minded and were quickly able to identify the disabled Hypoxicator. This then necessitated their inclusion into the intervention group. The study was still blinded at this point, as the participants were not in the position to determine whether or not their Hypoxicator had been disabled.

Protocol:

The present study's protocol was adapted from studies of IH undertaken by Vorobyev et al. (1993,1994) [3,4] and by Hellemans (1999) [25]. Both intervention and control groups underwent the protocol described below with the only difference being the IH each group received.

First 4 consecutive weeks:

Each morning, upon waking and while still lying flat in bed, the participants were asked to measure their blood pressure and HR via the supplied electronic sphygmomanometer and to write these details in the record booklet provided. The booklet also included a column for their medication dosage and one for any symptoms

to be filled in at the end of each day (see Table 1). If participants found that their blood pressure was falling then they were advised to discuss any modification in medication type or dosage with their doctor.

Each evening (5 days per week of IH / 2 days off) participants were instructed to use their Hypoxicator. This involved breathing through the Hypoxicator for 5 minutes, followed by breathing normal air for 5 minutes before using the Hypoxicator again. This was then repeated for a total of one hour (6 x 5 min. breathing through Hypoxicator interspersed with 6 x 5 min. breathing normal air). Participants undertook this hypoxic session only once a day, five days a week, for four weeks. Using the Hypoxicator for 5 days a week, allowed participants to have 2 nights off, enabling them to enjoy any social activities and to drink alcohol if they so desired. The researchers felt that this would therefore lead to a greater willingness to adhere to the study design.

All participants were instructed to undertake the hypoxic session in a seated position and to avoid hypoxic intervention for an hour before or after exercise. Participants were asked to undertake their hypoxic session an hour after having dinner, approximately an hour before going to bed, as generally this would be a low activity period and would also avoid any indigestion. Participants were also advised not to drink alcohol during the evening, on days of undertaking IH. These precautions were to avoid any injuries due to transient light-headedness / dizziness that may be experienced during the first 1 or 2 hypoxic sessions. These symptoms are the result of hyperventilation, a natural tendency to over breath, caused by the psychological effects of having to breath through a mask. These transient symptoms were also seen

in previous studies [2,3,4] and consequently the researchers informed the participants of the possibility of these symptoms occurring and to avoid them by breathing normally.

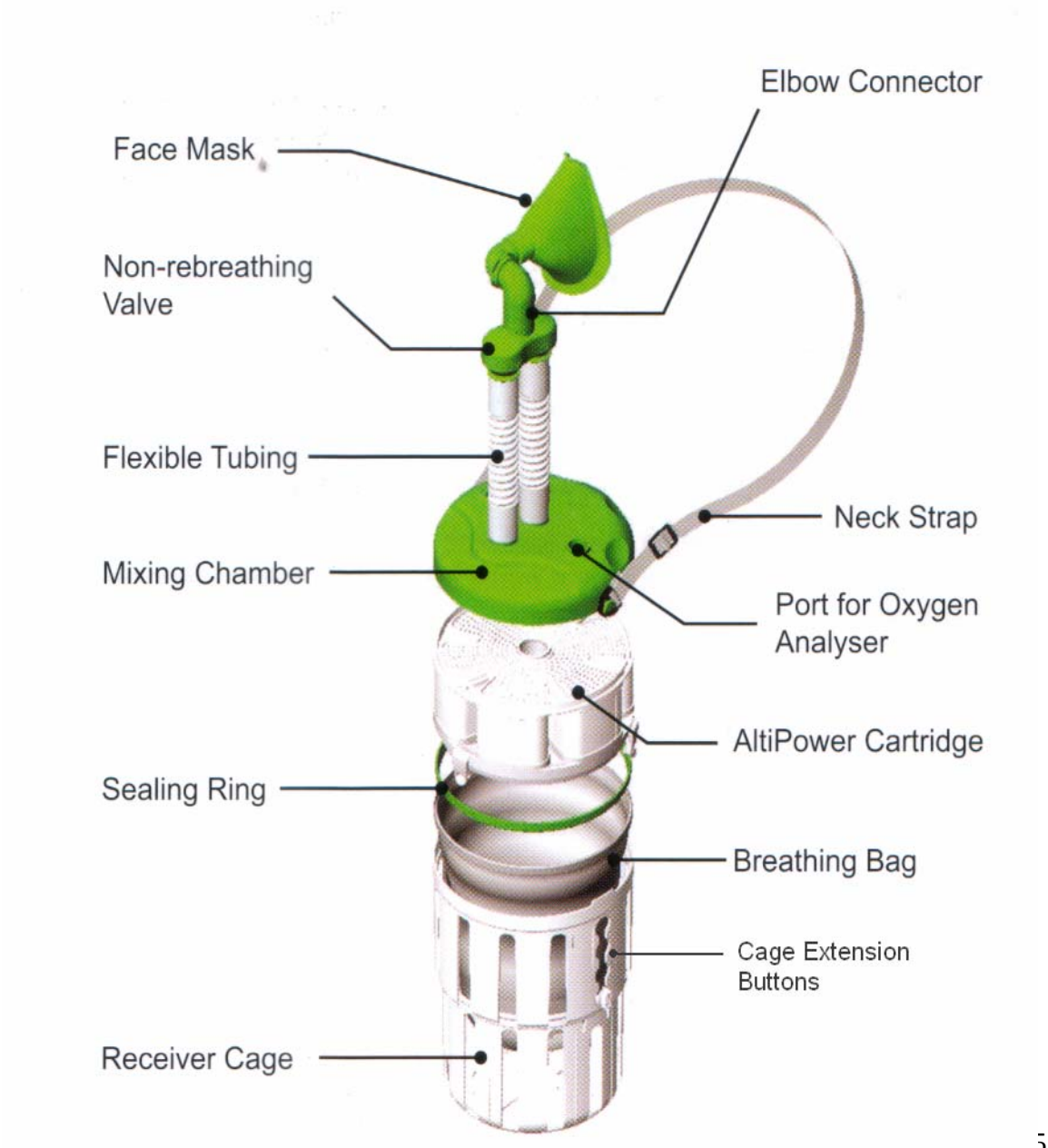
Second 4 consecutive weeks:

Each participant, in both the intervention and control groups, was instructed to measure and record their BP, HR, medication dosage and any symptoms, as per the first 4 weeks. Participants were also instructed not to use their Hypoxicators again. The 4-week follow up was to allow the researchers to investigate whether any changes in the participants' measurements were sustained for at least a month after discontinuing their hypoxic sessions. At the end of the 8 weeks, participants returned their record booklets.

Intervention Group – Materials:

Each participant in the intervention group received, with written and verbal instructions: an Altipower Hypoxicator (see below); a pulse-oximeter; an oxygen analyser; an automatic electric sphygmomanometer; a timer; and a booklet containing a chart of target SpO2 (arterial blood oxygen saturation as measured by a pulse-oximeter) levels to be reached each day (see Table 3) as well as tables to record BP, HR, medication usage/dosage and any symptoms experienced, each day.

Altipower Hypoxicator (exploded view)



