ReOxy®

ReOxy therapy - a unique patented rehabilitation method (IHHT® **-** Interval Hypoxia Hyperoxia Training) based on usage of positive cell protection molecular mechanisms that are triggered in response to changes in oxygen levels

Re – Revert

Oxy – Oxygen

ReOxy – Revert to normal Oxygen supply

ReOxy® is ...

- a new breathing therapy medical device
- a treatment using reduced and enriched oxygen gas mixtures – **Interval Hypoxic Hyperoxic Treatment** (IHHT®) that leads to more efficient transport and utilization of O2 by body tissue
- a method based on more then 10 years of research and clinical trials
- a non-pharmaceutical treatment with minimal side-effects
- a unique solution for elderly/senior patients and patients with reduced physical abilities

Made in Germany

Ai Mediq S.A. is …

- a global pioneer in implementation of non-pharmacological hypoxia-management treatment method in different spheres of medicine

- the first company in the world which commercialised the idea of using physiological effects of adaptation to short term episodes of hypoxia for clinical treatment purposes

- There were **no known means** to create the state of controlled hypoxia that would be safe for various patient and age groups while being capable of launching intra-cellular adaptation mechanisms.
- There was **no mechanism** to reach the beneficial hypoxia dose and algorithm to calculate such dose for each patient.

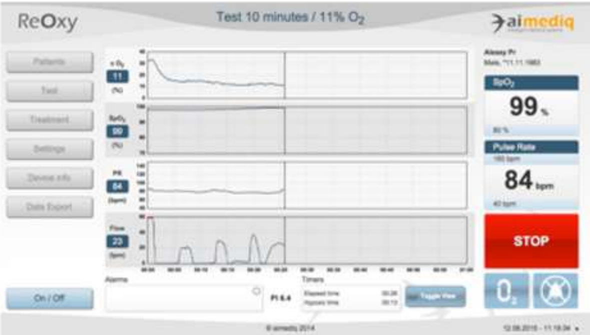
Ai Mediq is the first in the world to develop

- **The way to dose a hypoxic load** based on the bodily response to inhalation of gaseous mixture with reduced oxygen
- The **algorithm** for calculating **individual therapeutic hypoxia dose**
- **The new device ReOxy** to facilitate the interval hypoxic therapy method using biological feedback with automatic calculation of individual treatment hypoxia dose and duration

Product ReOxy®

Personalised Intermittent Hypoxia Hyperoxia treatment

Patient inhales individually prepared gas mixtures **via a facial mask** under flow meter control. The needed oxygen concentration (10-40 %) is calculated using data from built-in pulse oximeter

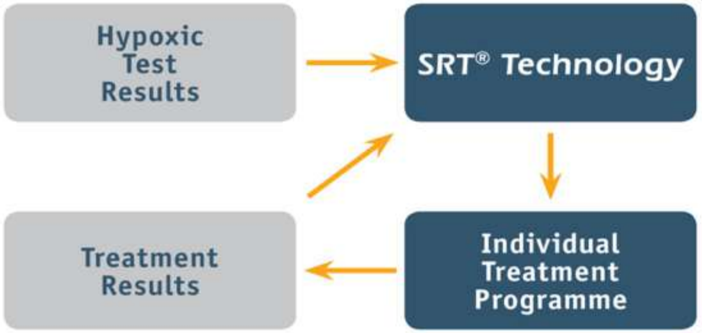


Sensory Multifunctional Unit
Displays key parameters for the ongoing treatment, generates and stores Test and Treatment reports for more over 500 patients.

Patented ambient air separation technology for production of gas mixtures with calculated concentration of medical oxygen and nitrogen

SRT® Technology using advanced software that reads and analyses information from a pulse oximeter to individually adjust the supplied air mixtures in response to changes in vital parameters (Sp02 and HR).

The disruptive innovation lies in the ability to provide personalised treatment for each patient by utilising unique patented Interval Hypoxia Hyperoxia Treatment – IHHT®
under biofeedback control using innovative **SRT®-technology.**



Easy to Operate:

1. Automatic Hypoxic Test:
evaluates zone of maximal therapeutic efficacy and calculates individual treatment parameters

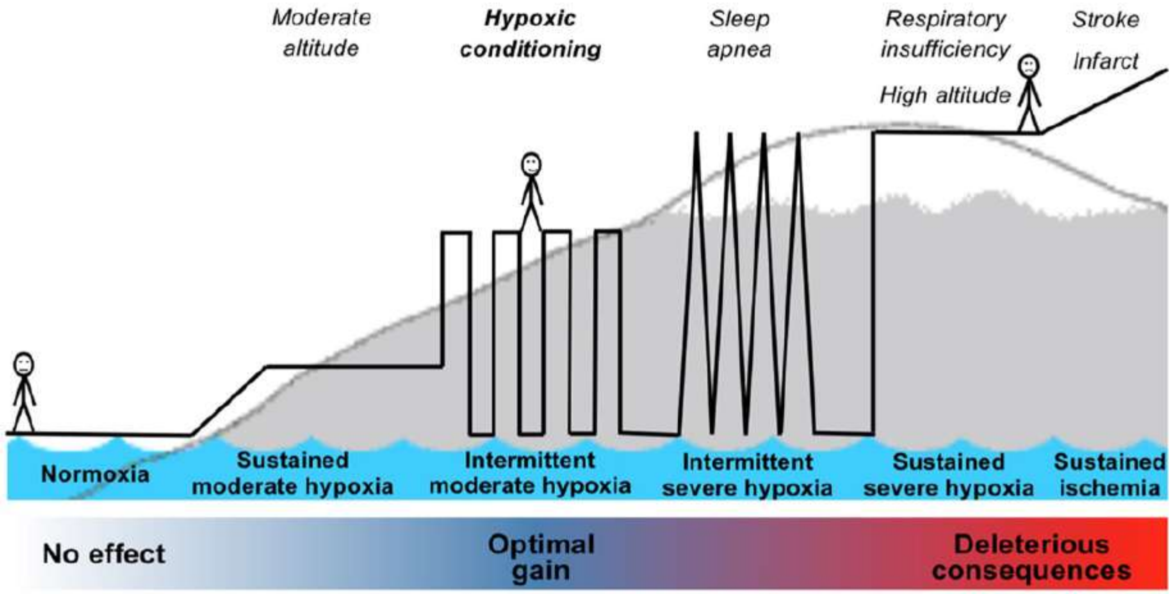
2. Automatic calculations for Individual Treatment:
the patient is sustained in zone of maximal therapeutic efficiency by adjusting the treatment parameters in response to changes in patient’s body;

Treatment results:
calculates and stores treatment parameters for next treatment session.

Therapeutic potential of intermittent hypoxia: a matter of dose

- the development of adaptation to hypoxia is significantly accelerated when the hypoxic effect is divided into several repetitive episodes, alternating with periods of reoxygenation, and its intensity is limited to the level at which there is a rapid recovery during the period of reoxygenation[1]

- to achieve adaptive changes, not only a sufficient hypoxic dose is required, but also a certain pattern of exposure, namely, repeated switching on and off of the stressor



[1] Glazachev O.S., Lyamina N.P., Spirina G.K. Intermittent hypoxic conditioning: experience and potential in cardiac rehabilitation programs. Russian Journal of Cardiology. 2021;26(5):4426. (In Russ.) doi: 10.15829/1560-4071-2021-4426

[2] Verges, Chacaroun et al. 2015 Hypoxic Conditioning as a New Therapeutic Modality. Frontiers in Pediatrics

[3] Therapeutic potential of intermittent hypoxia: a matter of dose. A. Navarrete-Opazo and G.S. Mitchell, PresS. Am J Physiol Regul Integr Comp Physiol 307: R1181–R1197, 2014. doi:10.1152/ajpregu.00208.2014.

