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ORIGINAL ARTICLE

A proof-of-concept trial of HELIOX with different fractions of helium in a human study modeling upper airway obstruction

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Abstract

Background Helium in oxygen (HELIOX) can relieve airway obstruction and lower the work of breathing because it increases the threshold at which turbulent gas flow is induced. Less turbulent and more laminar flow lowers the work of breathing. According to guidelines, the fraction of Helium in HELIOX should be maximized (e.g. to 79%). Here, we investigate whether HELIOX with less than 60% of Helium is able to relieve the sensation of dyspnea in healthy volunteers.

Methods 44 volunteers underwent resistive loading breathing different gases (medical air and HELIOX with a fraction of 25%, 50% or 75% helium in oxygen) in a double-blinded crossover design. Subjects rated their degree of dyspnea (primary outcome parameter) and the variability of noninvasively measured systolic blood pressure was assessed.

Results Dyspnea was significantly reduced by HELIOX-containing mixtures with a fraction of helium of 25% or more. Similarly, blood pressure variability was reduced significantly even with helium 25% during respiratory loading with the higher load, whereas with the smaller load an effect could only be obtained with the highest helium fraction of 75%.

Conclusion In this clinical trial, HELIOX with less than 60% of helium in oxygen decreased the sensation of dyspnea and blood pressure variability, a surrogate parameter for airway obstruction. Therefore, higher oxygen fractions might be applied without losing the helium-related benefits for the treatment of upper airway obstruction.

Trial registration Registration with clinical trials (NCT00788788) and EMA (EudraCT number: 2006-005289-37).

Keywords Upper airway obstruction · HELIOX · Work of breathing · Clinical proof-of-concept study

Abbreviations

BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CRP	C-reactive protein
ECG	Electrocardiography
FiHe	Fraction of inspired helium
FiO_2	Fraction of inspired oxygen
He	Helium
ID	Inner diameter
IRB	Institutional Review Board

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MA	Medical air
POC	Proof of concept
sBP	Systolic blood pressure
STAI	State-Trait-Angst-Inventar

Introduction

Helium is a nontoxic, tasteless and odorless gas with a low solubility in tissue (Hess et al. 2006). The medical use of helium is based on its ability to increase the threshold at which turbulent gas flow in the airway is occurring: in fluid mechanics the Reynolds number (*Re*), named after Osborne Reynolds (1842–1912) is a dimensionless quantity. It is calculated as $Re = \rho \times u \times L/\mu$ with ρ reflecting density of the flowing fluid, u being the fluid velocity, L being the length of the flow pattern and μ being the dynamic viscosity of the fluid. In the example at hand, principles from fluid mechanics are used to describe gas flow pattern in the airway to help predict flow patterns in different flow situations. At low Reynolds numbers, flows tend to be dominated by laminar flow and at high Reynolds number turbulence results. Turbulent flow is characterized by chaotic changes in pressure and flow velocity. In contrast in laminar flow regime fluid flows in organized laminar patterns. In essence less turbulent and more laminar flow lowers work of breathing. If one takes a look at the definition of the Reynolds number above, a reduction of the density ρ in the denominator of the equation lowers Re thereby increasing the chances of a laminar flow pattern which is why the admixture of helium could lower work of breathing (see also Truebel 2008). Helium in combination with oxygen (HELIOX) was first used by Barach in New York for the treatment of asthma and upper airway obstruction in 1934 (AL 1934, 1935). In the clinical setting, the inhaled gas mixture HELIOX usually consists of helium with a variable oxygen content of at least 21% up to a fractional inspired oxygen concentration (FiO_2) of 100% which would no longer be considered HELIOX. In some cases, additional admixtures, e.g. nitric oxide (NO) or other medical gases are added (Harris and Barnes 2008; Hess et al. 2006; McGarvey and Pollack 2008; Siobal 2009). HELIOX is mainly viewed as a rescue procedure in certain conditions affecting the upper and lower airways in which the gas could be delivered via nasal cannula, face mask or endotracheal tube from a gas tank at the bedside or via specifically equipped ventilators (Haynes 2006; McGarvey and Pollack 2008; Lazarus 2010; Truebel 2008; Beurskens et al. 2014; Haussermann et al. 2015; Long et al. 2016; Liet et al. 2015). In general, diseases affecting the (upper) airway resistance seem to be more amenable to the application of HELIOX than conditions that affect the pulmonary parenchyma (McGarvey and Pollack 2008; Levy et al. 2016). With new ventilators and gas blenders having reached the market, physicians and respiratory therapists now have the option to titrate inspired helium concentration (FiHe) to the needs of the individual patient to obtain maximum effect of helium with adequate oxygenation with the resulting FiO_2 ranging from 21 to 99% in spontaneously breathing subjects (Venkataraman 2006; McGarvey and Pollack 2008; Truebel 2008).

