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Breathing Hydrogen-Oxygen Mixture Decreases Inspiratory Effort in Patients with Tracheal Stenosis

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Keywords
Hydrogen-oxygen · Tracheal stenosis · Work of breathing · Airway resistance · Diaphragm function

Abstract
Background: Hydrogen-oxygen mixture (H_2-O_2) may reduce airway resistance in patients with acute severe tracheal stenosis, yet data supporting the clinical use of H_2-O_2 are insufficient. ***Objectives:*** To evaluate the efficacy and safety of breathing H_2-O_2 in acute severe tracheal stenosis. ***Methods:*** Thirty-five consecutive patients with severe acute tracheal stenosis were recruited in this prospective self-control study. Air, H_2-O_2 and O_2 inhalation was given in 4 consecutive breathing steps: air for 15 min, H_2-O_2 (6 L per min, H_2:O_2 = 2:1) for 15 min, oxygen (3 L per min) for 15 min, and H_2-O_2 for 120 min. The primary endpoint was inspiratory effort as assessed by diaphragm electromyography (EMGdi); the secondary endpoints were transdiaphragmatic pressure (Pdi), Borg score, vital signs, and impulse oscillometry (IOS). The concentration of H_2 in the ambient environment was obtained with 12 monitors. Adverse reactions during the inhalation were recorded. ***Results:*** The mean reduction in the EMGdi under H_2-O_2 was 10.53 ± 6.83%. The EMGdi significantly decreased during 2 H_2-O_2 inhalation steps (Steps 2 and 4) compared with air (Step 1) and O_2 (Step 3) (52.95 ± 15.00 vs. 42.46 ± 13.90 vs. 53.20 ± 14.74 vs. 42.50 ± 14.12% for Steps 1 through 4, $p < 0.05$). The mean reduction in the Pdi under H_2-O_2 was 4.77 ± 3.51 cmH_2O. Breathing H_2-O_2 significantly improved the Borg score and resistance parameters of IOS but not vital signs. No adverse reactions occurred. H_2 was undetectable in the environment throughout the procedure. ***Conclusions:*** Breathing H_2-O_2 may reduce the inspiratory effort in patients with acute severe tracheal stenosis and can be used for this purpose safely.

Introduction

Tracheal stenosis is an emerging problem that has been increasingly reported in recent years [1, 2], frequently associated with elevated airway resistance and thus increased inspiratory effort in patients with this condition. Interventional endoscopic and surgical proce-

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dures are currently effective approaches in the treatment of tracheal stenosis [3]. However, before these approaches could be delivered, the inspiratory effort in these patients sometimes may become more exhaustive during the waiting time and pre-interventional preparation, particularly in the emergency setting.

Oxygen therapy and noninvasive mechanical ventilation have limited effect on the emergency management of tracheal stenosis [4]. Gaseous helium (He) with a low density and a low molecular weight has been demonstrated to allow for a reduction in airway resistance and a decrease in the inspiratory effort of patients with upper airway obstruction [5–8]. However, the high cost for He storage and production precludes its widespread use in the clinic. To date, no method other than helium-inhalation can be satisfactory in reducing the inspiratory effort during the emergency management of tracheal stenosis.

Hydrogen (H_2) possesses helium-similar physical characteristics and is therefore a potential to reduce airway resistance in a narrow trachea. Moreover, H_2 can be produced conveniently (e.g., in an ambulance) and inexpensively by electrolyzing water. H_2 generator is a novel equipment and has reportedly been used in renal calcium oxalate deposition [9], cerebral ischemia-reperfusion injury [10], liver ischemia-reperfusion injury [11], chronic obstructive pulmonary disease model rats [12], and sanitation workers exposed to haze [13], with promising outcomes in alleviating inflammation and biological safety. However, data on clinical use of H_2 in patients with tracheal stenosis remain so far insufficient.

The aim of this study was to evaluate the efficacy and safety of breathing a hydrogen-oxygen mixture (H_2-O_2) produced by a H_2 generator in the emergency management of tracheal stenosis. We hypothesized that, based on previous studies on He and H_2-O_2, inhalation of H_2-O_2 mixture may have a useful role as an emergency management in reducing inspiratory effort and meanwhile, with an ensured security throughout the treatment.

Methods

Study Design

This prospective, single-blind, self-control study was conducted in accordance with Helsinki Declaration. The study protocol was approved by the Ethics Committees of First Affiliated Hospital of Guangzhou Medical University (Approval Number 2016-50), and has been registered online (clinicaltrials.gov [NCT02961387]). The use of oxygen and hydrogen in this study rigorously followed the Management Regulations for the Safety of Medical Gases issued by of Guangzhou Medical University. The primary endpoint was the patient's inspiratory effort, as assessed with a diaphragm electromyogram (EMGdi). Secondary endpoints were the transdiaphragmatic pressure (Pdi), vital signs, Borg score [14], and impulse oscillometry (IOS) during the gas inhalation. The presentation of the study was in accordance with CONSORT guidelines [15].