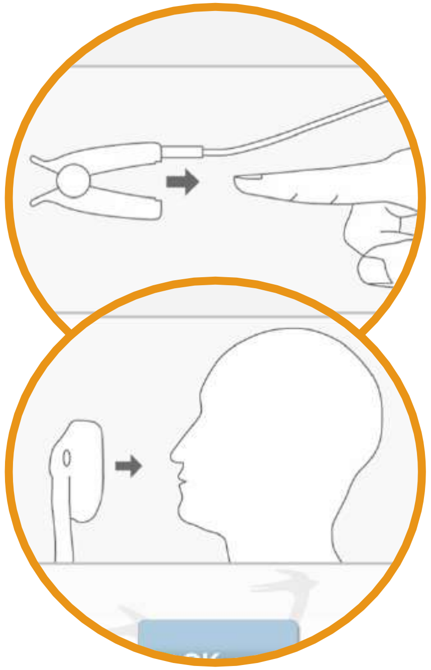
Modest hypoxia (10-16% inspired O2) and low cycle numbers (3–15 episodes per day) lead to beneficial effects without pathology.
“Low dose” IH (modest hypoxia, few episodes) may be a simple, safe, and effective treatment with considerable therapeutic potential for multiple clinical disorders[3].

ReOxy pre - treatment test

Preparation phase

10 sec

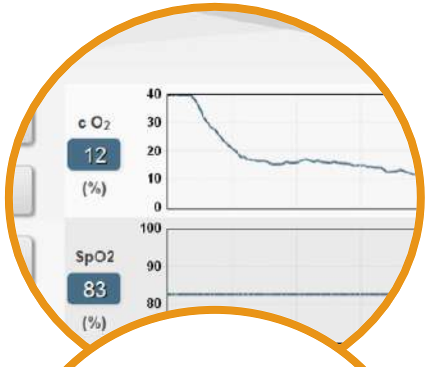
Put on pulsoxymeter sensor and mask



Desaturation phase

Up to 10 min

Patient breathes low oxygen air



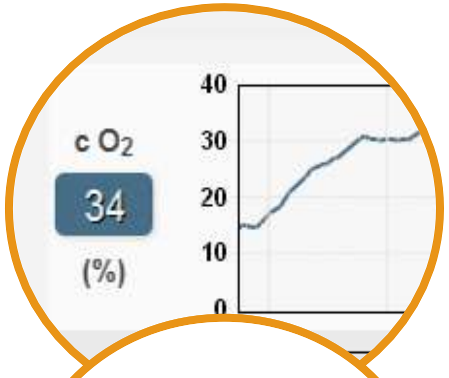
Oxygen in blood ⇩

Heart rate ⇧

Reoxygenation phase

About 1-3 min

Patient breathes high oxygen



Oxygen in blood ⇧

Heart rate ⇩

Easy to use: built-in intelligent software automatically calculates individual procedure parameters with respect to results of the pre-treatment hypoxic test

ReOxy pre - treatment test

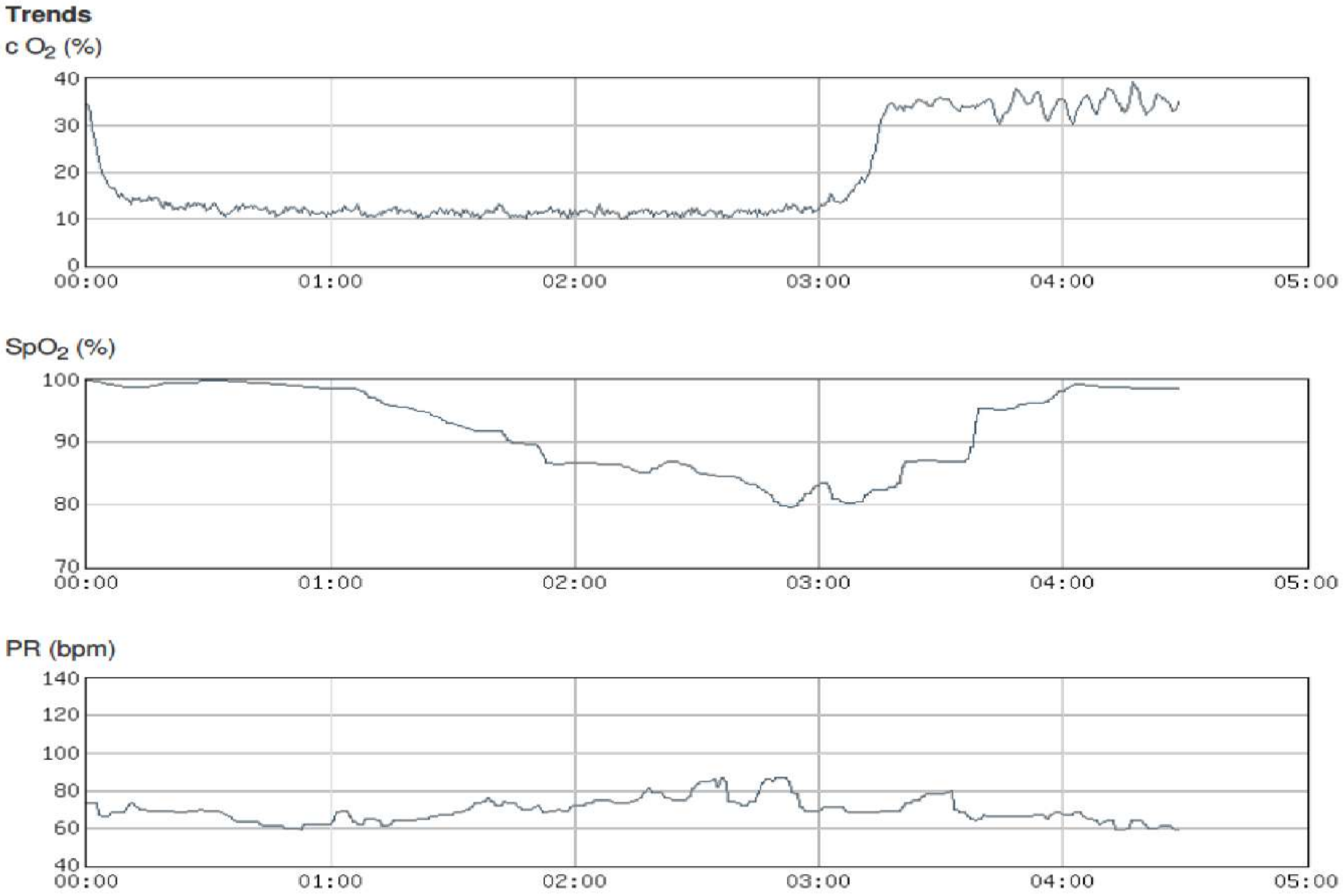
Results

Test results

Total duration	Hypoxic time	Test completition criteria
10:00 min:sec	02:24 min:sec	SpO_2 (84 %)
Min SpO_2	**Max SpO_2**	
82,8 %	99,9 %	
Min SpO_2 achievement time	**SpO_2 restitution time**	**Achievement time / Restitution time**
02:15 min:sec	00:59 min:sec	2,29
Baseline PR	**PR after procedure**	**Min PR**
66 bpm	66 bpm	66 bpm
BP before procedure	**BP after procedure**	**Max PR**
---	---	69 bpm