In most study protocols on the use of HELIOX in upper and lower airway obstruction, investigators used fractions of inhaled Helium between 60 and 80%, i.e. trying to keep the FiHe above 60% to maximize helium-associated effects (Allan et al. 2009; Chiappa et al. 2009; Diehl et al. 2003; Cambonie et al. 2006; Jolliet et al. 2003; Laveneziana et al. 2011; Colnaghi et al. 2012; Scorsone et al. 2010; Vogiatzis et al. 2011; Vorwerk and Coats 2010; Ho et al. 2002). Our study addressed the question, whether HELIOX with a FiHe below 60% is effective in reducing sensation of dyspnea during a controlled respiratory loading experiment.

Methods

The study was approved by the responsible institutional review board (University of Witten protocol-No.: 88/2006) and the German regulatory agency responsible for clinical trials with investigational drugs (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM; http://www.bfarm.de/), registration code 4032794-3_1_6 as well as clinicaltrials.gov (registration code NCT 00788788). The trial followed a randomized, double-blind, intra-individual, sixfold crossover design. The study was carried out in accordance to the declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/).

Study sequence

Study subjects received written information about the study via mail and those willing to participate came to the study site in the Helios-Klinikum in Wuppertal/Germany a few days prior to the study to receive a tour to the site including a health questionnaire and the informed consent form which was explained to them. Furthermore, blood and urine tests were conducted during this pre-visit as part of the screening procedure.

On the day of the study, the participants could again ask questions, were examined and had to provide the signed consent form. When the participants were disease free, laboratory values were within normal limits and in female participants the urine pregnancy test was negative, they proceeded to draw from a stack of closed envelopes. This way the order of treatments was randomized. In the envelope, a detailed instruction provided information to the participants on which room to enter (i.e. pre-study- and treatment-room) and what to do upon entering these rooms. It also contained a coded

information for the physician that operated the gas mixtures (see below; "technical investigator"). Since a second physician (i.e. the "study physician"), that was with the participant during the study measurement and that was taking care of the recording devices, was seated in a separate room from the one that mixed the gases, the study was conducted in a double-blind and randomized fashion.

Subjects

44 healthy adult male and female volunteers (Table 1) were enrolled after a written, informed consent had been obtained previously. For inclusion, questionnaires as well as a physical examination were required to rule out any signs of acute or chronic airway disease or cardiac pathology. Furthermore, a laboratory screen including total blood count, creatinine, transaminase profile as well as measurement of C-reactive protein (CRP) and a fasting blood sugar measurement had to reveal normal findings. A negative pregnancy test was mandatory for females.

Subjects were further excluded when signs and symptoms for mental health problems could be revealed by history taking. Furthermore, prior to the study potential participants were screened in respect to their current baseline anxiety level using of the German version of the STAI-G X1 questionnaire [State-Trait-Anxiety-Inventory (STAI); Verlag für Psychologie, Goettingen, Germany. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press]. Volunteers were excluded if their anxiety level exceeded a score of 60 according to a study by Osborne et al. (2000).

Measurements

Before entering the treatment room, subjects conducted a 2-min breathing trial ("pre-study") through a resistor in a separate room to accustom themselves with the study location and accommodate to the feeling of dyspnea imposed by a resistive load. 'This "pre-study" was added to the experimental protocol because a pilot study revealed some degree of adaptation after subjects' first experience with resistor-modified breathing (Enneper et al. 2005).

The degree of dyspnea during the experiment was rated by the subjects on a visual categorical scale ranging from 1 (no feeling of dyspnea) to 10 (maximum feeling of dyspnea) according to Borg (1982).