Patients

We recruited 35 consecutive patients with tracheal stenosis at the First Affiliated Hospital of Guangzhou Medical University from November 2016 to June 2017. The inclusion criteria were as follows: (A) dyspnea within the previous four weeks; (B) Borg score >2 on admission; and (C) ≥ grade III stenosis [16]. Patients underwent chest CT to evaluate the severity of tracheal stenosis. CT images were analyzed using the Lung CAD software (Autodesk, American). We defined the stenosis percentage as the ratio of the minimal area to the normal area of the trachea. The exclusion criteria were as follows: (A) comorbidities, such as COPD, asthma, vocal insufficiency or ventricular dysfunction, that could lead to dyspnea; (B) unable to tolerate study measurements due to severe dyspnea; and (C) no dyspnea. All subjects provided written informed consent.

Generation and Inhalation of Gas Mixtures

The medical H_2 generator (AMS-H-01, Asclepius Meditec Co., Shanghai, China) has been approved by the State Food and Drug Administration of Shanghai Medical Device Quality Supervision and Inspection Center (Approval No: ZC2016-1002th). It provided an output for the H_2-O_2 mixture comprising 33% oxygen and 66% of 6 L per minute by electrolysis of pure water, as previous reported [9–13, 17]. The generator with anti-static precautions and a one-way fire-retarding valve delivered the gas mixture to the patient through a nasal cannula immediately to avoid gas storage in the generator or pipeline. Moreover, the generator was equipped with built-in concentration monitors. All designs were developed to ensure safety and avoid combustion. O_2 was produced by a medical molecular sieve oxygen-generator (Ou-liang Medical Appliance Co., Shanghai, China). The flow rate of O_2 was set to 3 L/min. The oxygen-generator was re-designed, so that it looked identical in appearance as did the H_2 generator.

In a previous safety study, we had tested the safety of the hydrogen generator: 10 generators were switched on together in a tightly close room measured 80 m^3 (6.8 × 4.4 × 2.7 m) for 2 h continuously. Twelve H_2 monitors with a measurement accuracy of 0.1% (XP-3110, NEWCOSMOS, Japan) were placed at a 20-cm distance on 4 sides around the generators. Each side included 3 monitors in a vertical line (on the ceiling, middle and floor of the room). Two hours later, the maximum hydrogen concentration measured by the monitors was 0.8% (on the ceiling). Such a concentration was far below the explosion limits of hydrogen in the air (4%).

The present study was carried out in a well-ventilated room. Monitors were set in the same position as in the previous safety test during the whole study. All adverse reactions that were related to inhalation were also recorded to evaluate the safety of the procedure.

Patients inhaled air, H_2-O_2 (H:O = 66%:33%, 6 L/min) and O_2 (3 L/min), through nasal cannula; H_2-O_2 was included in the regimen twice. The study included 4 breathing steps: (1) air for 15 min; (2) H_2-O_2 for 15 min (H_2-O_2–1); (3) O_2 for 15 min; and (4) H_2-O_2 a second time for 120 min (H_2-O_2–2). Patients breathed air for 30 min as the washout period after each breathing step. The duration of first 3 periods was set to 15 min each, based on a previous study by Jaber [5].