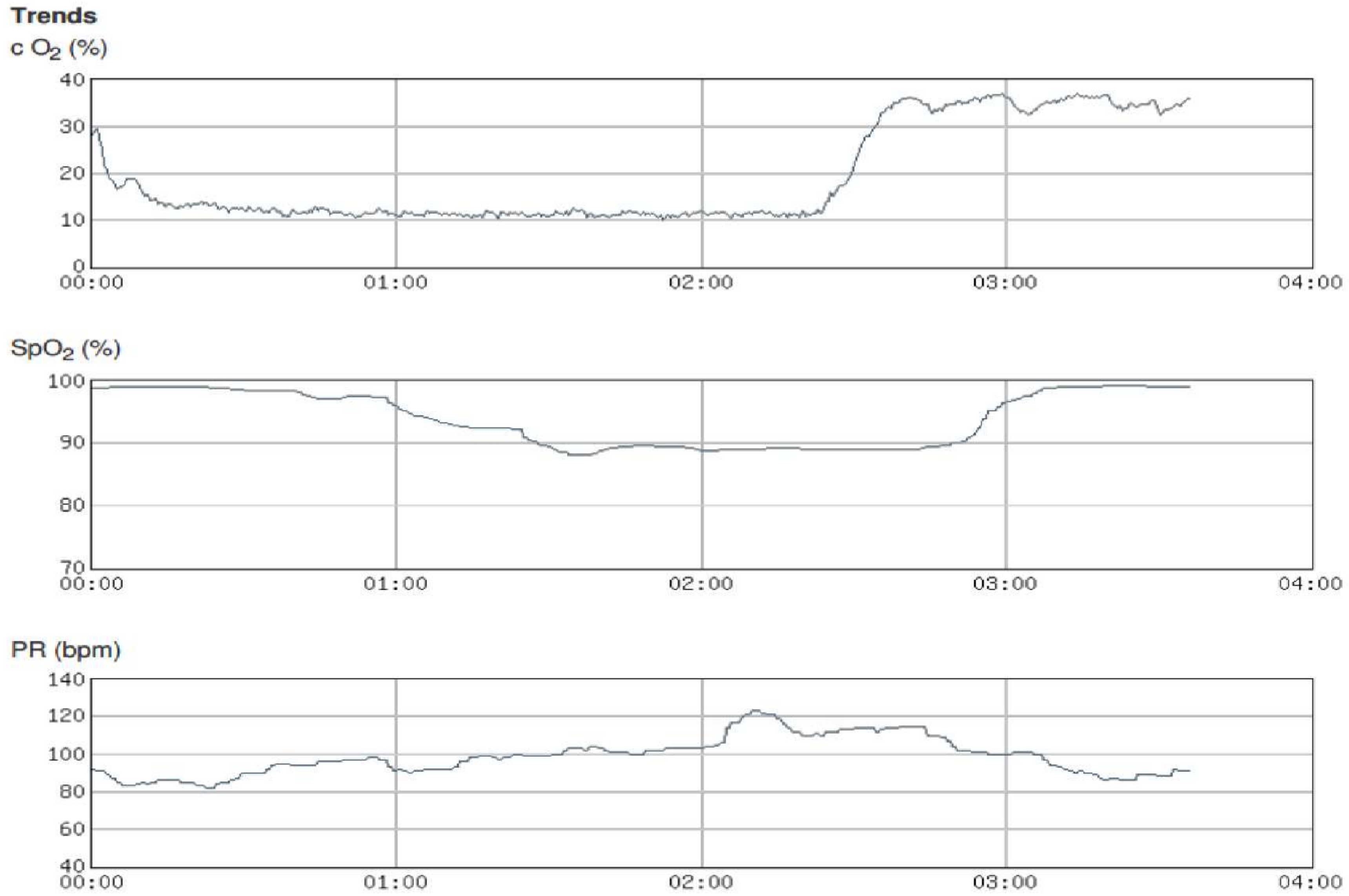
How it works?

ReOxy pre-treatment test, Example 1



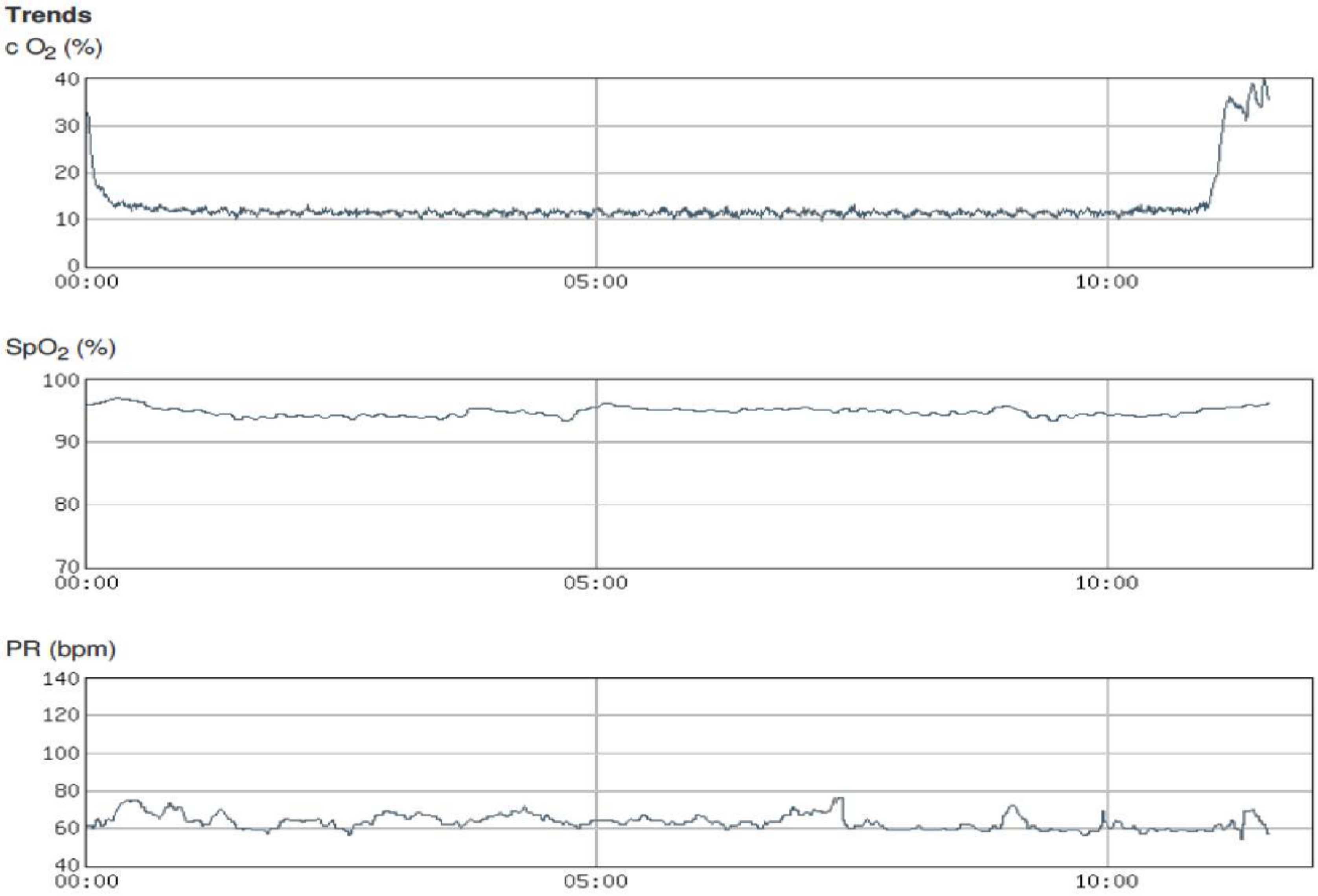
How it works?