During the study electrocardiogram (ECG) and noninvasive systolic blood pressure were monitored (sBP) with the Task Force® Monitor (TFM; CNSystems, Graz, Austria, for details please also see Enneper et al. 2005). Changes in systolic blood pressure were recorded continuously to detect respiratory effects on sBP-variability (also known as Pulsus paradoxus) caused by changes in airway resistance associated with study interventions (Lee et al. 2005; Goldman et al. 1995), i.e. the variation of systolic blood pressure is aggravated during resistive breathing and can be used as an indirect measure of upper airway obstruction. Further details on the effect size to judge the sample size as well the amplitude of the effect have been studied in a pre-study beforehand (Enneper et al. 2005). All subjects were studied in the seated position, with a nose clip in place and a pulse-oximeter attached to a finger (PVM-2700, Nihon Kohden Europe GmbH, Rosbach/Germany; where pulse-oximetry data could not be stored electronically). Each condition was recorded for exactly 2 min. Ample time (between 30 and 45 s) was provided before a recording period of 2 min was started to allow for distribution of the tested gas mixture in the subjects' respiratory tract and thereby achieve steady-state conditions.

After each gas mixture was changed, care was taken to flush all tubing and the reservoir bag with the next gas mixture to be tested. After the subjects were breathing the control gas [MA (medical air)] or a helium-containing gas mixture, they marked their degree of dyspnea on the visual categorical scale mentioned above. In total, the degree of dyspnea was rated 12 times per subject. The total time need to carry out the experiment per subject was about 150 min (excluding the initial screening and blood draw).

Test gases

A reservoir bag was filled with gas mixed in a separate room via gas tubing (Fig. 2). The Helontix™Vent (Linde Gas Therapeutics, Unterschleißheim, Germany) in constant

Table 1 Characteristics of the $n = 44$ included subjects

	Block 1 ($n = 11$)	SD	Block 2 ($n = 11$)	SD	Block 3 ($n = 11$)	SD	Block 4 ($n = 11$)	SD
Age (years)	26.4	± 6.7	26.7	± 6	23.8	± 1.3	25.0	± 3.2
BMI (m^2/kg)	20.7	± 1.8	22.7	± 3	22.5	± 3.5	22.4	± 2.3
Pre-study STAI-G	31.8	± 5.1	33.6	± 7.3	34.3	± 10.8	35.8	± 6.7
Pre-study Borg Dyspnea Score	4.7	± 1.7	5.2	± 1.1	4.2	± 1	3.8	± 1.4

Values are mean (SD); definition of abbreviation: *BMI* body mass index

flow mode at a flow rate of 12 l/min was used to mix different fractions of helium. Therefore, gas from containers (BOC Medical, Guildford Surrey, England) filled with 21% oxygen and 79% helium was mixed with oxygen (Conoxia™, Linde Gas Therapeutics) in the Helontix™Vent. Three different mixtures of helium in oxygen with a helium content of 25%, 50% and 75% in oxygen (FiHe 25, FiHe 50 and FiHe 75, respectively) were used. Before each HELIOX-exposure, Medical Air ("MA" in Fig. 1; Linde Gas Therapeutics) was used as control condition. Subjects at all times were unaware of the type of gas mixture. The person operating the Helontix™Vent ("technical investigator") was not in contact with the subject but volunteers were always supervised by a physician ("study physician").

Respiratory loading

Two different external resistors (see "R" in Fig. 1) were used. They were self-made by placing standard plastic endotracheal tubes of identical length (PVC; 30 cm length; inner diameter (ID) of either 5.0 mm ("tube A") or 4.0 mm ("tube B"); Rueschelit™, Teleflex Medical, Kernen, Germany) into identical opaque PVC tubing, to prevent their identification from outside. The resistors had identical connectors on both ends that fit into adaptors to connect the resistor to commercially available breathing tubes (Breathing tubes, Harvard Apparatus, Holliston, MA, USA; ID 35 mm). Subjects were breathing from a reservoir bag via an inspiratory resistor (tube A or B) and exhaling into the room via a fixed expiratory resistor which was needed for adequate seal of the three-way respiratory valve (see "V" in Fig. 1; Harvard Apparatus, ID 35 mm) which directed the gas stream.

Blinding and randomization protocol

By means of block randomization with sixfold intra-individual crossover, each subject was randomized to one of the exposure schedules displayed in Fig. 2. For practical reasons, it was not feasible to consider all 36 permutations of the six combinations of resistors and helium concentrations. To exclude large sequence effects, the order of resistors was considered as well as the extreme positions of lowest and highest helium concentrations since we expected some fatigue and a higher degree of dyspnea feeling at the last experiment, irrespective of the resistance loading and the gas mixture.