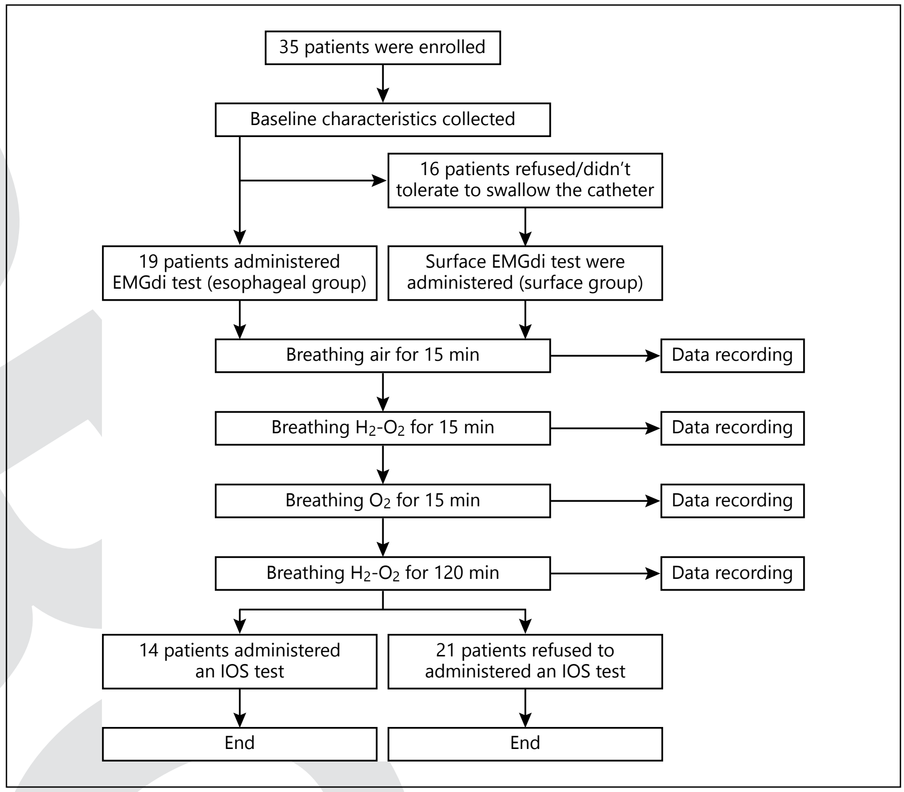

Fig. 1. Flowchart of the study.

Diaphragmatic Function Measurements

Patients' inspiratory effort was assessed by the diaphragmatic function. As reported previously [18, 19], the EMGdi and Pdi were recorded from a balloon-electrode catheter (Yinghui Medical Equipment and Scientific Ltd., Guangzhou, China), which was advanced through the nasal cavity into the esophagus and stomach. Patients who did not tolerate or refused to swallow the catheter were converted to a surface diaphragm EMG (sEMGdi) test instead, which was performed using chest wall surface electrodes. Surface electrodes were placed on left and right ribs 6–8 along the both anterior axillary line to record the sEMGdi for a bilateral assessment. All signals were recorded using a Powerlab system (ML796, ADInstruments, Australia). The EMGdi, Pes, and Pga were recorded during the last 2 min of each breathing step.

Impulse Oscillometry

The airway resistance of each patient was assessed using an IOS system (MasterScreen-IOS, Jaege, Germany). We adapted the IOS system to record the patients' parameters of airway resistance while breathing H_2-O_2. H_2-O_2 (6 L/min, H_2:O_2 = 2:1) was connected to the screen flap (Fig. 2) by a T-branch pipe, which mixed H_2-O_2 with air. The gas mixture was delivered into the spirometer and inhaled by the patient. Meanwhile, the patient's exhalation could pass through the T-pipe smoothly. The parameters were recorded synchronously as previously reported [20]. The whole- and center-airway parameters of IOS include lung resistance at 5 Hz (R5), lung resistance at 20 Hz (R20), and respiratory impedance at 5 Hz (Z5). The difference between lung resistance at 5 and 20 Hz (R5–R20) represents peripheral airway resistance [21].

Dyspnea and Vital Sign Assessments

The ratings of perceived exertion while breathing H_2-O_2 were evaluated with the Borg score. A >1 point reduction was defined as an improvement in dyspnea [22]. The patient's Borg score and vital signs (respiratory rate, heart rate, blood pressure, and pulse oximetry) were recorded before inhalation and during the last 2 min of each breathing step.

Analysis of Data

EMGdi was measured from the segments between the QRS complexes to avoid the influence of the electrocardiogram on the EMG, and reported from the electrode pair with the largest EMGdi amplitude for each breathing cycle [23]. The diaphragm EMG was converted to the root mean square (RMS) using a 100-ms time period constantly with the Labchart 7.3 software. A ratio of the EMGdi to the maximum EMGdi was used to calibrate for individual difference. Difference of EMGdi between breathing step of air and H_2-O_2–1 was recorded as Delta-EMGdi (ΔEMGdi), as well as Pdi (ΔPdi).

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). All characteristics were analyzed using the Kolmogorov-Smirnov test. Numerical data were presented as mean ± SD for a normal distribution or otherwise as median (interquartile range). Four-group comparisons were performed using one-way analysis-of-variance (ANOVA). The LCD correction was applied to adjust for multiple comparisons. Correlation analyses were conducted using Pearson's or Spearman's model. Paired *t* tests were used to assess differences between paired data. A $p < 0.05$ was considered statistically significant.

Table 1. Baseline characteristics of the 35 patients

Characteristic	Value
Patient number	35
Age, years	54.29±2.33
Gender, male:female	24:11
Height, cm	163.0±1.50
Weight, kg	58.05±1.37
Arterial blood gases	
pH	7.39±0.03
PaO_2, mm Hg	95.71±8.81
$PaCO_2$, mm Hg	37.29±1.89
Stenosis percentage, %	81.0±9.8
Dyspnea, Borg score	5.8±0.8
Cause of stenosis,	
Post-intubation or tracheotomy	14
Post-tuberculosis	4
Malignancy	17

Arterial blood gases were measured under ambient conditions. Values are the mean plus or minus the SD unless otherwise noted.