ReOxy pre-treatment test, Example 2

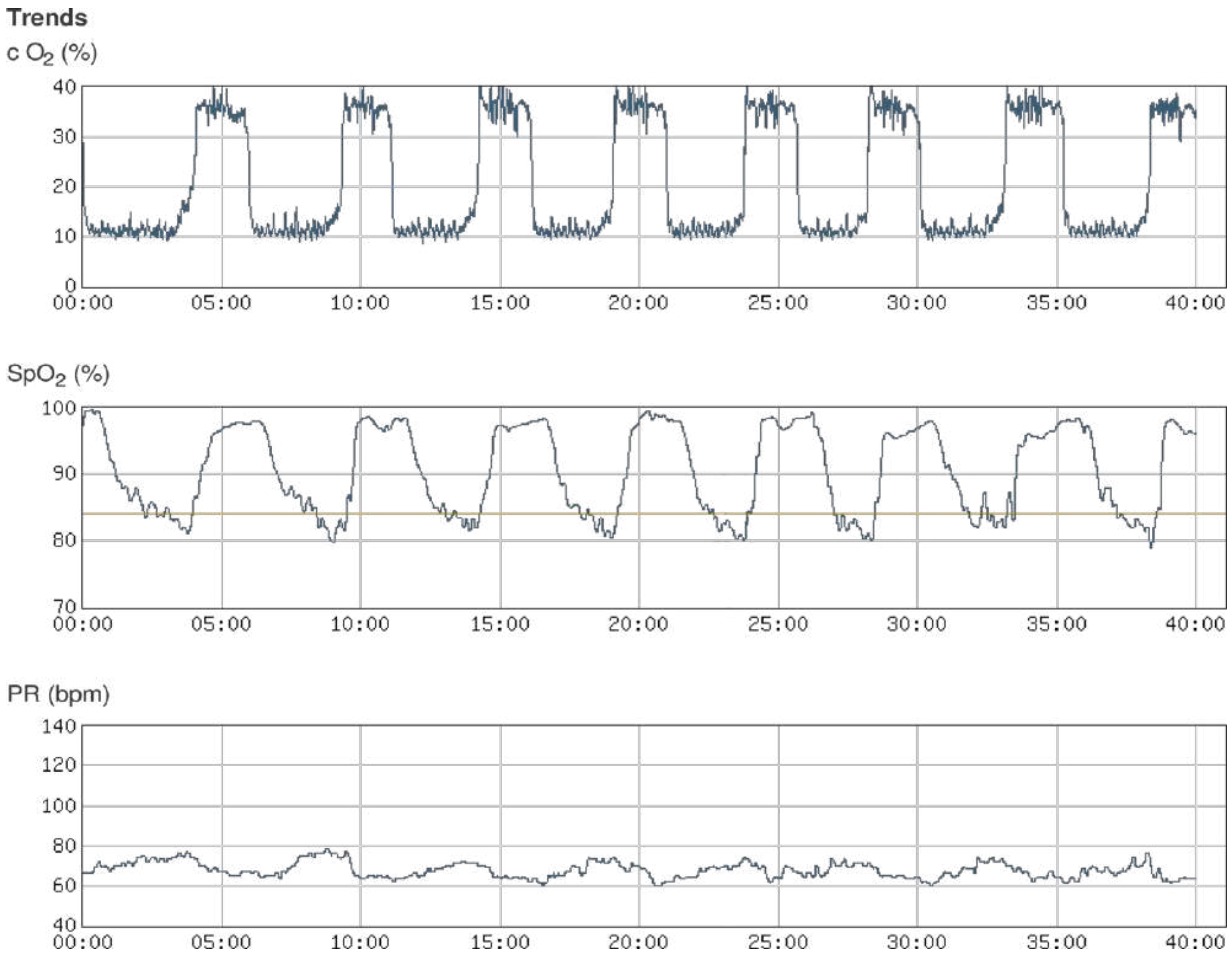


How it works?

ReOxy pre-treatment test, Example 3



ReOxy - treatment



- The blood saturation (SpO2) and heart rate (HR) are individually monitored during every treatment session
- One procedure - 6-8 cycles, total duration time - 30-40 min
- Treatment course - 10-15 treatment sessions (4 -7 sessions per week)

ReOxy - treatment

Rehabilitation

- Cardiac Rehab
- Pulmonary Rehab, incl. COVID 19
- Rehab after Trauma
- Spinal Cord Injuries

Pre-Rehabilitation

- Surgeries preparation/ Preconditioning

ReOxy - breathing therapy medical device
CE-marked and approved by TÜV Rheinland for professional use by healthcare facilities

Elderly

- Dementia
- Improving the quality of life
- Age-related diseases prevention

Healthy people

- Sport/Fitness
- Weight Loss
- Pre-acclimatization

Rehabilitation on 1 sq. m. in any medical facilities

ReOxy - treatment

unique solution for patients with reduced functional capacities

Safety of the ReOxy-therapy

- Continuous PR and SpO2 monitoring
- Multi-stage filtration of gas mixture supplied to patient
- Individual breathing set with anti-bacterial filter

Problems

The main element of rehabilitation is physical exercise, but ...

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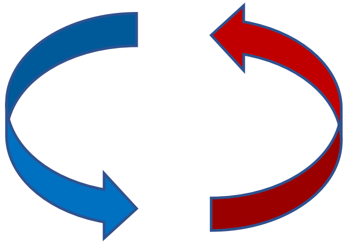


the patient cannot perform them due to reduced functional capabilities (elderly, orthopedic problems, co-morbidities, obesity) ...

It becomes a Catch 22 situation (a vicious circle): in order to improve their quality of life patients have to exercise, but the physical intolerance prevents them from doing so.

New realities - post-COVID syndrome and long-COVID

- Persistence of symptoms or development of new symptoms relating to SARS-CoV-2 infection late in the course of COVID-19 is an increasingly recognised problem facing the globally infected population and its health systems.
- Patients with long-COVID can experience multiple symptoms that involve the lungs and other parts of the body. These may include, but are not limited to, fatigue, weakness, cognitive blunting (‘brain fog’); mental health conditions including mood swings. Some symptoms such as fatigue may be continuous, while others are intermittent.

ReOxy in Cardiac Rehab

Clinical Effects	Patient Benefits
Ischaemic Heart Disease	
Improved tolerance to acute hypoxia/ischaemia episodes	• Lower frequency of angina episodes • Lower frequency of nitrates intake
Reduced damaging effect of acute hypoxia/ischaemia episodes	• Prevention of myocardial infarction
Chronic Heart Failure (in research)	
Improved tolerance to physical load Noncardiac comorbidities management: arterial hypertension, diabetes mellitus, obesity	• Reduced fatigue, breathlessness • Improved quality of life • Improved walking distance • Improved activities of daily living • Lowered blood pressure • Lowered weight
Rehabilitation after Myocardial Infarction and cardiac surgery	
Restored tolerance to physical load	• Substitute for or addition to exercise training • Faster recovery

ReOxy in Cardiac Rehab

Clinical Trials/ Coronary Artery Disease

Cardiovascular responses to Treadmill stress test in patients with CAD before and after the 3-week IHHT program

Parameter	Groupe	Before IHHT	After IHHT	Pre-post, %
Exercise time,s	IHHT	332,5±216,2	446,2 ± 179,1	+34,1 ± 8,6
	Controls	416,1 ± 254,3	423,2 ± 242,1	+ 2,7 ± 3,6
MET (metabolic equivalent)	IHHT	3,73 ± 2,17	4,32 ± 2,03	+15,8 ± 2,9
	Controls	4,43 ± 2,30	4,59 ± 2,09	+5,4 ± 4,9
Angina as a reason to stop running	IHHT	10 (33,4%)	5 (16,7%)	- 50,0
	Controls	5 (50%)	5 (50%)	0,0
Rate pressure product	IHHT	198,9 ± 65,8	168,8 ± 59,9	-15,2 ± 3,8
	Controls	191,5 ± 70,2	185,4 ± 54,5	-3,2 ± 4,6

O Glazachev, YU Pozdnyakov, A Urinskiy ED. Interval normobaric hypoxic hyperoxic training increases exercise tolerance in patients with coronary artery disease. Eur J Prev Cardiol. 2013;20(April).

ReOxy in Cardiac Rehab

Clinical Trial/ Coronary Artery Disease

Cardiopulmonary and hemodynamics variables in the IHHT group before, after IHHT, and at 1-month follow-up

	Before treatments	After Treatments	1-month follow-up
Angina as a reason to stop test, n (%)	12 (44.4%)	6 (22.2%)[1]	3 (11.1%)[2,3]
Exercise time, s, modified Bruce	354 ± 194	383 ± 141	395 ± 130[2]
Exercise time, s, Bruce	280 ± 126	295 ± 79	332 ± 113[2]
VO_{2peak}, mL O_2/min/kg	14.3 ± 4.2	16.1 ± 4.2[1]	15.4 ± 4.5[2]
SBP, mm Hg	151 ± 19	130 ± 13[1]	129 ± 11[2]
DBP, mm Hg	85 ± 11	73 ± 7[1]	75 ± 9[2]
Heart rate at rest, bpm	71.5 ± 11.4	67.7 ± 8.3[1]	66.6 ± 10.0[2]
Heart rate maximum, bpm	122 ± 19	120 ± 14[1]	116 ± 14[2]
Left ventricle ejection fraction, %	58.0 ± 6.2	62.6 ± 5.5[1]	61.6 ± 6.32[2]

Abbreviations: CTRL - control; IHHG - IHHT group; IHHT - Intermittent Hypoxia- Hyperoxia Training.