On the study day, an opaque envelope which contained the exposure schedule was drawn by the technical investigators. However, the study physician and the subject were blinded and only the technical investigator who prepared the experimental set was informed and connected tubes and gas containers.

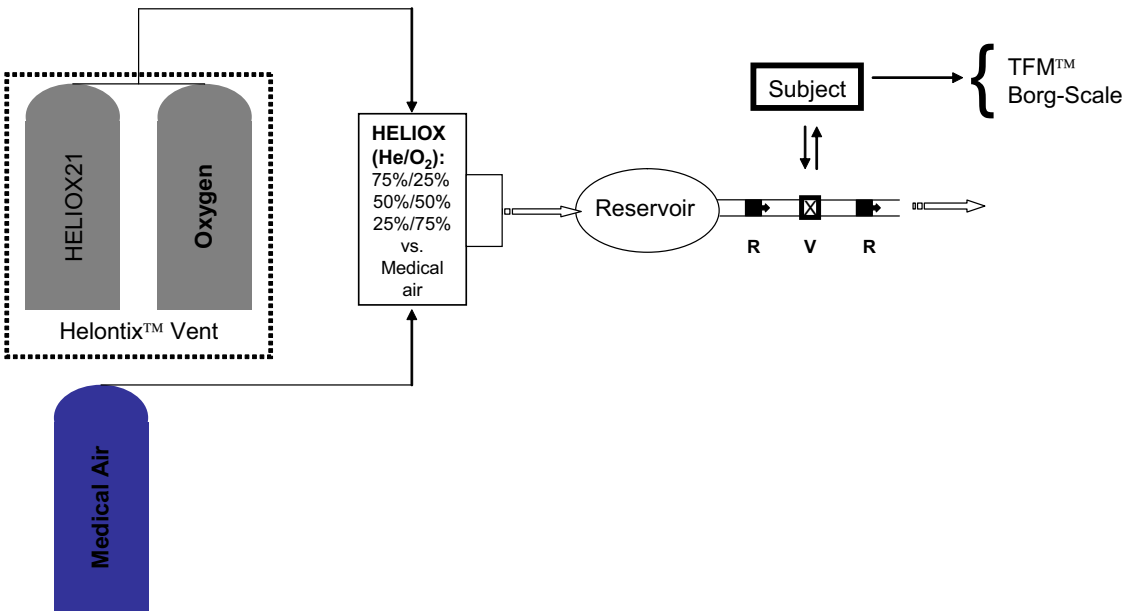

Fig. 1 Experimental setup [Definition of abbreviation: *He* helium, *HELIOX21* 21% oxygen supplied in helium (79%; BOC Ltd., UK), *TFM* task force monitor (CNSystems, Graz, Austria)]; R1 and R2 = Resistor 1 and 2, respectively, R1 was changed during the experiment ("tube A" vs. "tube B"; see Fig. 2); Helontix Vent = mechanical ventilator which was used to mix gases (Linde Gas Therapeutics, Lidingo, Sweden)