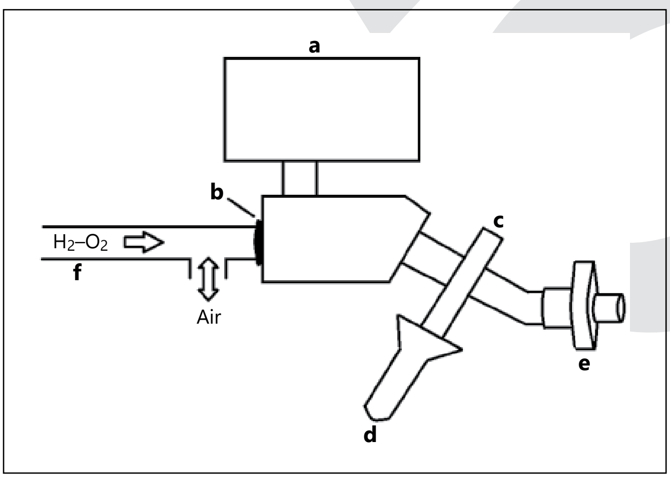

Fig. 2. Method for connecting H_2-O_2 to the IOS system. **a** Loud speaker, (**b**) screen flap, (**c**) Y-adapter, (**d**) pneumochomatograph, (**e**) mouthpiece, (**f**) a T-branch pipe, which connects H_2-O_2 to the IOS system.

Results

Baseline Characteristics

The baseline characteristics are displayed in Table 1. Thirty-five patients with tracheal stenosis were enrolled. Fourteen patients had post-intubation or tracheotomy stenosis, 4 had post-tuberculosis stenosis, 17 had malignant stenosis, and none had tracheomalacia-induced stenosis. Sixteen of the 35 patients (Surface Group) who could not tolerate or refused to swallow the esophageal catheter received the noninvasive surface EMG test instead. The other 19 patients (Esophageal Group) tolerated the esophageal catheter well. Twenty-one of the 35 patients did not tolerate or refused an IOS test, and the other 14 patients underwent IOS tests (Fig. 1).

Variability of EMGdi during Gas Mixture Inhalation

The EMGdi decreased significantly, as did the transdiaphragmatic pressure, while breathing H_2-O_2. In the Surface Group (n = 16), the sEMGdi of the left side was significantly lower with H_2-O_2−1 than with air or O_2 (18.40 ± 4.85% for H_2-O_2−1 vs. 22.52 ± 5.69% for air vs. 22.65 ± 5.79% for O_2). A significant reduction in the sEMGdi of the right side was observed with H_2-O_2−1 (16.28 ± 6.01% for H_2-O_2−1 vs. 22.14 ± 6.84% for air vs. 21.98 ± 6.79% for O_2). In the Esophageal Group (n = 19), a significant decrease in the EMGdi was observed with H_2-O_2−1 (42.46 ± 13.90% for H_2-O_2 vs. 52.95 ± 15.00% for air vs. 53.20 ± 14.74% for O_2). Among the 35 patients, no difference was observed between H_2-O_2−1 and H_2-O_2−2 or between air and O_2 (Table 2). The EMGdi decreased rapidly over 5 min after breathing H_2-O_2 and tended to be stable for 120 min. The trends in the variability of the EMGdi over time are shown in Figure 3. Figure 4 shows the EMGdi of a typical case.

Correlation between Diaphragmatic Function and Stenosis Percentage

For the 16 patients in the Surface Group, delta-surface EMGdi (ΔsEMGdi) in both the left and right sides was significantly correlated with the stenosis percentage (R_{left} = 0.659, R_{right} = 0.614, both $p < 0.05$). For the 19 patients in the Esophageal Group, a significant correlation between ΔEMGdi and the stenosis percentage was evident (R = 0.761, $p < 0.01$). There was no correlation between ΔPdi and stenosis percentage in the Esophageal Group ($p >$ 0.05).

Correlation between Diaphragmatic Function and Borg Score

In the Surface Group, ΔsEMGdi in both the left and right sides was correlated significantly with the Borg scores of 16 patients (R_{left} = 0.529, R_{right} = 0.616, all $p <$ 0.05). In the Esophageal Group, a significant correlation was evident between ΔEMGdi and Borg scores of 19 patients (R = 0.652, $p < 0.05$). There was no correlation between the ΔPdi and Borg score ($p > 0.05$).