Cardiopulmonary and hemodynamics variables comparison between the IHHT and CTRL groups after treatments and at 1-month follow-up

	Group	After	1-month follow-up
Angina as a reason to stop test, n (%)	IHHT	6 (22.2%)	3 (11.1%)[1]
	CTRL	4 (21.1%)	6 (31.6%)
Exercise time, s, modified Bruce	IHHG, n =13	383 ± 141[2]	395 ± 130
	CTRL, n = 5	280 ± 92	323 ± 64
Exercise time, s, Bruce	IHHT, n = 14	295 ± 79	332 ± 113
	CTRL, n =14	335 ± 121	355 ± 96
VO_{2peak}, mL O_2/min/kg	IHHT	16.1 ± 4.2	15.4 ± 4.5[1]
	CTRL	16.8 ± 3.9[3]	17.8 ± 4.9
SBP, mm Hg	IHHT	130 ± 13	129 ± 11
	CTRL	131 ± 18	131 ± 17
DBP, mm Hg	IHHT	73 ± 7	75 ± 9
	CTRL	78 ± 10	79 ± 10
Heart rate at rest, bpm	IHHT	67.7 ± 8.3	66.6 ± 10.0
	CTRL	68.9 ± 9.6	66.8 ± 10.2
Heart rate maximum, bpm	IHHT	120 ± 14	116 ± 14
	CTRL	124 ± 13	119 ± 17
Left ventricle ejection fraction %	IHHT	62.6 ± 5.5	61.6 ± 6.3
	CTRL	62.2 ± 7.2	61.3 ± 6.0

Dudnik E et al.. High Alt Med Biol. 2018 Dec;19(4):339-343. doi: 10.1089/ham.2018.0014. Epub 2018 Sep 22.

Preparation to Cardiac Surgeries

Application of intervalic hypoxic-hyperoxic entrainment to prevention of intra- and early postoperational complications in coronary bypass grafting, RCT

I. M. Sechenov First Moscow State Medical University, Moscow, Russia.

80 coronary heart disease patients with direct indications for the operation (myocardial revascularization with bypass grafting) in 5 days before surgery

- Hypoxic group – 4 daily ReOxy treatment (IHHT) sessions (40 min/total hypoxia time – 20-30 min), last session - 12-24 hours before surgeries
- Hypoxic placebo control group – Identical respiratory session (inhaling only normoxic air instead of hypoxic interval respiration)
- RIP (Remote ischaemic preconditioning) group (3 cycles of 10 min of ischaemia were applied to the right lower limb at the level of the upper third of the thigh by inflation of a blood pressure cuff to 200 mm Hg, followed by 10 min reperfusion while the cuff was deflated

Significant complications and adverse reactions

were not observed during IHHT:

- There were no episodes of angina pectoris, syncopal or presyncopal events.
- During the first procedures, some patients had complaints of short-term unexpressed dizziness, which did not require interruption of the procedure.

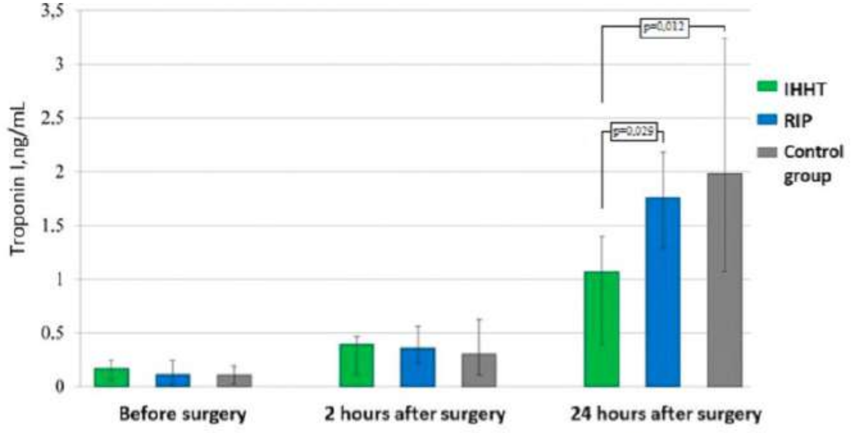
All RIP group participants noted discomfort from mechanical pressure during inflation of the cuff at the thigh, which was the reason for most refusals to participate further.

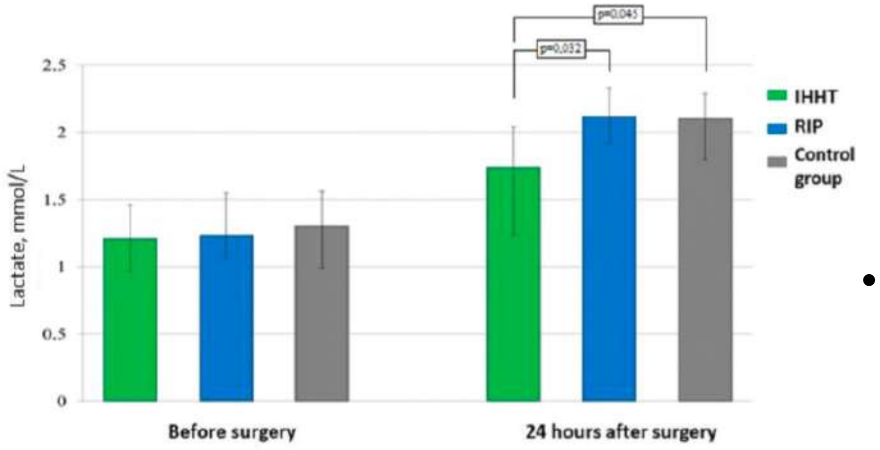
7 patients refused further participation in the study after the first procedure.

Preparation to Cardiac Surgeries

Application of intervalic hypoxic-hyperoxic entrainment to prevention of intra- and early postoperational complications in coronary bypass grafting, RCT

I. M. Sechenov First Moscow State Medical University, Moscow, Russia.





- Troponin dynamics indicate that patients in the IHHT group had less damage of myocardium in the post-operative period and they also showed a lower degree of serum lactate accumulation compared with RIP patients and IHHT-controls.
- The benefits of IHHT compared with RIP may be explained by a stronger systemic effect of hypoxia–hyperoxia on the patient's body compared with local ischaemia of an individual limb.
- The number of complications did not differ significantly between the three groups

Preparation to Thoracic Surgeries

ReOxy treatment in preparation to surgery of the patients with thoracoabdominal oncology process. Pilot study

National Federal Oncology Medical Research Centre, Moscow, Russia.

20 patients with thoracoabdominal oncology process and low physical performance and functional capacity before surgery
Experimental Group: ReOxy treatment (IHHT), 5 sessions/week
Control Group: standart care

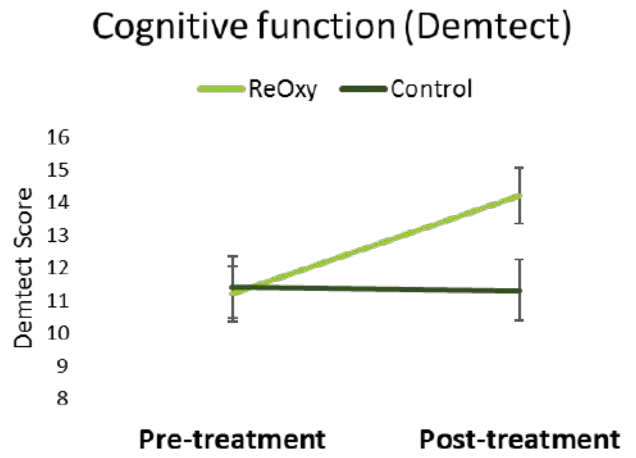
Preliminary results:
Our recent pilot data show that 5 daily ReOxy treatment sessions significant improvement in functional capacity
(significant improvement in 6MWT in the IHHT group)
Current stage – patients' recruitment.