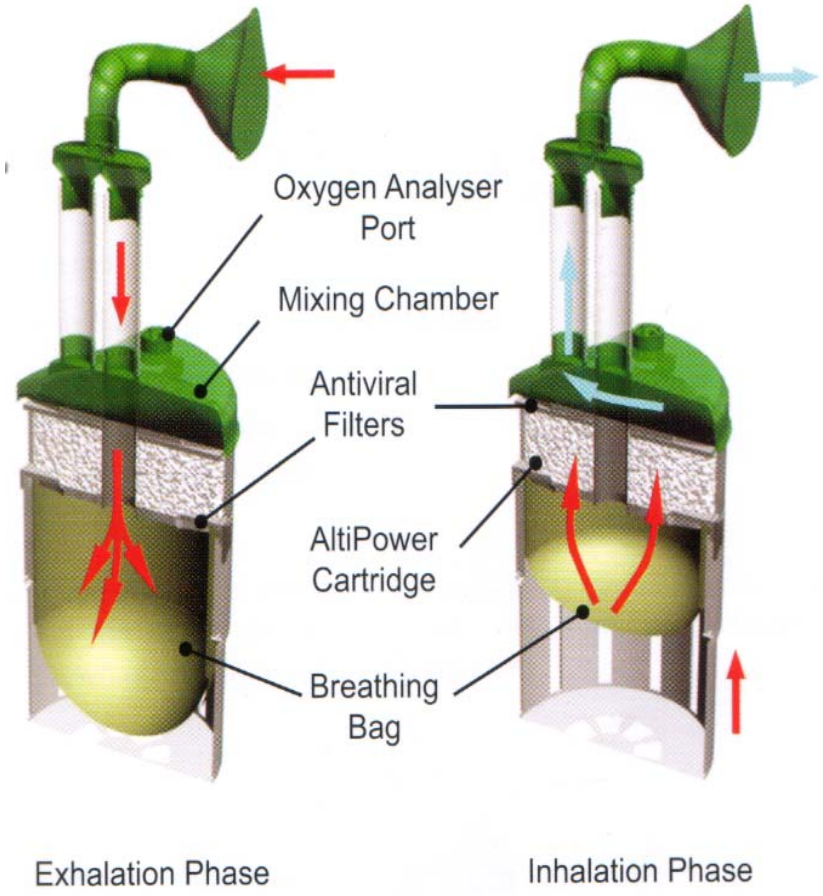
Participants were given a familiarisation and demonstration session on how to use the hypoxicator, pulse-oximeter, oxygen analyser (used to measure the concentration of oxygen within the hypoxicator that the participant will be breathing) and the automatic electric sphygmomanometer.

Intervention Group – IH Protocol:

Participants were instructed to place the pulse-oximeter on their middle finger for the duration of each IH session (1 hour). Participants were instructed to breath through the hypoxicator as per the protocol above, whilst maintaining a close watch on their SpO2 level displayed on their pulse-oximeter. Participants were informed that when their SpO_2 fell below the selected level for that hypoxic session they were to remove their mask and take one breath of normal air before returning the mask to his/her face to resume the hypoxic session. SpO_2 levels fluctuate throughout the session and the participants were instructed to try and maintain their SpO_2 values at the level that was set for that session (see Table 3). The O_2 % participants inhaled through the Hypoxicator was gradually lowered during the 4-week course of hypoxia in a step-wise fashion in accordance with the manufacturer's recommendations. These recommendations were developed by BiomedTech (17 Roberna St, Moorabbin, Victoria), in collaboration with sports medicine physician Dr. John Hellemans (Hi Pro Health Ltd. 55A Ellice St., Mt. Victoria, Wellington, New Zealand). The oxygen inhaled was decreased by using the preset buttons, on the side of the hypoxicator's lower chamber (see Figure 1). This caused a greater quantity of hypoxic air to be re-breathed, hence lowering the available oxygen content. This protocol of slowly lowering the minimum O_2 percentage to be reached each day helped the participant to gradually acclimatise to progressively lower O_2 levels. Although previous research has shown little side effects when going straight to 10% O_2 (SpO2 ~ 84) [2,3,4], this was simply an extra precaution to ensure the safety of the study's volunteers.

Intervention Group – Altipower Hypoxicator:

As seen in the diagram below, air is exhaled through the mask and tube and into the bag. The air in the bag is expired air and as such has a slightly lower oxygen



concentration due to approximately 25% of the available oxygen being absorbed by the lung tissue. On inhalation, the air passes from the bag, via anti-viral filters, through a soda lime filter. This filter acts to extract the carbon dioxide and water vapour prior to inhalation. The air then reaches the top chamber, where it is able to mix with a small quantity of fresh air, let in via a one-way valve on the top of the hypoxicator, before passing up the tube via the non-rebreathing valve and back into the lungs.

Altipower Hypoxicator – Flow Diagram:

Control group - Materials:

Each participant in the control (placebo) group received with instructions: a disabled Altipower Hypoxicator (see below); an automatic electric sphygmomanometer; a timer; and a booklet containing tables to record BP, HR, medication usage/dosage and any symptoms experienced, each day. Participants were given a familiarisation and demonstration session on how to use the hypoxicator and the automatic electric sphygmomanometer.

Disabled Altipower Hypoxicator

The control group's Hypoxicators were disabled by removing the plastic bag from the cage, with the result that participants simply breathed normal air through the filter. As the filter only removes carbon dioxide and water, the participants' oxygen levels remained unchanged. Other changes had to be made to the placebo Hypoxicator: the removal of the oxygen analyser and replacement with a rubber stopper; the removal of the bottom part of the cage (aesthetic reasons to disguise placebo); and the removal of all logos that could be removed (i.e. stickers, neck strap). Participants in the control group received slightly different instructions designed to conceal the fact that their

Hypoxicators were inoperative. If a participant asked, the researchers had to incorrectly inform control participants that the filter removed oxygen from the air, and this was how the device worked. Training was kept to the minimum time possible in order to avoid excess questioning and the instruction manual was a brief, one page document (see Figure 2)

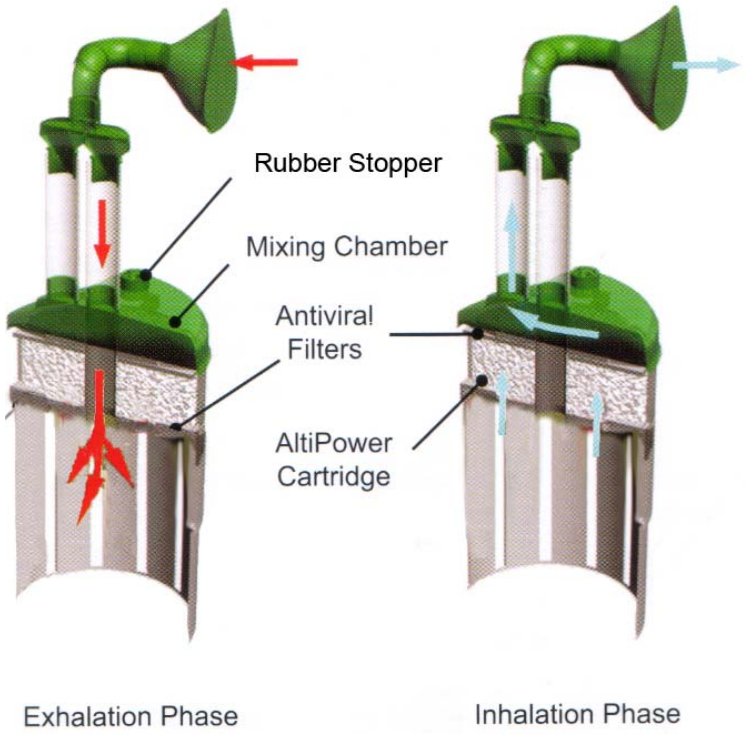
Control Group – IH Protocol:

Participants in the control group were simply informed to breath through the device for 5 minutes, followed by breathing normal air for five minutes, before returning to the Hypoxicator. This process was repeated for a total of one hour.

Control Group – Disabled Altipower Hypoxicator:

As seen in the diagram below, air is exhaled through the mask and tube. This air passes straight out into the atmosphere, as there is nothing to restrict it. On inhalation, normal room air passes via anti-viral filters, through a soda lime filter. This filter acts to extract the carbon dioxide and water vapour prior to inhalation. This filter does not alter the oxygen concentration of the air being inhaled by the control group participants. The air then reaches the top chamber, before passing up the tube via the non-rebreathing valve and back into the lungs.

Disabled Altipower Hypoxicator – Flow Diagram:



As participants in both control and intervention groups used the Hypoxicators, unsupervised in their own homes, the researchers felt it necessary to telephone the participants. These calls were made on day 3, 8 and 18 after the participant's individual starting date and were made to ensure correct usage of the Hypoxicator and sphygmomanometer, and to address any concerns that they may have had. Some of the concerns raised were; transient light-headedness in two participants on their first two days; a couple of broken clips that attach the filter to the bottom cage; and one person had difficulty breathing (later found to be due to her purposefully shallow breathing).

All measurements of blood pressure and HR taken at the Victoria University Osteopathic Clinic (301 Flinders Lane, Melbourne, Victoria), were repeated three times to ensure accuracy in accordance with the guidelines set out by Oparil et al (1989)[10]. Participants were not required to measure their own BP and HR the standard three times each morning as their readings were taken upon waking and prior to getting out of bed, thus eliminating variables such as orthostatic BP changes, exercise, caffeine or “white-coat syndrome,” which may affect the readings.