Table 2. Diaphragmatic function during the four breathing steps

Diaphragmatic function index	Air (step 1)	H_2-O_2–1 (step 2)	Δ%	O_2 (step 3)	H_2-O_2–2 (step 4)	Δ%	*p* value*	*p* value**
$sEMG_{di\text{-}L}$%max	22.52±5.69	18.40±4.85	18.3	22.65±5.79	18.31±4.86	19.2	**0.024**	**0.032**, 0.947, **0.029**, **0.028**, 0.961, **0.025**
$sEMG_{di\text{-}R}$%max	22.14±6.84	16.22±6.18	26.7	21.98±6.79	16.28±6.01	25.9	**0.008**	**0.012**, 0.943, **0.013**, **0.015**, 0.977, **0.016**
EMG_{di}%max	52.95±15.00	42.46±13.90	19.8	53.20±14.74	42.50±14.12	20.1	**0.022**	**0.028**, 0.957, **0.029**, **0.025**, 0.992, **0.025**
Pdi, cmH_2O	27.30±7.64	22.52±5.48	17.6	27.37±7.69	22.39±5.53	18.2	**0.022**	**0.031**, 0.970, **0.026**, **0.028**, 0.949, **0.024**

Δ%, percentage change compared with breathing Air or O_2; $sEMG_{di\text{-}L}$%max and $sEMG_{di\text{-}R}$%max, percentage of maximal left/right surface-EMGdi, respectively, from 16 patients; EMG_{di}%max, percentage of maximal EMGdi from 19 patients; Pdi, transdiaphragmatic pressure. Values are the mean ± SD.

* Difference between groups for the four periods.

** Comparison (in the following order) between breathing air and H_2-O_2–1, air and O_2, air and H_2-O_2-2, H_2-O_2–1 and O_2, H_2-O_2–1 and H_2-O_2–2, O_2 and H_2-O_2–2. All comparisons have been subjected to LSD correction.

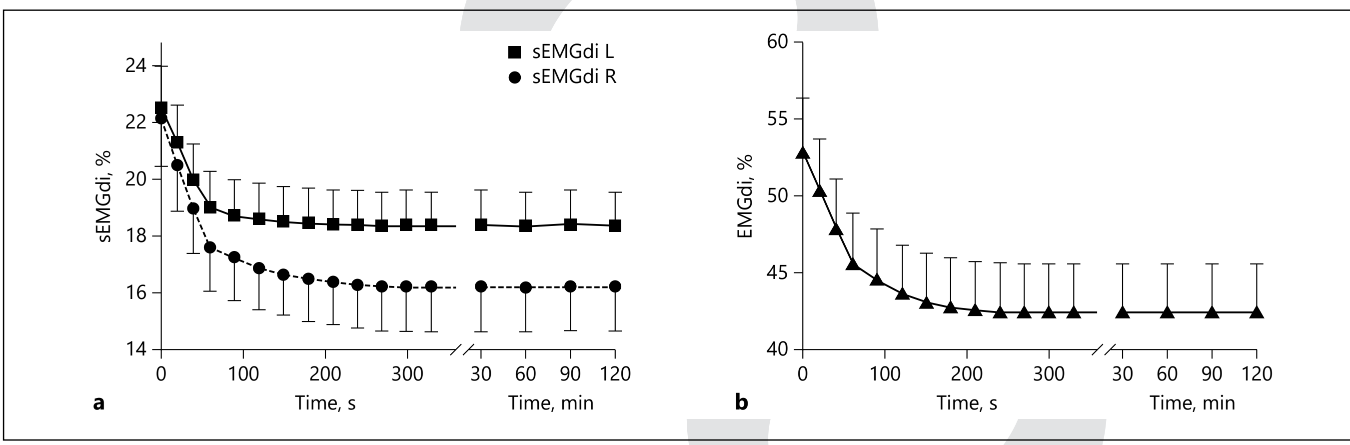

Fig. 3. a Trends in the variability of left and right sEMGdi of 16 patients over time, (**b**) trends in the variability of EMGdi of 19 patients over time.

Pdi, Vital Signs, Borg Score, and Airway Resistance

In the Esophageal Group (n = 19), a significant decrease in the Pdi was observed with H_2-O_2–1 compared with air or O_2 (22.52 ± 5.48 cmH_2O for H_2-O_2 vs. 27.30 ± 7.64 cmH_2O for air vs. 27.37 ± 7.69 cmH_2O for O_2) and is shown in Table 2. No difference existed between H_2-O_2–1 and H_2-O_2–2 or between air and O_2.

Vital signs, including respiratory rate, heart rate, blood pressure, and pulse oximetry, are shown in Table 3. None of the vital signs differed significantly among the 4 breathing steps.