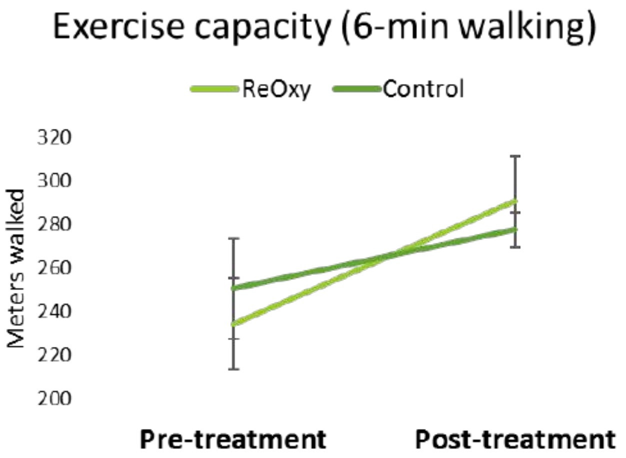
ReOxy in Elderly

Clinical Trials/ Geriatric patients

Changes of test results (DemTect, CDT, 6MWT and NRS) from pre to post for the hypoxic and normoxic groups and correlations between changes of the overall group

Variable	Delta pre–post Hypoxic group	Delta pre–post Normoxic group	*P* value (Mann–Whitney *U* test)
DemTect	+3 (+16.7%)	−0.07 (−0.39%)	**<.001**
CDT	+1.07 (+10.7%)	−0.8 (−8%)	**.03**
6MWT (m)	+56.26 (+24.1%)	+27.13 (+10.8%)	**.02**
NRS	−1.56 (−15.6%)	−1.0 (−10%)	**.07**





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Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 114-122
Alzheimer's & Dementia

Featured Article

Intermittent hypoxic–hyperoxic training on cognitive performance in geriatric patients

Urike Bayer[a], Rudolf Likar[b], Georg Pinter[a], Haro Stettner[c], Susanne Demschar[b], Brigitte Trummer[b], Stefan Neuwersch[b], Oleg Glazachev[d], Martin Burtscher[e,*]

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[b]Department of Anesthesiology and Intensive Care Medicine, Klinikum Klagenfurt, Klagenfurt, Austria
[c]Department of Statistics, Alpen-Adria University Klagenfurt, Klagenfurt, Austria
[d]Research Centre, I.M. Sechenov First Moscow State Medical University, Moscow, Russia
[e]Department of Sport Science, Medical Section, University of Innsbruck, Innsbruck, Austria

Abstract

Introduction: Intermittent hypoxic–hyperoxic training (IHHT) may complement a multimodal training intervention (MTI) for improving cognitive function and exercise tolerance in geriatric patients.

Methods: Thirty-four patients (64–92 years) participated in this randomized controlled trial. Before and after the 5- to 7-week intervention period (MTI + IHHT vs. MTI + ambient air), cognitive function was assessed by the Dementia-Detection Test (DemTect) and the Sunderland Clock-Drawing Test (CDT), and functional exercise capacity by the total distance of the 6-Minute Walk Test (6MWT).

Conclusion:

- IHHT turned out to be easily applicable to and well tolerated by geriatric patients up to 92 years.
- IHHT contributed significantly to improvements in cognitive function and functional exercise capacity in geriatric patients.

Alzheimers Dement (N Y). 2017 Feb 8;3(1):114-122. doi: 10.1016/j.trci.2017.01.002. eCollection 2017 Jan. Intermittent hypoxic-hyperoxic training on cognitive performance in geriatric patients.

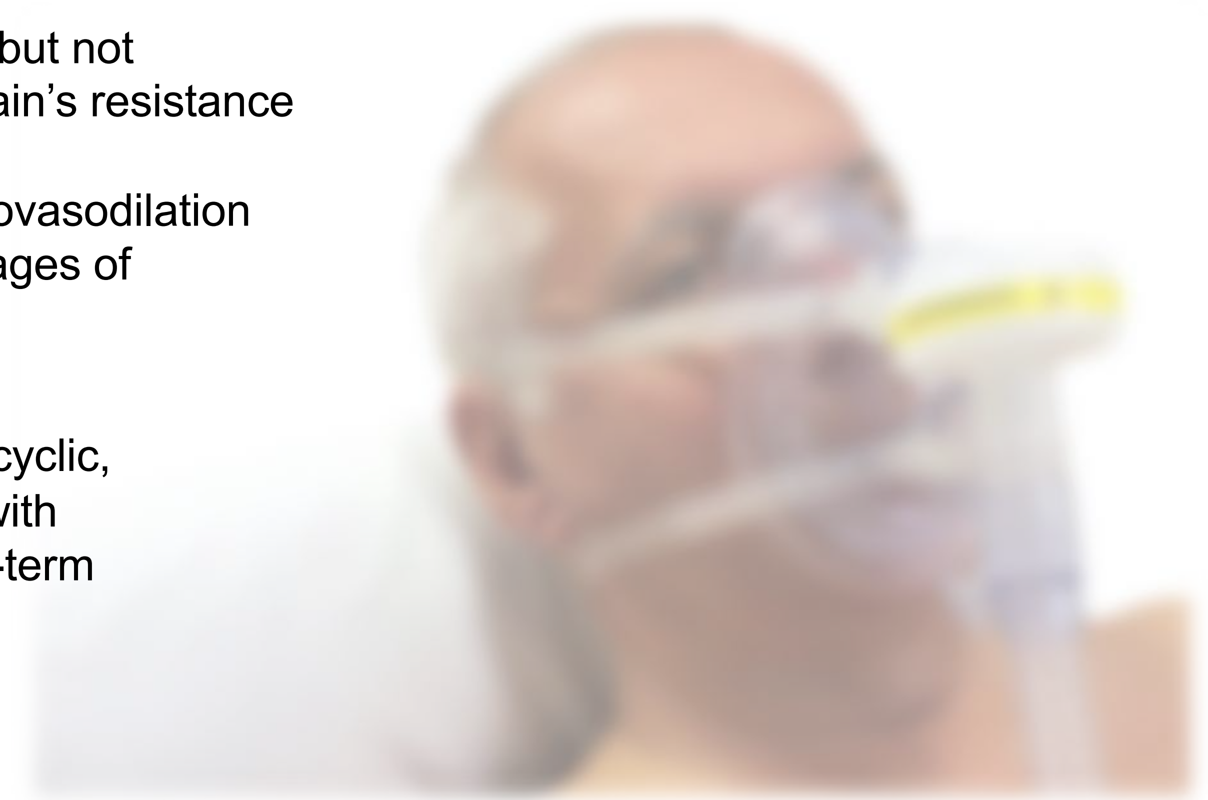
ReOxy in Elderly

Clinical Trials/ Geriatric patients/

Intermittent Hypoxia Training for Treating Mild Cognitive Impairment: A Pilot Study

- The moderate hypoxia, which causes hypoxemia, but not ischemia, evokes adaptations that increase the brain's resistance to hypoxia or ischemia.
- Moreover, IH-induced hypoxemia activates cerebrovasodilation and may improve cognitive function in the early stages of neurodegenerative disease.

Results
The 8-week program of IH exposures eliciting brief, cyclic, moderate hypoxemia was tolerated by older adults with cognitive impairment without advent incidents, short-term memory and concentration ability were improved.



J Alzheimers Dis Other Demen Jan-Dec 2020;35:1533317519896725.
doi: 10.1177/1533317519896725.

ReOxy in Respiratory Rehab (background)

- increase in ventilatory reserves
- improvement of pulmonary microcirculation
- improvement of gas exchange functions of the lungs
- reduction of the oxidative-antioxidant imbalance

- improvement of external respiration functions
- decrease in shortness of breath during physical exertion
- reduction in the frequency of asthma attacks, coughing
- increase physical performance

As early as the nineteenth century there was social wisdom and medical knowledge that respiratory illnesses may improve in the mountains. The sanatoriums for respiratory patients, traditionally, were located at moderate altitude in the mountains

- Dutch Asthma Center, Davos, Clavadel, at 1,686m over the sea level (Switzerland)
- Istituto Pio XII, Misurina, Auronzo at 1,756m (Italy)

Turban and Spengler, 1906 (Davos)

133 among their 143 patients with bronchial asthma that spent their holidays in this mountain the town did not present any acute episode of asthma and that 81% reported persistent improvement of the illness

The triad altitude exposure-hypoxia-acclimatization produces a number of physiological changes, some of which are accepted as related to the improvement of bronchial asthma:

(a) different breathing control pattern (Harrison et al., 2002; Serebrovskaya et al., 2003),

(b) mitochondrial changes that optimize oxygen metabolism during the normal acclimatization process (Levett et al., 2012),

(c) the decrease in free radicals and the associated anti-inflammatory and immunosuppressive effects (Meehan, 1987; Simon et al., 1994; Serebrovskaya et al., 2003; Ohta et al., 2011; Oliver et al., 2013).