Statistical Analysis:
Blood pressure (systolic and diastolic) and heart rate data are each reported in terms of the confidence interval around the average measure (i.e.mean ± standard deviation). Three repeated measures ANCOVA's (group (2) x time (8)) were utilised to determine changes in the blood pressure (systolic (SBP) and diastolic (DBP)) and heart rate (HR), with the baseline measure as the covariate. Descriptive statistics and frequency distributions were utilised to track changes in medication dosage and any adverse symptoms that presented over the course of the study. All statistical tests were computed using SPSS version 12 with a significance level set at $p \leq 0.05$ for all statistical procedures.

Once all data is collected, further analyses will be conducted by simple t-test comparison of the baseline data with data from week 4 and again with data from week 8.

The first 3 measurements of SBP, DBP and HR taken by the participant were averaged to give a baseline measurement. These results were used as the small amounts of hypoxia (90 SpO_2) the participants experienced over these three days was insufficient to cause any changes in their BP or HR. Previous research has found that 10 hypoxic sessions are required before any statistically significant changes are seen in BP or HR. SBP, DBP and HR data for the 8 weeks was averaged for each participant for each week.

Results:

At this stage of the process, data has been collected from six participants for their first 14 days. There are four participants (three male, one female) in the intervention group; two (one male and one female) in the control group. Their ages ranged from 20 to 63 (mean age 39.2±19.3) and all participants had been diagnosed with essential hypertension, with 50% using anti-hypertensive medication.

For SBP, DBP and HR, Mauchly's Test of Sphericity was not significant and therefore sphericity was assumed. No effect was observed between intervention or control groups for SBP (p=0.944), DBP (p=0.225) or HR (p=0.353). Also no effect was observed within groups between baseline and week 1 or week 2 for SBP (p= 0.285), DBP (p=0.356) or HR (p=0.976)

For full SPSS statistical results, see Appendices.

Table of Results

		Intervention	***Control***
Baseline	SBP (mm Hg)	133 ± 9	130 ± 19
	DBP (mm Hg)	79 ± 6	71 ± 8
	HR (beats/min)	69 ± 8	74 ± 0
Week 1	SBP (mm Hg)	130 ± 9	128 ± 15
	DBP (mm Hg)	76 ± 6	76 ± 4
	HR (beats/min)	68 ± 10	76 ± 5
Week 2	SBP (mm Hg)	131 ± 15	128 ± 17
	DBP (mm Hg)	76 ± 6	79 ± 4
	HR (beats/min)	68 ± 11	72 ± 2

Discussion:

At baseline, there were no significant differences between the control and intervention groups for SBP, DBP and HR. At this stage of the research with only 6 participants, no statistically significant differences in either BP or HR have been observed in the first two weeks of the trial. The researchers believe this to be for two reasons; the small number of participants thus far and, having only obtained data up to week 2 of the 8-week trial (i.e. 10 hypoxic sessions). This period of time was probably too short for adaptation to take place, especially as in previous studies it was concluded that a significant decrease in blood pressure did not occur until approximately 10 sessions (2 weeks) (6 x 5 minutes of hypoxia per session) had been completed for those suffering with mild hypertension. 12-13 sessions were required for those with moderate to severe hypertension [2,3,4].

Meerson (1991) found that after a course of IH, the subjects' (n=22) BP and HR both lowered, returning the hypertensive patients back within normal BP range. These effects were later confirmed, using larger samples of participants (n=41, 75, 123), with IH showing positive effects of decreasing BP in 70.7%, 84.3% and 80.5% of people respectively. [2,3,4,26] Further studies showed that this decrease in BP was sustained for 6-12 months before rising again after the trial stopped, consequently allowing 79.2% of patients who were previously on drug therapy to stop their anti-HT therapy for up to 12 months [3,4]. The researchers expect that any positive results, seen at the conclusion of this study will be sustained for at least the one-month post-intervention period.

It is expected that similar statistically significant results will be seen at the conclusion of this study, over the eight weeks and between the control and the intervention group. The researchers expect no significant changes in the control group, with changes of up to 30mm Hg decrease in systolic blood pressure in the intervention group, as seen in previous research [2,3,4]. This significant change however, will only be expected in approximately 80% of participants, as previous studies [2,3,4] have demonstrated that this form of treatment has no effect in a small percentage of people. It is unclear from the literature as to why this is the case. One possible explanation is that EH is a multifactorial disease and some sub-groups of EH may be caused by physiological mechanisms that are unaffected by IH. In this study, due to the extensive exclusion criteria leading to a pathologically "clean" participant, the researchers felt that they may have a larger percentage of participants showing significant change.

At this stage of data collection, no participants have yet needed to alter their medication dosage. A previous study demonstrated that IH lowered BP sufficiently enough to allow 79.2% of participants to discontinue their anti-hypertensive medication [4]. It is envisaged that by the end of the study, some participants may have lowered their blood pressure significantly enough that their hypertensive medication may no longer be required, however all decisions regarding medication and dosage are strictly made by the patient and their practitioner.

Safety is a key factor in the use of intermittent hypoxic therapy and many studies have been conducted in which no adverse effects have been observed. Using IH with oxygen concentrations at 9-10%, "side effects are minimal or absent" [25]. No adverse side effects were found when using a hypertensive population at these levels

either [2,3,4]. Some transient side effects observed were light headedness/dizziness, hypo or hyper-ventilation and tachycardia, however these symptoms passed after commencing respiration of normal air [25]. The final result of IH is that it was found to significantly lower blood pressure and that no significant adverse effects were observed. [2,3,4,25]

In this study, no adverse side effects were observed. One participant (intervention) reported feeling some transient dizziness and light-headedness when using the hypoxicator for two of the days. This was, however, found to be due to incorrect use of the equipment. The researchers found it imperative to spend an adequate amount of time with the participants whilst they were training in the use of the hypoxicator and equipment used in the study. In future studies it may be beneficial to visit the participants in their home around day 4 or 5 to ensure that they are doing everything correctly. There were two pulse-oximeters that mal-functioned during the course of the study. As a result the researchers adapted their training protocol to ensure that no mistakes would be made and that any errors with the use of the equipment would be identified quickly.

A further challenge that the researchers faced was the need to blatantly lie to participants in the control group. As the integrity of the study was based on the control group not knowing that their hypoxicators were non-functioning, and mindful that they could learn about them on the internet, it was vital to give the control group as little information as possible in respect to the workings of the machine, including removing all possible refernce to the name of the manufacturer. This was a particularly difficult task and one that could be avoided in future studies by

redesigning the sham hypoxicators to match the working models and by subsequently double blinding the researchers as to who was in the control or intervention group. Another problem was a participant with a “technical” background or science training, as they could quickly work out whether they had an operating hypoxicator or not.

A double blinded study, although technically hard to do, due to the nature of the device being used, would be the most ideal situation in future research. The student researcher, who performed all training of participants, knew precisely which participant was in which group and subsequently had to adapt the training protocol to suit the participant. This was particularly difficult when it came to any participant who was deemed as “technically / scientifically minded” and these participants more often than not, had to be placed into the intervention group as questions that they asked, meant that to much detail had to be provided for inclusion into the control group. As such, the original plan of randomly placing participants into either of the groups based on sex, age and BP was not followed to the extent the researchers desired. Another aspect that could be refined in future research would be to obtain all participants details, and not start the study until the total number of participants required, have been collected. This would thus enable a randomisation process to occur and one could easily separate participants into two groups as matched pairs consistent with the original study design.

In future research it would be wise to take a blood pressure reading upon waking and another upon rising as the cyclical “circadian” rhythm of blood pressure, peaks on arising from bed, and falls during the night upon sleeping [27]. Another enhancement could be made by having participants wear an ambulatory blood pressure monitor for

one day a week, as this would provide many measurements and as such help to remove some of the uncertainty and variability that surrounds blood pressure measurement.

Conclusion:

Previous studies have shown that IH can significantly reduce blood pressure in patients with Essential Hypertension. At this stage of the study, the researchers do not have sufficient data to gain any statistically significant results nor see any trends, as IH has been shown to have no significant impact until at least two weeks of intervention. Further analyses will be undertaken at the completion of data collection.