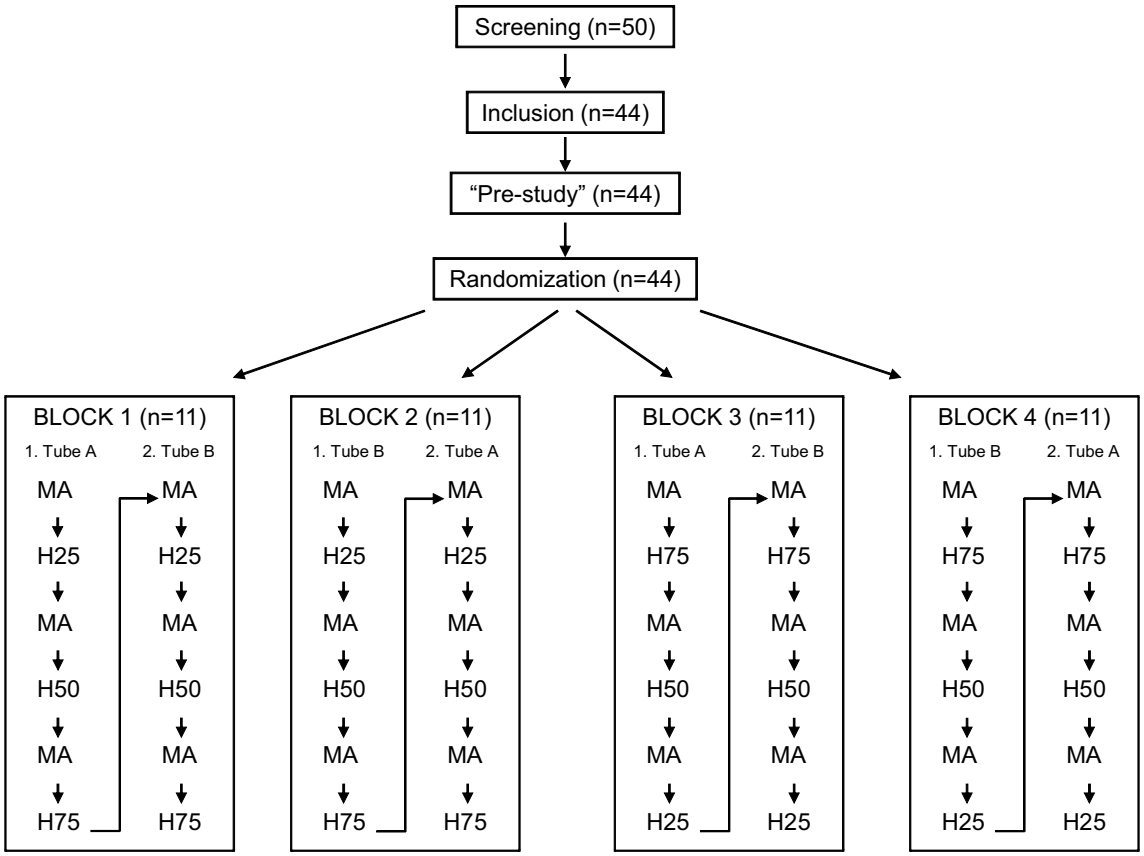

Fig. 2 Study profile. The $n=44$ subjects (6 subjects excluded for upper airway infection) fulfilled all inclusion criteria were randomized to four different blocks (BLOCK 1–4). In each block, the order of tested resistors as well as the sequence of mixed gases introduced into the experiment were predetermined. After the crossover during the second run in each block, the next resistor was used again with the same gases as in the first run. According to the block randomization at the end of each experiment, every subject was exposed to the same resistors and the same gases but in a varying order. Measurements with the Task Force Monitor (CNSystems) were carried out while subjects were breathing each gas mixture for periods of 2 min with amble time provided to allow for equilibration of the respiratory tract with the tested gas mixture. The total time needed to carry out the experiment per subject was about 150 min (excluding the initial screening examination and blood draw) (definition of abbreviation: *MA* medical air. *H25, H50 and H75* mixture of a fraction of 25%, 50% and 75% helium (FiHe) in oxygen, respectively, *TB and TA* Tubes B and A)

Statistical analysis

During a pilot study in ten healthy subjects, the tolerability of resistance loading and expected changes in dyspnea and blood pressure had been investigated (Enneper et al. 2005). Based on this pilot study, we estimated that significant changes for the Borg dyspnea score and the variability of the systolic blood pressure could be detected with a tube of 5 mm ID with HELIOX at a FiHe of 79%. Assuming a reduction in the Borg dyspnea score rating with HELIOX containing 50% of helium instead of 79%, we presumed that a fourfold increase in sample size would be sufficient to examine our hypothesis at an alpha level of 0.05. It was expected that effects should be even more pronounced with the narrower (4.0 mm ID) tube. The GraphPad Prism 5 statistical software was used for data analysis (GraphPad Software, La Jolla, CA). The mean and standard deviation for Borg dyspnea scores and variability of the sBP were computed for data collected over a period of 2 min for each gas–resistor combination. As a measure of variability of systolic blood pressure (sBP), the standard deviation (SD) of the blood pressure was chosen and its averaged values were compared during resistive loading conditions breathing different test gases vs. medical air (MA; Fig. 1) using a one-way, repeated-measures ANOVA with Student–Newman–Keuls post hoc test. For the comparison MA vs. resistive breathing in each case, the MA-period preceding the HELIOX-exposure was chosen. Differences were considered significant at a corrected p-value of less than 0.05.