Front Physiol. ***2018 Jul*** *9;9:814. Viscor G et al. Physiological and Biological Responses to ShortTerm Intermittent Hypoxia Exposure: from Sports and Mountain Medicine to New Biomedical Applications*

ReOxy in Respiratory Rehab

Clinical Trials/ Pulmonary Diseases

Intermittent hypoxia increases exercise tolerance in patients at risk for or with mild COPD

Table 3
Lung function, resting cardiorespiratory and blood data before and after the 3-week breathing program.

	Hypoxia group ($n = 9$)		Control group ($n = 9$)		ANOVA *P*-value
	Pre	Post	Pre	Post	
FVC (l)	3.53 (0.90)	3.57 (0.95)	3.50 (0.77)	3.49 (0.73)	0.43
FEV_1 (l)	2.54 (0.62)	2.67 (0.60)[a]	2.32 (0.56)	2.28 (0.53)	*0.001*
FEV_1/FVC (l)	72.3 (5.7)	75.7 (5.2)[a]	66.2 (4.4)	65.1 (4.5)	*0.01*
DLCO (% pred)	64.4 (19.2)	67.8 (16.7)	71.2 (17.3)	69.0 (15.3)	*0.02*
Heart rate (bpm)	77.2 (12.6)	75.2 (11.3)	71.2 (17.3)	75.4 (13.1)	0.30
Systolic blood pressure (mmHg)	137.0 (11.1)	120.9 (10.3)[a]	141.9 (22.8)	120.0 (11.2)[a]	0.40
Diastolic blood pressure (mmHg)	88.4 (11.7)	81.1 (7.0)[a]	85.4 (13.4)	77.8 (9.4)[a]	0.66
Arterial oxygen saturation (%)	96.6 (0.7)	97.0 (0.9)	97.2 (0.7)	96.7 (0.7)[a]	*0.004*
Haemoglobin (g/dl)	14.6 (0.8)	14.5 (1.0)	15.1 (1.0)	14.9 (1.1)	0.79
Hematocrit (%)	43.4 (3.2)	42.6 (3.9)	44.0 (2.8)	43.6 (3.5)	0.76
Total haemoglobin mass (g)	843.1 (143)	874.8 (138)[a]	798.4 (157)	798.8 (150)	*0.04*
Plasma volume (ml)	3809 (523)	4034 (509)[a]	3528 (695)	3557 (593)	0.18
Total cholesterol (mg/dl)	199.6 (31.2)	190.9 (23.8)	202.3 (46.6)	191.1 (46.8)	0.82
Triglycerids (mg/dl)	167.2 (99.0)	141.4 (73.8)	165.0 (50.1)	201.0 (63.2)[a]	*0.04*

Data are means (SD).
Abbreviations: Forced expiratory vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), lung diffusion capacity for carbon monoxide (DLCO).
[a] Denotes significant changes within groups.

M. Burtscher et al. Respiratory Physiology & Neurobiology 165 (2009) 97–103 24

ReOxy in Respiratory Rehab

Clinical Trials/ Pulmonary Diseases

Table 4
Exercise data (cycle ergometry) before and after the 3-week breathing program.

	Hypoxia group ($n=9$)		Control group ($n=9$)		ANOVA P-value
	Pre	Post	Pre	Post	
Peak power (W/kg)	2.07 (0.79)	2.27 (0.87)[a]	1.89 (0.62)	1.90 (0.56)	*0.04*
Total exercise time (min)	12.4 (4.8)	13.7 (5.3)[a]	11.3 (3.7)	11.3 (3.4)	*0.04*
VO_2 peak (ml/min/kg)	32.0 (10.2)	34.6 (11.3)[a]	29.7 (7.0)	30.7 (8.3)	0.13
Heart rate peak (bpm)	162.9 (16.0)	158.4 (16.3)	165.6 (13.8)	156.9 (17.7)	0.15
VE peak (l/min)	89.1 (26.1)	94.9 (24.5)	76.7 (21.3)	81.8 (25.2)	0.89
SaO_2 peak (%)	93.9 (2.2)	95.4 (1.7)[a]	95.6 (1.7)	95.2 (1.3)	0.05
Rate of perceived exertion	5.4 (1.1)	5.7 (1.8)	5.3 (0.9)	5.3 (0.7)	0.50
Exercise time $_{AT}$ (min)	5.7 (3.7)	6.4 (3.3)[a]	5.8 (1.9)	5.4 (1.4)	*0.01*
VO_{2AT} (ml/min/kg)	21.2 (6.5)	22.3 (6.0)[a]	19.0 (4.0)	18.5 (2.7)	0.13
Heart rate$_{AT}$ (bpm)	128.8 (14.8)	133.7 (11.5)	124.3 (10.5)	128.3 (8.9)	0.87
SaO_{2AT} (%)	92.4 (2.1)	94.2 (1.9)[a]	93.2 (1.9)	93.1 (1.5)	*0.03*
VE_{AT} (l/min)	49.1 (13.0)	46.0 (7.9)	44.0 (10.5)	44.8 (8.8)	0.27
VE/VO_{2AT}	30.6 (5.6)	27.2 (5.0)[a]	31.0 (6.1)	32.0 (4.5)	*0.02*
VE/VCO_{2AT}	30.6 (5.5)	27.3 (5.1)[a]	31.0 (6.2)	32.1 (4.6)	*0.02*

Data are means (SD).
Abbreviations: Peak oxygen uptake (VO_2 peak), peak minute ventilation (VE peak), peak arterial oxygen saturation (SaO_2 peak); oxygen uptake at the anaerobic threshold (VO_{2AT}), arterial oxygen saturation at the anaerobic threshold (SaO_{2AT}), minute ventilation (VE_{AT}), and ventilatory equivalents for oxygen and carbon dioxide at the anaerobic threshold (VE/VO_{2AT}, VE/VCO_{2AT}).

M. Burtscher et al. Respiratory Physiology & Neurobiology 165 (2009) 97–103 25

ReOxy in Respiratory Rehab

Rehabilitation after COVID-19

Post-corona rehabilitation

- restoration of lost physical performance
- increase respiratory capacities (dyspnoea severity and lung function, decrease in shortness of breath during physical exercise)
- cognitive function improvement
- quality of life improvement

It has been shown that the Interval Hypoxia Training leads to the restoration of lost physical performance by improving tissue oxygenation (improved microcirculation) and economizing oxygen consumption during exercise.

Aerobic exercise in post-COVID-19 patients is often accompanied by oxygen desaturation, resulting in shortness of breath and cessation of exercise.

Moderate hypoxic loads in interval mode - an alternative tool for patient adaptation to subsequent physical exercise.

To facilitate **patient safety** from potential cross-infection the following approach is envisaged with respect to contact between potentially infected patient and the breathing therapy device:

- The ReOxy device has a 2-stage intake filtering system, an output filtering system, and a number of unidirectional valves enforcing one-way movement of the gas mixtures.
- Each patient uses an Individual breathing kit. The construction of the kit incorporates one-way valves that ensure that the patient is inhaling the air from the machine only and exhales air beyond the machine.
- In an unlikely event that fails, the machine is still protected by a HEPA filter (Intersurgical Ltd.) that is designed to filter 99.97% of infections.
- External surfaces of the device were deliberately designed to accommodate users of hospital cleaners.
- The remaining part that is a contact between patient and the device is a pulse-oximetry sensor. Normally is multiple-use one, but we can offer a single-use accessory that is in contact with the patient’s finger.

ReOxy in Respiratory Rehab

Rehabilitation after COVID-19

Hypoxic training in rehabilitation of patients at the early stages of recovery after SARS-CoV-2 pneumonia
Controlled randomised clinical trial, in progress
Sechenov First Moscow State Medical University, Moscow, Russia

44 patients (61,5±6,6 ys) in early recovery period after previous SARS-CoV-2 pneumonia

- Control Groupe (23 patients) – Standard rehabilitation programme
- Hypoxia Groupe (21 patients) – Standard rehabilitation programme + ReOxy treatment (10 session)

Preliminary results*:

- no side effects associated with ReOxy treatment
- significant between-group differences in physical endurance ($p<0.05$) by measured “sit and stand” test
- more favourable physical recovery in the second group and similar improvement of psycho-emotional status in both groups.