Disclosure:

Grant Kemlo is a masters student at Victoria University. Dr. Jim Kiatos is a lecturer / supervisor at Victoria University. Cameron Gosling is a lecturer / supervisor at Victoria University. Grant Kemlo reports having met Oleg Basovich through a family member. Oleg Basovich is the owner/inventor of the Altipower Hypoxicator and the BioMedTech Company that manufactures them. Grant Kemlo, Dr. Jim Kiatos and Cameron Gosling report having accepted no personal payment for undertaking this study.

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Table 1:

Exclusion Criteria:

- Any acute somatic disease
- Any respiratory infection
- Known intolerance to hypoxia
- Any chronic disease with symptoms of cardiac decompensation
- Any acute exacerbation of a chronic illness
- Sickle cell anaemia
- Anaemia of any type with a Haemoglobin < 120g/L
- Conditions requiring intensive care
- Severe or terminal stage of a disease
- Any arrhythmias
- Pregnancy
- Heart Disease: previous heart attack, any valve disease, palpitations, chest pain, angina, heart surgery, stents or balloons, peripheral vascular disease, pacemaker, prior epileptic fits, congestive heart failure, congenital and/or acquired heart and vascular defects / diseases
- Respiratory disease: asthma, smoker (more than 10 p/day), emphysema, chronic lung disease, cancer, serious chronic respiratory conditions affecting arterial oxygenation
- Kidney disease
- Diabetes
- Endocrine disorders- thyroid

Adapted from guidelines described by Hellemans et al, 1999 [1] and Strelkov, 1988.[2]

[1] Hellemans, J. Korolev, A. *Intermittent Hypoxic Training: Protocol Guide.* Hi Pro Health Ltd. Auckland, New Zealand. March 1999.
[2] Strelkov RB. *Normobaric Hypoxytherapy. Methodological Recommendations*. Ministry of Public Health. Moscow, 1988

Table 2:

Week 39 IH Research Project Starting Date:_____ Name:_____

IH? = whether or not you are to use the hypoxicator on that day

Symptoms?= if any abnormal feelings are experienced that day, please write down the feeling and at what time it occurred.

Day	IH? Y/N Yes/No	Blood Pressure (mm Hg)	Heart Rate (Beats/min)	Medication / Dosage	Symptoms?
1	Y				
2	Y				
3	Y				
4	Y				
5	Y				
6	N				
7	N				

Table 3:

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Protocol for Hypoxic Sessions

Day No.	Target O_2 %	Cutoff SpO_2 %
1	14	90
2	14	90
3	14	90
4	12	88
5	12	88
6	-	-
7	-	-
8	12	88
9	11	86
10	11	86
11	11	86
12	10	84
13	-	-
14	-	-
15	10	84
16	10	84
17	10	84
18	10	84
19	9	80
20	-	-
21	-	-
22	9	80
23	9	80
24	9	80
25	9	80
26	9	80
27	-	-
28	-	-

***Only go to these lower levels if you experience no unpleasant sensations, such as headache dizziness or nausea. Otherwise use values as per Day 8.**

Adapted from Hellemans, J. Korolev, A. *Intermittent Hypoxic Training: Protocol Guide.* Hi Pro Health Ltd. Auckland, New Zealand. March 1999.

Figure 1:

Altipower Hypoxicator – Exploded View

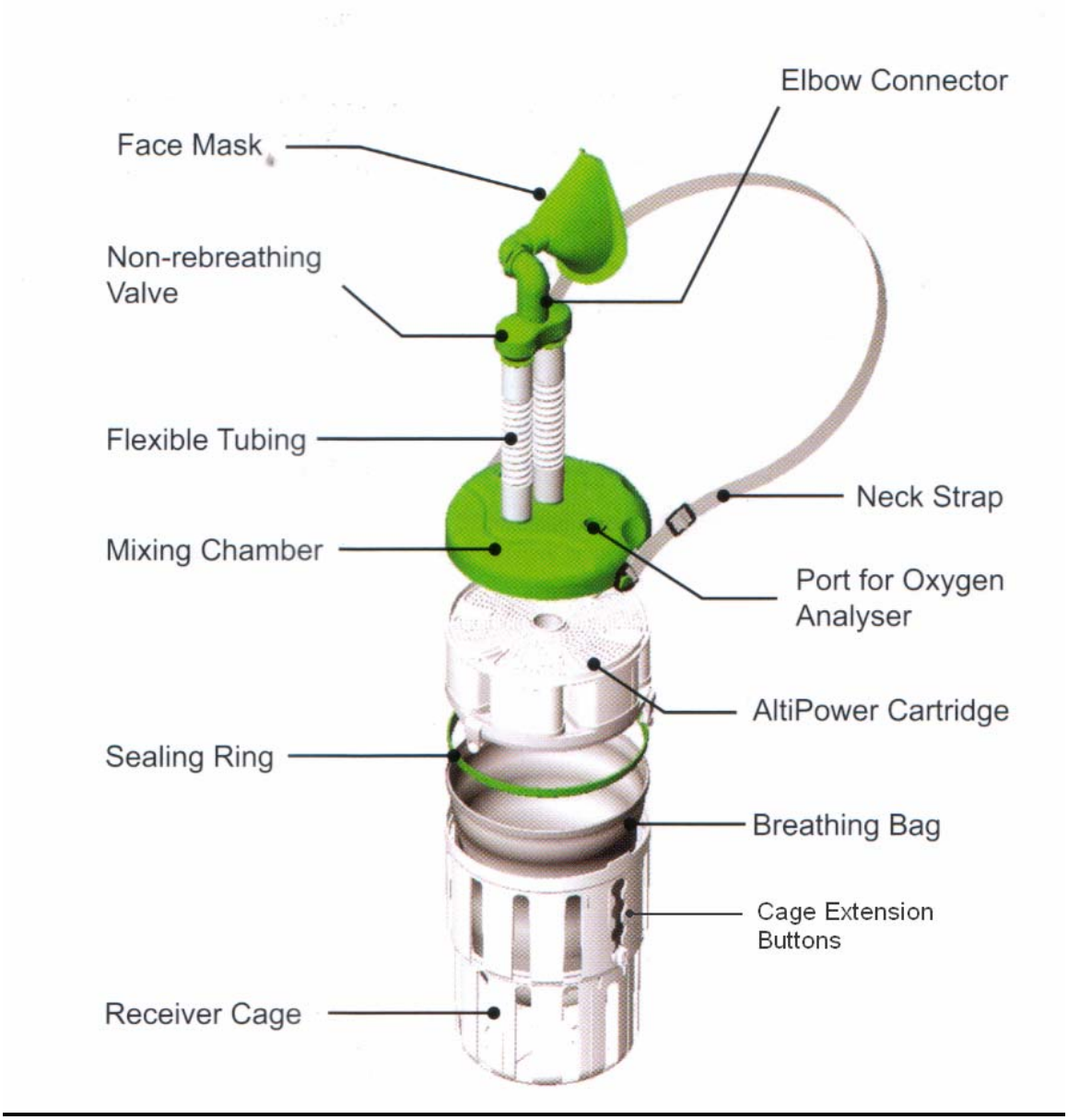

Figure 2:

QUICK GUIDE

TO HYPOXICATOR USAGE

This portable hypoxicator is intended for personal use to conduct Intermittent Hypoxic Training. IHT is a technique for improving ones oxygen metabolism. An IHT course consists of 20 sessions. Each session is typically 60 minutes long with the user breathing reduced oxygen air through a mask for 5 minutes, alternated with a 5 minute rest period of breathing normal air.

1.SAFETY

The hypoxicator is intended for use by generally healthy people. If you are unsure if you should use the device, please consult your healthcare practitioner.

WARNING: *Intermittent Hypoxic Training (IHT) should not be conducted by people with MS (multiple sclerosis), acute febrile illness, terminal illness and grade 2 and 3 COPD (patients with chronic obstructive pulmonary disease who already have low arterial oxygen saturation).*

2.PACKAGE CONTENTS

The hypoxicator consists of a mask and non-rebreathing tube and valve system attached to a mixing chamber. This is cliped onto the hypoxicator cartridge which in turn fits onto a spacer that ensures the free flow of air to the cartridge.

3.PREPARATION

The hypoxicator is supplied fully assembled and ready to use. Simply remove it from the packaging, find a comfortable chair, take a few minutes to relax and then begin breathing through the mask.