Results

Subject characteristics

Out of 50 subjects screened for the study, six were excluded due to upper airway infection. Table 1 summarizes the baseline characteristics of the $n = 44$ remaining subjects in the four groups as well as results of the STAI-G questionnaire self-assessment and "pre-study" dyspnea assessment (Borg dyspnea score) breathing through tube A (i.e. with an inner diameter of 5 mm). The groups 1–4 refer to the randomization groups and contain 11 subjects per group. The four groups were not statistically different with respect to the reported variables (Fig. 2).

The effects of HELIOX with different FiHe on Borg dyspnea score and systolic blood pressure variation are summarized in Fig. 3 during the resistive loading experiment: The patient reported Borg dyspnea score was improved with both resistors down to a FiHe of 25%. In a similar fashion when the narrower tube (ID 4.0 mm) was used as resistor, a mixture of helium to oxygen even at a fraction of 25% decreased the variability of systolic blood pressure significantly. With the larger tube (ID 5.0 mm) as resistor, no significant effect on sBP-variability was detected when a Fi_{He} of 25 and 50% were tested, i.e. only the test gas with an F_{He} of 75% reduced sBP-variability significantly. In general, the higher resistive loading condition was also associated with a greater Borg dyspnea score and larger degree of sBP-variability (Fig. 3).

Assessment of Borg dyspnea scores and haemodynamics (sBP) during the conditions "H75" at the beginning of the study (Block 1 with tube A ("TA") in Fig. 1) vs. "H75" at the end of Block 4 with tube A ("TA") and "H25" at the beginning vs. the end of a block with all tubes tested did not reveal a statistical significant difference, i.e. the subjects' dyspnea assessment and the haemodynamic measurements (sBP-variability) were independent of the timing during the course of the experiment as in our previous trail (Enneper et al. 2005).

As demonstrated in the pilot study, the mean values for sBP during all tested conditions and with both tubes were not found to be statistically different (data not shown in Fig. 3) (Enneper et al. 2005).

All 44 subjects could finish the experiment without any reported adverse events including no pulse-oximetry readings below 95%.