All but 4 (31 of 35) patients exhibited a decrease in the Borg score. The mean reduction in the Borg score under H_2-O_2–1 was 2.02 ± 0.86 points. The Borg score significantly decreased during two H_2-O_2 inhalation steps com-

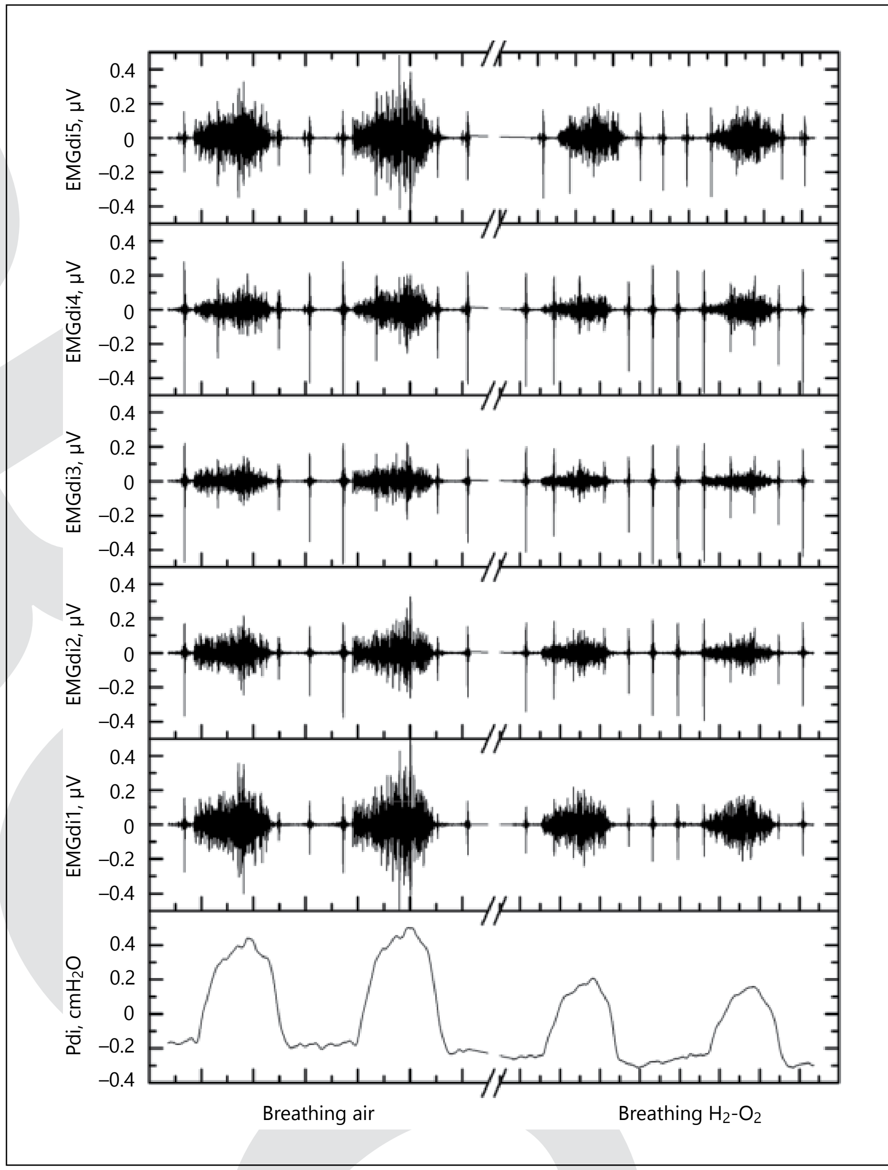

Fig. 4. Diaphragm electromyogram (EMG) recording from the oesophageal balloon-electrode catheter of a typical case. When breathing H_2-O_2, EMGdi and Pdi decreased compared Swith breathing O_2.

pared with air and O_2 (6.71 ± 1.15 vs. 4.69 ± 0.53 vs. 6.66 ± 1.16 vs. 4.74 ± 0.56 points for Steps 1 through 4, $p < 0.05$). No difference existed between H_2-O_2–1 and H_2-O_2–2 or between air and O_2.

Twenty-one of the 35 patients did not tolerate or refused an IOS test. The IOS was performed on the other 14 patients successfully. While breathing H_2-O_2, R5 decreased from 281 ± 110 to 261 ± 106% (t = 3.08, p = 0.02), R20 decreased from 212 ± 056 to 203 ± 058% (t = 3.05, p = 0.02), Z5 decreased from 300 ± 169 to 182 ± 141% (t = 3.24, p = 0.02), whereas R5-R20 were not changed (69 ± 77 vs. 58 ± 65%, t = 2.02, p = 0.064).

Safety

The H_2 concentration was undetectable during the whole procedure (H_2 concentration in the air <0.1%). All patients completed the study successfully without any inhalation-related discomfort. No adverse reaction occurred during the study.

Discussion

To the best of our knowledge, this study may be the first to pioneer the effects of a H_2-O_2 mixture in the emergency management of tracheal stenosis. When breathing

Table 3. Vital signs in the 4 breathing steps

Vital signs	Air	H_2-O_2–1	O_2	H_2-O_2–2	*p* value
RR, breaths/min	19.4±4.2	19.7±4.1	19.5±4.0	19.5±4.0	ns
HR, beats/min	86.3±10.2	87.0±8.7	86.7±9.4	88.5±11.1	ns
SBP, mm Hg	123.4±9.3	121.2±11.8	121.1±12.0	130.0±14.7	ns
DBP, mm Hg	76.4±10.5	73.6±11.4	72.0±8.2	78.1±9.0	ns
SPO_2, %	97.7±0.6	97.4±0.7	97.4±0.5	97.4±0.6	ns

Values are the mean ± SD. RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ns, nonsignificant.