4.THE IHT SESSION

Conduct one session per day. Using the 5 minute sand timer provided to monitor the duration of the period, first breath through the mask for 5 minutes, then invert the timer abnd breath normal air for 5 minutes. Alternate breathing through the mask with normal air breathing every 5 minutes for a session duration of one hour. It is important to relax during the session and to breath as you normally would.

5.AFTER THE SESSION

The mixing chamber with tubes and mask should be removed from the cartridge at the end of the session and any moisture in the chamber and tubes should be shaken off. To remove the mixing chamber turn it anti-clockwise to unclip and then lift it off. The mixing chamber should be left off the cartridge between sessions. To refit it, align the arrow on the mixing chamber to the red mark on the cartridge and then turn clockwise to secure it.

Appendices:

Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14
113	Systolic	124	124	118	117	110	117	117	106	116	112	114	115	112	119
	Diastolic	78	76	67	70	70	71	70	67	70	66	66	67	66	76
	BPM	74	79	75	78	74	76	74	75	73	73	69	70	67	77
211	Systolic	134	134	120	121	124	127	127	119	141	121	116	147	129	129
	Diastolic	76	77	76	67	60	71	71	65	78	70	57	87	71	71
	BPM	71	79	73	64	76	73	73	88	88	65	82	73	79	79
517	Systolic	138	137	130	139	131	127	146	122	130	133	143	146	118	128
	Diastolic	81	75	78	79	74	70	77	76	67	80	80	93	72	71
	BPM	53	66	55	58	60	61	54	58	49	48	56	50	58	57
614	Systolic	102	123	125	111	111	124	125	102	127	114	110	118	126	118
	Diastolic	65	83	48	79	65	73	94	64	80	82	76	76	77	77
	BPM	68	74	79	71	82	80	102	72	70	66	77	65	81	80
202	Systolic	153	138	139	128	142	127	143	130	144	154	136	126	137	152
	Diastolic	82	76	73	74	82	82	82	76	76	91	75	74	85	88
	BPM	79	73	69	75	82	65	64	67	76	69	72	63	75	71
617	Systolic	131	137	163	130	130	138	138	154	158	130	130	153	168	158
	Diastolic	93	79	93	73	81	84	84	88	90	81	81	86	99	90
	BPM	67	77	59	73	63	68	68	64	65	63	83	70	68	65

Results Table

Systolic BP Results Table

Subject	Treatment	SBP Baseline	Week 1	Week 2
113	1	122	118	113
211	1	129	127	129
517	1	135	135	131
614	2	117	117	116
202	2	143	139	140
617	1	144	138	150

Diastolic BP Results Table

Subject	Treatment	DBP Baseline	Week 1	Week 2
113	1	74	72	68
211	1	76	71	71
517	1	78	76	77
614	2	65	72	76
202	2	77	79	81
617	1	88	84	88

HR Results Table

Subject	Treatment	HR Baselir	Week 1	Week 2
113	1	76	76	72
211	1	74	73	79
517	1	58	54	54
614	2	74	79	73
202	2	74	72	70
617	1	68	68	68

SPSS 12: Data Analyses

Systolic Blood Pressure

General Linear Model

Warnings

Box's Test of Equality of Covariance Matrices is not computed because there are fewer than two nonsingular cell covariance matrices.

Within-Subjects Factors

Measure: MEASURE_1

time	Dependent Variable
1	VAR00004
2	VAR00005

Between-Subjects Factors

		Value Label	N
Treatment	1.00	Intervention	4
	2.00	Control	2

Descriptive Statistics

	Treatment	Mean	Std. Deviation	N
Week 1	Intervention	129.5000	8.96289	4
	Control	128.0000	15.55635	2
	Total	129.0000	9.85901	6
Week 2	Intervention	130.7500	15.15201	4
	Control	128.0000	16.97056	2
	Total	129.8333	14.04872	6

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
time	Pillai's Trace	.352	1.626[b]	1.000	3.000	.292	.352	1.626	.149
	Wilks' Lambda	.648	1.626[b]	1.000	3.000	.292	.352	1.626	.149
	Hotelling's Tra	.542	1.626[b]	1.000	3.000	.292	.352	1.626	.149
	Roy's Largest	.542	1.626[b]	1.000	3.000	.292	.352	1.626	.149
time * VAR0	Pillai's Trace	.360	1.685[b]	1.000	3.000	.285	.360	1.685	.153
	Wilks' Lambda	.640	1.685[b]	1.000	3.000	.285	.360	1.685	.153
	Hotelling's Tra	.562	1.685[b]	1.000	3.000	.285	.360	1.685	.153
	Roy's Largest	.562	1.685[b]	1.000	3.000	.285	.360	1.685	.153
time * VAR0	Pillai's Trace	.002	.006[b]	1.000	3.000	.944	.002	.006	.050
	Wilks' Lambda	.998	.006[b]	1.000	3.000	.944	.002	.006	.050
	Hotelling's Tra	.002	.006[b]	1.000	3.000	.944	.002	.006	.050
	Roy's Largest	.002	.006[b]	1.000	3.000	.944	.002	.006	.050

a. Computed using alpha = .05

b. Exact statistic

c.
Design: Intercept+VAR00003+VAR00002
Within Subjects Design: time

Mauchly's Test of Sphericity[b]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a] Greenhouse-Geisser	Huynh-Feldt	Lower-bound
time	1.000	.000	0	.	1.000	1.000	1.000

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed depend
proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected t
the Tests of Within-Subjects Effects table.

b.
Design: Intercept+VAR00003+VAR00002
Within Subjects Design: time

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		ype III Sur of Squares	df	ean Squar	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
time	Sphericity Assu	32.070	1	32.070	1.626	.292	.352	1.626	.149
	Greenhouse-G	32.070	1.000	32.070	1.626	.292	.352	1.626	.149
	Huynh-Feldt	32.070	1.000	32.070	1.626	.292	.352	1.626	.149
	Lower-bound	32.070	1.000	32.070	1.626	.292	.352	1.626	.149
time * VAR0	Sphericity Assu	33.222	1	33.222	1.685	.285	.360	1.685	.153
	Greenhouse-G	33.222	1.000	33.222	1.685	.285	.360	1.685	.153
	Huynh-Feldt	33.222	1.000	33.222	1.685	.285	.360	1.685	.153
	Lower-bound	33.222	1.000	33.222	1.685	.285	.360	1.685	.153
time * VAR0	Sphericity Assu	.115	1	.115	.006	.944	.002	.006	.050
	Greenhouse-G	.115	1.000	.115	.006	.944	.002	.006	.050
	Huynh-Feldt	.115	1.000	.115	.006	.944	.002	.006	.050
	Lower-bound	.115	1.000	.115	.006	.944	.002	.006	.050
Error(time)	Sphericity Assu	59.153	3	19.718					
	Greenhouse-G	59.153	3.000	19.718					
	Huynh-Feldt	59.153	3.000	19.718					
	Lower-bound	59.153	3.000	19.718					

a. Computed using alpha = .05

Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	time	ype III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
time	Linea	32.070	1	32.070	1.626	.292	.352	1.626	.149
time * VAR00	Linea	33.222	1	33.222	1.685	.285	.360	1.685	.153
time * VAR00	Linea	.115	1	.115	.006	.944	.002	.006	.050
Error(time)	Linea	59.153	3	19.718					

a. Computed using alpha = .05

Levene's Test of Equality of Error Variances[a]

	F	df1	df2	Sig.
Week 1	3.079	1	4	.154
Week 2	.014	1	4	.910

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

a.

Design: Intercept+VAR00003+VAR00002
Within Subjects Design: time

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Intercept	4.723	1	4.723	.254	.649	.078	.254	.066
VAR0000	1311.571	1	1311.571	70.510	.004	.959	70.510	.999
VAR0000	.634	1	.634	.034	.865	.011	.034	.052
Error	55.804	3	18.601					

a. Computed using alpha = .05

Transformation Coefficients (M Matrix)

Average

Measure: MEASURE_1

Transformed Variable: AVERAGE

Week 1	.707
Week 2	.707

time[a]

Measure: MEASURE_1

	time
Dependent Variable	Linear
Week 1	-.707
Week 2	.707

a. The contrasts for the within subjects factors are:
time: Polynomial contrast

Estimated Marginal Means

1. Grand Mean

Transformation Coefficients (M Matrix)

	Measure
Dependent Variable	MEASURE_1
Week 1	.500
Week 2	.500

Estimates

Measure: MEASURE_1

		95% Confidence Interval	
Mean	Std. Error	Lower Bound	Upper Bound
129.498[a]	1.322	125.293	133.704

a. Covariates appearing in the model are evaluated at the following values: Baseline = 131.6667.