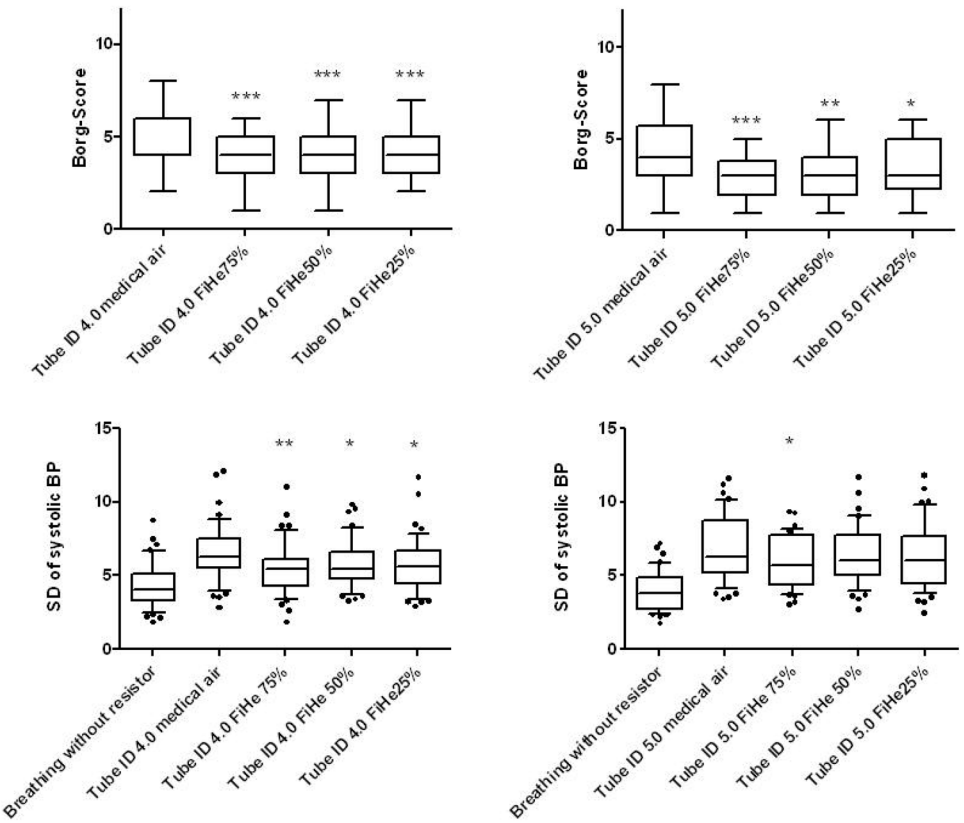

Fig. 3 **a** Borg dyspnea score ratings and **b** standard deviation (SD) of systolic blood pressure (sBP) are summarized during resting condition and resistive loading with two different resistors (tubes with internal diameter (ID) of 4.0 and 5.0 mm, resp.). Statistical comparison took place between the condition when the breathing circuit contained medical air vs. three different mixtures of HELIOX (with a fraction of 75, 50 and 25% in oxygen (FiHe 75%, 50% and 25%) of inspiratory helium). For completeness, the sBP-variation during unloaded breathing was also added into the figure ("breathing without resistor")

Discussion

During an acute loading experiment, it was found that HELIOX with a FiHe of less than 60% can reduce patient reported Borg dyspnea scores and sBP-variability. These findings contradict previous views with respect to the efficacy of HELIOX with lower FiHe (Ho et al. 2002; Levy et al. 2016). HELIOX appears to be more efficient in affecting outcome parameters when the diameter through which the respiratory gas has to flow is smaller, i.e. at higher loading conditions which fits well with the concept that helium is especially effective when turbulent airflow pattern is present (Hess et al. 2006; Truebel 2008), since it is not uncommon for patients with upper airway obstruction (e.g. after prolonged mechanical ventilation and swelling of laryngeal tissue after extubation) to also have an increased need for oxygen. Thus, the addressed question if reduced fractions of helium could effectively lower the work of breathing is of potential clinical relevance, because one can maximize oxygen fractions in gas mixtures applied to patients with upper airway obstruction as well as avoid using helium-containing gas mixtures in patients that do not need or benefit from it. Since helium is expensive and logistically difficult to supply, unnecessary costs can be avoided. This clinical "Proof of Concept" (phase IIa) study clearly showed that depending on the degree of airway narrowing lower FiHe still could be effective. Our experimental design has not been applied before, but could serve as a model for future proof of concept studies in upper airway obstruction. Clinical trials with helium should carry forward these findings in a phase IIb/III study design by generating evidence in a prospective manner addressing the issue of a "minimal effective" helium concentration in a real world scenario, i.e. in patients with acute upper airway obstruction. Given the rare and unforeseen occurrence of acute upper airway obstruction, e.g. after extubation and the degree of variability, comorbidities, potential co-medications and other confounding factors, the conduct of such a clinical phase II/III studies appears challenging. Furthermore, our study design only reflects upper airway obstruction, whereas the application of HELIOX in conditions with lower airway obstruction (e.g. COPD and asthma) could also provide benefit (Hunt et al. 2010; Vogiatzis et al. 2011; Chiappa et al. 2009).

Conclusion

Despite Heliox's usage in clinical medicine over more than 75 years, the question of its effectiveness when less helium is added to inhalation gas has not been conclusively addressed. Our study for the first time demonstrated that even low fractions of helium can significantly lower the feeling of dyspnea, especially at higher resistance.

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Author contributions Conception and design: HT, SS, JS, TL, PT; acquisition of data: HT, ABR, HD, SS, JS; statistical planning: TO, DC; analysis and interpretation of data: HT, SW, TO; drafting of the manuscript HT, TO, DC, SS, JS, TL, PT; PB final approval: all authors.

Compliance with ethical standards

Conflict of interest PD Dr. Hubert Truebel organized and conducted the trial as lead PI while working at HELIOS Klinikum Wuppertal/Germany until 2008. Since then he is a fulltime employee of Bayer Pharma AG. Support (including gas supply and access to a HELONTIX Vent) was received from Linde Gas Therapeutics/Germany as well as through an INSPIRA research grant by BOC/UK to cover insurance and travel costs of subjects. Philip Boehme received founding from Bayer Pharma Ag. No conflicts of interest were reported by all other authors.

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