H_2-O_2, the diaphragmatic functions (EMG and Pdi), vital signs (respiratory rate, heart rate, blood pressure and pulse oximetry), Borg score and airway resistance (resistant parameters of IOS: Z5, R5 and R20) of each patient were observed. The patient's diaphragmatic function, Borg score and IOS parameters were significantly improved, which indicated that breathing the H_2-O_2 mixture could reduce airway resistance and decrease inspiratory effort.

Many studies have reported that breathing He is an effective method for the emergency management of acute upper airway obstruction [5–8, 24, 25]. Mechanistically, gaseous He has a much smaller density than the air, hence a much lower Reynolds number (Re). The lower density is responsible for the lower turbulence and airway resistance when He passes through the narrow airway [22, 26, 27]. H_2 and He have similar physical characteristics and the same molecular weight (both are 2). From a physics perspective, therefore, breathing H_2 can also decrease airway resistance and relieve dyspnea in patients with tracheal stenosis. In the present study, there were 3 patients with subglottic stenosis in whom a Montgomery T-tube stenting has been in place (data not shown). For the 3 patients, we used a monitor with a small pipe passing through the external limb of Montgomery T-tube to detect the level of H_2 in the trachea while breathing H_2-O_2 (comprised 66% H_2) at 6 L/min. The concentration of H_2 in the trachea was found to be approximately 30–35%. Given that a low concentration (20%) of He has proved sufficient to have an effect on reducing airway resistance [27], we speculated that breathing H_2-O_2 (H_2: 66%, 6 L/min) in our study could be at least as effective in the emergency management of tracheal stenosis.

EMGdi and Pdi were 2 objective indexes to assess the neural drive that reflected the inspiratory effort [23]. The EMGdi was the primary end-point because it could assess the neural drive more sensitively and accurately than the Pdi [19, 28, 29]. For those patients who did not tolerate swallowing the catheter, the surface EMGdi test was performed instead, as previously reported [30]. The use of the He-O_2 mixture in patients with upper airway obstructions has been reported in several studies, but most of them were observational or case reports [4, 7, 31–33] without objective assessments. Martin et al. [34] demonstrated the effects of an He-O_2 mixture on the airway with increased resistance by using the pulmonary function test. However, reliable assessments were difficult because the results were strongly influenced by patient cooperation. Studies by Samir et al. [3] and Galius et al. [4, 5] assessed inspiratory effort by Pdi, and examined whether breathing a He-O_2 would reduce the inspiratory effort in patients with upper airway obstructions. The mean decreases in Pdi while breathing He-O_2 were 19 and 30% for left and right sides respectively. In the present study, the mean reductions in the sEMGdi were 18.3 and 26.5% for left and right sides respectively; the mean reduction in the EMGdi in the Esophageal Group was 20.0%, and that in the Pdi was 17.6% while breathing H_2-O_2, compared to air or O_2. The effect of H_2-O_2 was similar to that of He-O_2 as found by those 2 investigating teams [4, 5].

A scatter plot was generated to identify the trends in the variability of EMGdi at every 30 s throughout the inhalation. As shown, the EMGdi decreased rapidly over 5 min and tended to remain stable until 120 min while breathing H_2-O_2. No significant difference in the EMGdi existed between H_2-O_2–1 and H_2-O_2–2, indicating that H_2-O_2 acted rapidly and that the effect peaked within 5 min. These findings were similar to those of an earlier study [22]. No significant difference in the EMGdi was observed between breathing air and O_2, which indicated that breathing O_2 could not decrease the inspiratory effort for these patients. This was not surprising because the dyspnea in the patients included in this study arose from obstructive hypoventilation but not pulmonary diffusion insufficiency. The ineffectiveness of oxygen therapy as a treatment for patients with tracheal stenosis has been well confirmed.

The Borg score was used to evaluate the patient-perceived exertion in this study, classifying the level of patient-perceived exertion into 10 grades. We speculated that using Borg score to evaluate the level of patient-perceived exertion could be more accurate than a self-designed 5-score questionnaire as adopted in the study by Jaber et al. [5] All but 4 (31 of 35) of our patients showed decreases in their Borg scores, suggesting that breathing H_2-O_2 improved the patient's comfort level and objective indexes.