2. Treatment

Transformation Coefficients (M Matrix)

	Measure
Dependent Variable	MEASURE_1
Week 1	.500
Week 2	.500

Estimates

Measure: MEASURE_1

			95% Confidence Interval	
Treatment	Mean	Std. Error	Lower Bound	Upper Bound
Intervention	129.253[a]	1.528	124.389	134.117
Control	129.744[a]	2.166	122.849	136.638

a. Covariates appearing in the model are evaluated at the following values: Baseline = 131.6667.

Diastolic Blood Pressure

General Linear Model

Warnings

Box's Test of Equality of Covariance Matrices is not computed because there are fewer than two nonsingular cell covariance matrices.

Within-Subjects Factors

Measure: MEASURE_1

time	Dependent Variable
1	VAR00004
2	VAR00005

Between-Subjects Factors

		Value Label	N
Treatment	1	Intertvention	4
	2	Control	2

Descriptive Statistics

	Treatment	Mean	Std. Deviation	N
Week 1	Intertvention	75.75	5.909	4
	Control	75.50	4.950	2
	Total	75.67	5.086	6
Week 2	Intertvention	76.00	8.832	4
	Control	78.50	3.536	2
	Total	76.83	7.139	6

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
time	Pillai's Trace	.243	.964[b]	1.000	3.000	.398	.243	.964	.109
	Wilks' Lambda	.757	.964[b]	1.000	3.000	.398	.243	.964	.109
	Hotelling's Tra	.321	.964[b]	1.000	3.000	.398	.243	.964	.109
	Roy's Largest	.321	.964[b]	1.000	3.000	.398	.243	.964	.109
time * VAR0	Pillai's Trace	.283	1.184[b]	1.000	3.000	.356	.283	1.184	.123
	Wilks' Lambda	.717	1.184[b]	1.000	3.000	.356	.283	1.184	.123
	Hotelling's Tra	.395	1.184[b]	1.000	3.000	.356	.283	1.184	.123
	Roy's Largest	.395	1.184[b]	1.000	3.000	.356	.283	1.184	.123
time * VAR0	Pillai's Trace	.436	2.316[b]	1.000	3.000	.225	.436	2.316	.191
	Wilks' Lambda	.564	2.316[b]	1.000	3.000	.225	.436	2.316	.191
	Hotelling's Tra	.772	2.316[b]	1.000	3.000	.225	.436	2.316	.191
	Roy's Largest	.772	2.316[b]	1.000	3.000	.225	.436	2.316	.191

a. Computed using alpha = .05

b. Exact statistic

c.
Design: Intercept+VAR00003+VAR00002
Within Subjects Design: time

Mauchly's Test of Sphericity[b]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
time	1.000	.000	0	.	1.000	1.000	1.000

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b.
Design: Intercept+VAR00003+VAR00002
Within Subjects Design: time

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		ype III Sur of Squares	df	ean Squar	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
time	Sphericity Assu	4.005	1	4.005	.964	.398	.243	.964	.109
	Greenhouse-G	4.005	1.000	4.005	.964	.398	.243	.964	.109
	Huynh-Feldt	4.005	1.000	4.005	.964	.398	.243	.964	.109
	Lower-bound	4.005	1.000	4.005	.964	.398	.243	.964	.109
time * VAR0	Sphericity Assu	4.918	1	4.918	1.184	.356	.283	1.184	.123
	Greenhouse-G	4.918	1.000	4.918	1.184	.356	.283	1.184	.123
	Huynh-Feldt	4.918	1.000	4.918	1.184	.356	.283	1.184	.123
	Lower-bound	4.918	1.000	4.918	1.184	.356	.283	1.184	.123
time * VAR0	Sphericity Assu	9.618	1	9.618	2.316	.225	.436	2.316	.191
	Greenhouse-G	9.618	1.000	9.618	2.316	.225	.436	2.316	.191
	Huynh-Feldt	9.618	1.000	9.618	2.316	.225	.436	2.316	.191
	Lower-bound	9.618	1.000	9.618	2.316	.225	.436	2.316	.191
Error(time)	Sphericity Assu	12.457	3	4.152					
	Greenhouse-G	12.457	3.000	4.152					
	Huynh-Feldt	12.457	3.000	4.152					
	Lower-bound	12.457	3.000	4.152					

a. Computed using alpha = .05

Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	time	ype III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
time	Linea	4.005	1	4.005	.964	.398	.243	.964	.109
time * VAR00	Linea	4.918	1	4.918	1.184	.356	.283	1.184	.123
time * VAR00	Linea	9.618	1	9.618	2.316	.225	.436	2.316	.191
Error(time)	Linea	12.457	3	4.152					

a. Computed using alpha = .05

Levene's Test of Equality of Error Variances[a]

	F	df1	df2	Sig.
Week 1	.011	1	4	.923
Week 2	10.211	1	4	.033

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

a.

Design: Intercept+VAR00003+VAR00002
Within Subjects Design: time

Tests of Between-Subjects Effects

Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Intercept	4.708	1	4.708	.288	.629	.087	.288	.068
VAR0000	309.258	1	309.258	18.889	.022	.863	18.889	.815
VAR0000	128.812	1	128.812	7.868	.068	.724	7.868	.484
Error	49.117	3	16.372					

a. Computed using alpha = .05

Transformation Coefficients (M Matrix)

Average

Measure: MEASURE_1
Transformed Variable: AVERAGE

Week 1	.707
Week 2	.707

time[a]

Measure: MEASURE_1

	time
Dependent Variable	Linear
Week 1	-.707
Week 2	.707

a. The contrasts for the within subjects factors are:
time: Polynomial contrast

Estimated Marginal Means
1. Grand Mean

Transformation Coefficients (M Matrix)

	Measure
Dependent Variable	MEASURE_1
Week 1	.500
Week 2	.500

Estimates

Measure: MEASURE_1

		95% Confidence Interval	
Mean	Std. Error	Lower Bound	Upper Bound
77.647[a]	1.270	73.606	81.688

a. Covariates appearing in the model are evaluated at the following values: Baseline = 76.33.

2. Treatment

Transformation Coefficients (M Matrix)

	Measure
Dependent Variable	MEASURE_1
Week 1	.500
Week 2	.500

Estimates

Measure: MEASURE_1

			95% Confidence Interval	
Treatment	Mean	Std. Error	Lower Bound	Upper Bound
Intertvention	73.457[a]	1.535	68.572	78.342
Control	81.837[a]	2.309	74.488	89.185

a. Covariates appearing in the model are evaluated at the following values: Baseline = 76.33.

Heart Rate

General Linear Model

Warnings

Box's Test of Equality of Covariance Matrices is not computed because there are fewer than two nonsingular cell covariance matrices.