Conclusion. Hypoxic-hyperoxic therapy is effective and safe approach in rehabilitation of patients with previous SARS-CoV-2 pneumonia. Current stage – patients’ recruitment. The preliminary results are published**.**

** Kostenko A.A., Koneva E.S., Maliutin D.S., Tsvetkova A.V., Bisheva D.R., Vasilieva E.S., Bazarov D.V., Shestakov A.V., Kotenko K.V. Hypoxic training in rehabilitation of patients at the early stages of recovery after SARS-CoV-2 pneumonia. Problems of balneology, physiotherapy and exercise therapy. 2022;99(4-2):11–16. (In Russ.). https://doi.org/10.17116/kurort20229904211*

ReOxy in Respiratory Rehab

Rehabilitation after COVID-19

Randomised Placebo Controlled Trial on Respiratory Therapy with Interval Hypoxic/ Hyperoxic Treatment (IHHT) During Rehabilitation in Patients After Corona-Virus Disease [RICOVER] , in progress

Charité, Universitätsmedizin Berlin, Median Kliniken Group, Germany

84 patients in in-patient rehabilitation after COVID-19 illness and severe respiratory infection
(6MWT distance <450m or <550m plus drop SaO2 ≤85% or BORG Skala ≥3 during 6MWT)
<u>Experimental Groupe</u>: ReOxy treatment (IHHT), 3 sessions/week on top of standard care during in-patient rehabilitation, 5 Weeks
<u>Control Groupe</u>: Identical respiratory session (inhaling only normoxic air instead of hypoxic interval respiration) on top of standard care, 5 Weeks

Preliminary results:
Our recent pilot data show that 5 week of intervention yield significant improvement in functional capacity (significant improvement in 6MWT in the IHHT group)

ReOxy in Respiratory Rehab

Rehabilitation after COVID-19

Clinical Efficacy of Individually Dosed Intermittent Hypoxia-Hyperoxia Therapy in Osteoarthritis (OA) Patients with Post-Covid Syndrome (RCT, placebo controlled)*

Moscow Centre for Research and Practice in Medical Rehabilitation, Restorative and Sports Medicine, Moscow, Russia

50 patients with OA (84% females, age of 43 to 68 years) and at least 6 symptoms of post-COVID syndrome
COVID-19 were diagnosed from 12 to 26 weeks before the study.
<u>Study group</u>: ReOxy treatment (IHHT), 5 sessions/week on top of standard care during out-patient rehabilitation, 2 Weeks. The duration of 1- 4 procedures – 30 min, 5 - 10 procedures – 40 min.
<u>Placebo control group</u>: Identical respiratory session (inhaling only normoxic air instead of hypoxic interval respiration) on top of standard care, 2 Weeks
<u>Comparison group</u>: only standard rehabilitation programme, 2 Weeks.

Results. In the study group, pain decreased by 51.4% ($p < 0.01$), Lequesne index – by 34.8% ($p < 0.05$), WOMAC – by 44.7% ($p < 0.05$), reactive anxiety level – by 23.7% ($p < 0.05$), depression symptoms – by 52.9% ($p < 0.01$), breathlessness – by 71.2% ($p < 0.01$), general health improved by 52.1% ($p < 0.01$). There were statistically significant differences from the control group in all parameters ($p < 0.05$) and from the comparison group in most indicators ($p < 0.05$), excluding the Lequesne index

***** Orlova E.V., Lyamina N.P., Skorobogatyth N.V., Pogonchenkova I.V. Clinical Efficacy of Individually Dosed Intermittent Hypoxia-Hyperoxic Therapy in Osteoarthritis Patients with Post-Covid Syndrome. *Bulletin of Rehabilitation Medicine. 2022; 21(2): 6-16.* https://doi.org/10.38025/2078-1962-2022-21-2-6-16

IHT/IHHT application in comorbid patients

Author, year (ref.)	Nosology	Study type	Patients/ trials number	Treatment mode	Results
Glazachev OS, 2021	IHD, CHF, AH	SR with meta-analysis	431	IHT/IHHT at rest	- ↓ HR - ↓SBP, DBP
Ignatenko GA, 2019	IHD, AH	RCT	219	IHT/IHHT at rest	- ↓SBP, DBP - normalization of diurnal variability of the BP - ↓ angina attacks
Muangritdech N, 2020	AH I	RCT	47	- IHT at rest - IHT + PE	- ↑ Nox - ↓SBP, DBP in both group - ↑ 6 MWT distance - ↑ Nox
Lyamina NP, 2011	AH I	RCT	57	IHT at rest	- ↑ NO synthesis - ↓ BP to the level of healthy individuals - ↓ BP values persisted for at least 3 months
Glazachev OS, 2010	Metabolic syndrome	RCT	35	IHHT at rest	- ↓BP - ↓cholesterol level - ↓endothelial dysfunction - ↑microcirculation - ↑tolerance to physical load
Lizamore CA, 2017	IHD, CHF, COPD	SR	4 RCT	- IHT at rest - IHT + PE - CHE	- ↑ submaximal tolerance to physical load, execution time to failure - ↑ heart rate variability
Chacaroun S, 2020	Obesity	RCT	35	- IHT at rest - CHE	- ↓SBP, DBP in both group - improved heart rate variability - improved hypoxic ventilatory response

IHT/IHHT application in comorbid patients

First author, year of publication	Nosology	Study type	Patients/ trials number	Treatment mode	Results
Chacaroun S, 2020	Obesity	RCT	35	- IHT at rest - CHE	- ↓SBP, DBP in both group - improved heart rate variability - improved hypoxic ventilatory response
Bestavashvili A, 2022	Metabolic syndrome	RCT	65	IHHT at rest	- ↓SBP, DBP in both group - ↓ total cholesterol, LDL, ALT, AST, NTproBNP - ↓ hepatic fibrosis and steatosis indices
Ramos-Campo DJ, 2019	Obesity	SR with meta-analysis	13 RCT -336 patients	PE under hypoxic condition	- ↓body weight, fat mass, LDL, SBP and DBP, but no difference from the control group (exercise under normoxic conditions) - ↑ muscle mass - ↓ triglycerides
Jung K, 2020	Obesity	RCT	32	PE under hypoxic condition	- ↓SBP and DBP - ↓ total cholesterol, triglycerides - elimination of signs of endothelial dysfunction and improvement of rheological properties of blood
De Groote E, 2021	Obesity Diabetes mellitus	SR	17 RCT	PE under hypoxic condition	- conflicting data on weight loss, fat mass and exercise tolerance - the effectiveness of hypoxic training depends on the type of exercise and the mode of hypoxic load
Serebrovska TV, 2019	Prediabetes	CT	18	IHT at rest	- ↑ insulin sensitivity - ↓ fasting glycemia - ↑ tolerance to hypoxia - ↑ HIF-1a mRNA in blood leukocytes Maximum effect one month after the completion of the course

IHT/IHHT application in comorbid patients

First author, year of publication	Nosology	Study type	Patients/ trials number	Treatment mode	Results
Neuhoff CG, 2018	Diabetes mellitus	SR	4 RCT	Hypoxic Exposure and IHT at rest	- conflicting data on lowering fasting glucose levels
Kim SW, 2021	Diabetes mellitus		4 RCT	PE under hypoxic condition	- improved glucose uptake and insulin sensitivity
Ignatenko GA, 2018	IHD: stable angina NYHA II-III + COPD	RCT	90	IHHT at rest	- ↓frequency of non-permanent/persistent cough, - ↓ frequency of dyspnea at rest/after exercise - reclassification to less heavy NYHA class - ↑ tolerance to PE
Borukaeva IK, 2019	Bronchial asthma mild to moderate	RCT	46	IHT at rest	- ↑ tidal volume, alveolar ventilation - ↑ efficiency of gas exchange between alveolar air and blood
Bayer U, 2017	Dementia + IHD, CHF, AH	RCT	34	IHHT at rest	- ↑ 6 MWT distance - ↑ cognitive functions
Wang H, 2020	Mild Cognitive Impairment + IHD, AH, DM	Pilot study	7	IHT at rest	- ↑ cognitive functions - ↓SBP, DBP
Jung M, 2020	Dementia Multimorbidity patients Healthy	SR with meta-analysis	18	PE under hypoxic condition	- ↑ cognitive functions

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