For the 4 patients who presented with no improvements in their Borg scores, their stenosis percentages in the CT image were 68, 60, 59, and 69%. These patients showed the mildest degrees of tracheal narrowing among the 35 patients. Additionally, these patients showed minimal improvement of EMGdi measurements compared to those of the other patients. H_2-O_2 works by reducing turbulence in the narrow trachea. The effect of H_2-O_2 could be modest with mild degree of airway narrowing where turbulence occurs less [27]. Therefore, milder stenosis (or lower Borg score) could be associated with fewer improvement of EMGdi (or less improvements in Borg score). In fact, there was a positive correlation between △EMGdi and the degree of tracheal narrowing (and Borg score) in this study.

No significant alterations in the respiratory rate, heart rate, blood pressure, and pulse oximetry during the 4 breathing steps indicated that breathing H_2-O_2 did not interfere with the vital signs, and this is inconsistent with the finding of previous studies [5, 35, 36].

IOS can be used to assess obstruction in large and small airways sensitively [37, 38]. Several studies have reported that IOS may be more sensitive than spirometry for discriminating patients with center airway obstruction [39–41]. In this study, R5, R20, Z5, and R5-R20 by IOS were used to evaluate airway resistance. While breathing H_2-O_2, all parameters reflecting large airway resistance (R5, R20, and Z5) decreased significantly, whereas parameters reflecting peripheral airway resistance (R5–R20) were not changed, indicating that the mechanism of H_2-O_2 toward relieving dyspnea was to reduce airway resistance.

He-O_2 can relieve dyspnea in patients with tracheal stenosis. Helium's expensiveness and inconvenience related to its use limits its widespread use in clinical settings (for example, He could not be used in an ambulance). H_2 has not previously been used in clinical settings due to its explosiveness until recently. In this study, we monitored the concentration of H_2 in the environment during the entire study. H_2 diluted in the ambient environment quickly and the concentration of H_2 never exceeded 0.1% in the air, which was far from the explosion level (4%). So it may be used safely in clinical.

Nevertheless, it should be important to note that breathing H_2-O_2 could not relieve the stenosis percentage. The major benefit of H_2-O_2 inhalation was to relieve dyspnea and alleviate patient discomfort during the perioperative period. Although the IOS parameters decreased significantly while breathing H_2-O_2, they remained substantially above normal. Without subsequent management by surgery or interventional bronchoscopy, the dyspnea in these patients may deteriorate and progress into acute respiratory failure or suffocation. Therefore, despite the clinical benefits for patients with tracheal stenosis found in the present study, H_2-O_2 inhalation could be recommended merely as an effective dyspnea-reliever but absolutely should not substitute for further aggressive treatment.

Our study has several limitations. First, the study lacked a He-breathing control group for comparison between He-O_2 and H_2-O_2. Second, to avoid increasing the patient's inspiratory effort, we did not perform flow measurements. Therefore, an exploration of the comprehensive mechanism was not possible. Third, sample sizes were relatively small, rendering a multi-center randomized control trial warranted to fully demonstrate the effect of H_2-O_2 in patients with tracheal stenosis. Fourth, both H_2 generator and O_2 generator in this study are set to only 2 flow rate options: 3 and 6 L/min, which might affect objective evaluating method of single blind. However, according to Bernoulli's equation (wp = 0.5·ρ·v^2, wp denotes wind pressure [KN/m^2], ρ denotes gas density [kg/m^3], v denotes flow velocity [m/s]), 6 L/min of O_2 provides 2.69 times of wind pressure compared with 6 L/min of H_2-O_2, whereas 6 L/min of H_2-O_2 provides only 1.48 times of wind pressure compared with 3 L/min of pure O_2 at standard condition. Hence, the flow rate of O_2 was set to 3 L/min to compare against 6 L/min of H_2-O_2.

In summary, we demonstrated that the inhalation of H_2-O_2 can decrease the EMGdi, Pdi, Borg score and IOS resistance parameters significantly, without modifying the respiratory rate, heart rate, blood pressure or pulse oximetry. In terms of safety, no adverse reactions occurred and H_2 was undetectable in the ambient environment during breathing H_2-O_2. These clinical benefits may inspire future studies for further clarification and validation.

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Ethics Statement

The Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Approval Number: 2016–50).

Financial Disclosure and Conflicts of Interest

All other authors declared no potential conflict of interest.

Patient Consent

Obtained.

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Author Contributions

Conceived and designed the experiments: S.-Y.L., Z.-Q.Z., and C.-H.Z.; Performed the experiments: Z.-Q.Z., Z.-Q.S., X.-Y.L., Y.C, C.-H.Z., X.-B.C., C.-L.T., and L.-Q.Z.; Analyzed the data: Z.-Q.Z., X.-Y.L., and L.-Q.Z.; Contributed to writing the manuscript: S.-Y.L., C.-H.Z., and Z.-Q.Z., Final approval of the version to be published: Z.-Q.Z., C.-H.Z., Z.-Q.S, X.-Y.L., Y.C., X.-B.C., C.-L.T., L.-Q.Z., and S.-Y.L.

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