Within-Subjects Factors

Measure: MEASURE_1

time	Dependent Variable
1	VAR00004
2	VAR00005

Between-Subjects Factors

		Value Label	N
Treatment	1	Intervention	4
	2	Control	2

Descriptive Statistics

	Treatment	Mean	Std. Deviation	N
Week 1	Intervention	67.75	9.743	4
	Control	75.50	4.950	2
	Total	70.33	8.824	6
Week 2	Intervention	68.25	10.532	4
	Control	71.50	2.121	2
	Total	69.33	8.383	6

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
time	Pillai's Trace	.004	.012[b]	1.000	3.000	.920	.004	.012	.051
	Wilks' Lambda	.996	.012[b]	1.000	3.000	.920	.004	.012	.051
	Hotelling's Tra	.004	.012[b]	1.000	3.000	.920	.004	.012	.051
	Roy's Largest	.004	.012[b]	1.000	3.000	.920	.004	.012	.051
time * VAR0	Pillai's Trace	.000	.001[b]	1.000	3.000	.976	.000	.001	.050
	Wilks' Lambda	1.000	.001[b]	1.000	3.000	.976	.000	.001	.050
	Hotelling's Tra	.000	.001[b]	1.000	3.000	.976	.000	.001	.050
	Roy's Largest	.000	.001[b]	1.000	3.000	.976	.000	.001	.050
time * VAR0	Pillai's Trace	.286	1.201[b]	1.000	3.000	.353	.286	1.201	.124
	Wilks' Lambda	.714	1.201[b]	1.000	3.000	.353	.286	1.201	.124
	Hotelling's Tra	.400	1.201[b]	1.000	3.000	.353	.286	1.201	.124
	Roy's Largest	.400	1.201[b]	1.000	3.000	.353	.286	1.201	.124

a. Computed using alpha = .05

b. Exact statistic

c.
Design: Intercept+VAR00003+VAR00002
Within Subjects Design: time

Mauchly's Test of Sphericity[b]

Measure: MEASURE_1

Within Subjects Ef	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a] Greenhouse-Geisser	Huynh-Feldt	Lower-bound
time	1.000	.000	0	.	1.000	1.000	1.000

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed depend proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected t the Tests of Within-Subjects Effects table.

b.
Design: Intercept+VAR00003+VAR00002
Within Subjects Design: time

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		ype III Sur of Squares	df	ean Squar	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
time	Sphericity Assu	.117	1	.117	.012	.920	.004	.012	.051
	Greenhouse-G	.117	1.000	.117	.012	.920	.004	.012	.051
	Huynh-Feldt	.117	1.000	.117	.012	.920	.004	.012	.051
	Lower-bound	.117	1.000	.117	.012	.920	.004	.012	.051
time * VAR0	Sphericity Assu	.010	1	.010	.001	.976	.000	.001	.050
	Greenhouse-G	.010	1.000	.010	.001	.976	.000	.001	.050
	Huynh-Feldt	.010	1.000	.010	.001	.976	.000	.001	.050
	Lower-bound	.010	1.000	.010	.001	.976	.000	.001	.050
time * VAR0	Sphericity Assu	11.801	1	11.801	1.201	.353	.286	1.201	.124
	Greenhouse-G	11.801	1.000	11.801	1.201	.353	.286	1.201	.124
	Huynh-Feldt	11.801	1.000	11.801	1.201	.353	.286	1.201	.124
	Lower-bound	11.801	1.000	11.801	1.201	.353	.286	1.201	.124
Error(time)	Sphericity Assu	29.490	3	9.830					
	Greenhouse-G	29.490	3.000	9.830					
	Huynh-Feldt	29.490	3.000	9.830					
	Lower-bound	29.490	3.000	9.830					

a. Computed using alpha = .05

Tests of Within-Subjects Contrasts

Measure: MEASURE_1

Source	time	ype III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
time	Linea	.117	1	.117	.012	.920	.004	.012	.051
time * VAR00	Linea	.010	1	.010	.001	.976	.000	.001	.050
time * VAR00	Linea	11.801	1	11.801	1.201	.353	.286	1.201	.124
Error(time)	Linea	29.490	3	9.830					

a. Computed using alpha = .05

Levene's Test of Equality of Error Variances[a]

	F	df1	df2	Sig.
Week 1	46.150	1	4	.002
Week 2	.671	1	4	.459

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

a.

Design: Intercept+VAR00003+VAR00002
Within Subjects Design: time

Tests of Between-Subjects Effects

Measure: MEASURE_1

Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Intercept	17.919	1	17.919	1.104	.370	.269	1.104	.118
VAR0000	568.327	1	568.327	35.029	.010	.921	35.029	.964
VAR0000	.617	1	.617	.038	.858	.013	.038	.052
Error	48.673	3	16.224					

a. Computed using alpha = .05

Transformation Coefficients (M Matrix)

Average

Measure: MEASURE_1

Transformed Variable: AVERAGE

Week 1	.707
Week 2	.707

time[a]

Measure: MEASURE_1

	time
Dependent Variable	Linear
Week 1	-.707
Week 2	.707

a. The contrasts for the within subjects factors are:
time: Polynomial contrast

Estimated Marginal Means

1. Grand Mean

Transformation Coefficients (M Matrix)

	Measure
Dependent Variable	MEASURE_1
Week 1	.500
Week 2	.500

Estimates

Measure: MEASURE_1

		95% Confidence Interval	
Mean	Std. Error	Lower Bound	Upper Bound
69.747[a]	1.245	65.785	73.708

a. Covariates appearing in the model are evaluated at the following values: Baseline = 70.67.

2. Treatment

Transformation Coefficients (M Matrix)

	Measure
Dependent Variable	MEASURE_1
Week 1	.500
Week 2	.500

Estimates

Measure: MEASURE_1

			95% Confidence Interval	
Treatment	Mean	Std. Error	Lower Bound	Upper Bound
Intervention	70.007[a]	1.464	65.348	74.666
Control	69.486[a]	2.125	62.723	76.249

a. Covariates appearing in the model are evaluated at the following values: Baseline = 70.67.

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1. Shapiro AMJ, Lakey JRT, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000;343:230-8.

2. Goadsby PJ. Pathophysiology of headache. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. Wolff's headache and other head pain. 7th ed. Oxford, England: Oxford University Press, 2001:57-72.

3. Kuczmarski RJ, Ogden CL, Grammer-Strawn LM, et al. CDC growth charts: United States. Advance data from vital and health statistics. No. 314. Hyattsville, Md.: National Center for Health Statistics, 2000. (DHHS publication no. (PHS) 2000-1250 0-0431.)

4. U.S. positions on selected issues at the third negotiating session of the Framework Convention on Tobacco Control. Washington, D.C.: Committee on Government Reform, 2002. (Accessed March 4, 2002, at http://www.house.gov/reform/min/inves_tobacco/index_accord.htm.)

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Generic names should be used. When proprietary brands are used in research, include the brand name and the name of the manufacturer in parentheses after the first mention of the generic name in the Methods section.

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The basis for these guidelines is described in Bailar JC III, Mosteller F. Guidelines for statistical reporting in articles for medical journals: amplifications and explanations. Ann Intern Med 1988;108:266-73.

* Exact methods should be used as extensively as possible in the analysis of categorical data. For analysis of measurements, nonparametric methods should be used to compare groups when the distribution of the dependent variable is not normal.
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results.

* Except when one-sided tests are required by study design, such as in noninferiority trials, all reported P values should be two-sided. In general, P values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places; P values smaller than 0.001 should be reported as P<0.001. Notable exceptions to this policy include P values arising in the application of stopping rules to the analysis of clinical trials and genetic-screening studies.
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INFORMATION TO PARTICIPANTS:

Project Title:

An Investigation into the Effects of Intermittent Hypoxia on Patients with Diagnosed Essential Hypertension.

You are invited to be a part of a study into the effects of Intermittent Hypoxia on high blood pressure. Put simply, Intermittent Hypoxia (IH) is intermittently breathing low oxygen air. The level of oxygen you will be breathing is similar to what you would experience at, higher altitudes. This study aims to test whether IH can decrease blood pressure in patients with diagnosed high blood pressure both short and long term. The study will also test whether IH can result in a lowering of your medication dosage, whilst reducing your high blood pressure.

As a participant you will be given a hypoxicator (a small machine that provides you with air with a lower amount of oxygen), an automatic blood pressure monitor (used to take your blood pressure each morning) and all relevant equipment required for the use of the hypoxicator. There will be a control group (having non-working hypoxicators) and an intervention group (having working hypoxicators). As a participant you will be randomly placed into one of these two groups.

Although the equipment sounds complicated, it is actually very simple to use; to ensure that all of your questions are answered, you will also receive full training on how to use the equipment. Finally, you will be issued with an instruction manual on

how to use your hypoxicator and a booklet to record your blood pressure, heart rate and medication dosage each day.

Each morning upon waking you will be required to take your blood pressure, using the automatic blood pressure device, and record it in the booklet provided. Towards the end of each weekday you will use the hypoxicator for one hour (five minutes on, five minutes off). You will be asked to use the hypoxicator in a seated position and you should avoid using the device for an hour before exercising, or an hour after exercise. You are asked to undergo your hypoxic session between approximately an hour after you have had dinner, and an hour or so prior to going to bed, as generally this will be a quite sedentary period low in activity. Alcohol should not be taken during the evening, including with meals. These requirements are for your safety, to avoid any unwanted side effects such as dizziness.

After the first 4 weeks you will be asked to stop using the hypoxicator and come in to the university to hand in your booklet and to show the researcher that you are testing your blood pressure correctly. You will be asked to continue measuring your blood pressure each morning for a further 4 weeks as well as recording your daily medication requirements your heart rate. After this you will be asked to come once again to the university where you will test your blood pressure one last time and hand in the data you have collected over the past 8 weeks.

If you choose to be a participant in this study it is mandatory that you inform your doctor, and that both you and your doctor read and sign the informed consent sheets attached. As your blood pressure may change during the course of this study it is very important that you inform your doctor of any changes. As a participant, you will have to have at least one visit with a doctor prior to the commencement of this study, a doctor that is well informed of the study will be supplied if required. This doctor will only be charging the Medicare levy and will be available, within reasonable hours, by telephone, should you experience a lowering of your blood pressure or any other abnormal symptoms. This will allow all required, study related, doctor’s visits to be free of charge to you. Should you wish to see your own doctor, rather than the doctor

provided, you are free to do so, however any costs incurred in this process shall be paid for by yourself.

Through the course of this study you may experience some of the normal temporary sensations associated with adjustment to higher altitudes (lower oxygen) such as dizziness, heavier breathing or increased sweating. You are advised that if any of these phenomena occur that you are to remove the mask and take a deep breath or two of normal air before again breathing the low oxygen air. There is also a very small chance of the low oxygen air causing an abnormal heart beat. Should you experience any abnormal feelings such as tightness across the chest or a very rapid or slowed heart beat you are to stop breathing the hypoxic air immediately and breathe normal air until the feelings disappear. You are then to inform your doctor of these sensations before using the hypoxicator further. The principal investigator will telephone you on day 3, 8 and 18 of the study to check on your progress. You should also inform the researchers, on the numbers provided with your kits, if you experience any abnormal sensations or if you are uncertain regarding any aspect of the equipment or the procedure. If at any point you wish to withdraw from the study due to health or any other reasons you are free to do so.

Any queries about your participation in this project may be directed to the researchers If you have any queries or complaints about the way you have been treated, you may contact the Secretary, University Human Research Ethics Committee, Victoria University Of Technology, PO Box 14428MC, Melbourne, 8001 (Telephone no: 03 9919-4710).

Consent Form 1 (Participant Consent)

PARTICIPANT CONSENT FORM

Project Title:

An Investigation into the Effects of Intermittent Hypoxia on Patients with Essential Hypertension.

CERTIFICATION BY PARTICIPANT

I,

(Your Name)

of

(Your Address)

certify that I am at least 18 years old and less than 65 years old and that I am voluntarily giving my consent to participate in the study entitled:

"An Investigation into the Effects of Intermittent Hypoxia on Patients with Essential Hypertension"

being conducted at Victoria University of Technology by:

I certify that the objectives of the study, together with any risks and safeguards associated with the procedures listed hereunder to be carried out in the research, have been fully explained to me by:

, student researcher,

and that I freely consent to participation involving the use on me of these procedures.

The following risks, inconveniences and discomforts have been explained to me:

- All participants will be randomly assigned into a control or intervention group.
- It is required that participants use the hypoxicator to breath low oxygen air for 5 minutes, then normal air for 5 minutes before breathing hypoxic air again. This is repeated for one hour a day, 5 days a week for 4 weeks continuous.

- Possible side effects of breathing air with reduced oxygen, such as dizziness, heavier breathing, temporarily increased heart rate and or increased sweating due to breathing hypoxic air.
- Possible decrease in blood pressure as a result of the hypoxic breathing. A theoretical side effect of this lowering of blood pressure, is a hypotensive (low-pressure) episode, which may lead to feeling faint. For this reason it is advised that the hypoxic air be breathed in the evening after dinner and an hour or so prior to going to bed so as to coincide with a time at which heavy activity is avoided. It is also advised that the hypoxic air not be breathed with an hour either side of playing sport or the equivalent heavy activity load.
- It is required that participants take their blood pressure each morning for 8 weeks. Participants are required to take the blood pressure upon waking and prior to getting out of bed, with the automatic electric sphygmomanometer (supplied).
- In the event of any adverse feelings or a decrease in blood pressure, participants must inform both their doctor and one of the researchers (phone numbers supplied).
- As a participant, the principal investigator will phone you on day 3, 8 and 18 of the study to check on your progress.
- By signing this consent form you agree to let whichever doctor you chose to see for the duration of this study have access to your past medical records as these contain essentially important information in respect to modifications that may be required to your medication.

I certify that I have had the opportunity to have any questions answered and that I understand that I can withdraw from this study at any time and that this withdrawal will not jeopardise me in any way.

I have been informed that the information I provide will be used in published results, but that no identifying details will be made public.

Signed (Participant)

..... **Date: .....**

Any queries about your participation in this project may be directed to the researchers If you have any queries or complaints about the way you have been treated, you may contact the Secretary, University Human Research Ethics Committee, Victoria University Of Technology, PO Box 14428MC, Melbourne, 8001 (Telephone no: 03 9919-4710).

Consent Form 2 (For Doctors)

Dear Doctor,

Your patient has shown an interest in being a participant in our study, which is examining the effects of intermittent hypoxia (IH) on their essential hypertension (EH).

IH is the intermittent breathing of hypoxic air, similar to that experienced at altitudes of 1800 (15% O_2) – 5800m (9% O_2). IH is thought to effect a lowering of blood pressure via a number of mechanisms including:

- increasing vascular endothelial growth factor (VEGF) secretion,
- decreasing heart rate,
- increasing erythropoietin release.

IH has been used for many years by Soviet cosmonauts and by many professional athletes (such as the Brisbane Lions) with the aim of increasing endurance. IH has been tested on people with essential hypertension in several overseas studies. No serious adverse effects have been noted, with most studies reporting no adverse effects *at all*. Patient's on IH may experience slight, temporary, dizziness during their initial use of the apparatus and may also experience an increase in respiration rate, however these symptoms dissipate as soon as they resume breathing normal air.

Your patient will receive an hypoxicator (apparatus which delivers hypoxic air), and any relevant equipment and training necessary for its use. They will also receive an electronic sphygmomanometer. All participants will be fully trained by the researchers in the use of all equipment as well as all safety precautions fully explained.

Participants will be asked to use the machine for 5 minutes, breathing hypoxic air, and then to breathe normal air for 5 minutes before returning to the hypoxic air. This will continue for 1 hour a day, 5 days a week for 4 weeks. Participants will be asked to take their blood pressure each morning upon waking, prior to getting out of bed, with an automatic electric sphygmomanometer (supplied), and record it in the booklet provided. At the end of the 4 week period they will be asked to stop using the hypoxicator but continue to take their daily blood pressure for a further 4 weeks.

Inclusion Criteria:

- Medically diagnosed Essential Hypertension
- May or may not be on anti-hypertensive medication
- Must still currently have a raised blood pressure of 140/90 mm Hg or higher.

Exclusion Criteria:

- Any acute somatic disease
- Any respiratory infection
- Known intolerance to hypoxia
- Any chronic disease with symptoms of cardiac decompensation
- Any acute exacerbation of a chronic illness
- Sickle cell anaemia
- Anaemia of any type with a Haemoglobin < 120g/L
- Conditions requiring intensive care
- Severe or terminal stage of a disease
- Any arrhythmias
- Pregnancy
- Heart Disease: previous heart attack, any valve disease, palpitations, chest pain, angina, heart surgery, stents or balloons, peripheral vascular disease, pacemaker, prior epileptic fits, congestive heart failure, congenital and/or acquired heart and vascular defects / diseases
- Respiratory disease: asthma, smoker (more than 10 p/day), emphysema, chronic lung disease, cancer, serious chronic respiratory conditions affecting arterial oxygenation
- Kidney disease
- Diabetes
- Endocrine disorders- thyroid

As per guidelines set by Hellemans et al, 1999 and Strelkov, 1988. Adapted by

As your patient's blood pressure may lower during the course of this study adjustments to their anti-hypertensive regime may be required. It is asked that you make yourself available for the occasional phone call when this may occur.

I thank you for your time and should you have any further enquiries please contact either

Sincerely,

I have read the above information and do hereby consent to

…….. taking part in this study.
(Your patient's name)

Signed

..... Date: .....
(Participant's General Practitioner)