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Oxygen Generation by Combined Electrolysis and Fuel-cell Technology: Clinical Use in COPD Patients Requiring Long Time Oxygen Therapy

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Abstract
Background: Oxy-Gen lite, a recently developed combined electrolysis and fuel cell technology, de-novo generates oxygen with high purity for medical use from distilled water and room air. However, its use in patients with chronic respiratory failure has never been evaluated.
Objectives: To test the clinical applicability and safety of Oxy-Gen lite technology, we enrolled 32 COPD patients with chronic hypoxemia and long-term oxygen therapy (LTOT) in a controlled, randomized, multicenter clinical trial.
Materials and Methods: Standard continuous oxygen therapy with a maximal flow rate of 2 L/min was tested against pulsatile oxygen delivery by Oxy-Gen lite. Oxygen saturation at seated-rest was recorded over 30 min and used as a primary read-out parameter. Oxygen saturation was also recorded during mild physical strain (speaking out loud) or overnight's sleep.
Results: Both methods of oxygen supply established oxygen saturations within the normal range (i.e., upper plateau of the sigmoid oxyhaemoglobin dissociation curve) compared to breathing room air ($p<0.0001$). Mean oxygen saturation under standard continuous oxygen flow or Oxy-Gen lite technology during rest, physical strain or sleep proved statistically equivalent (95%CI < 2.5% of reference saturation).
Conclusion: The use of Oxy-Gen lite in COPD patients with hypoxemia and LTOT ≤ 2 L/min is safe and results in oxygen saturation comparable to standard oxygen therapy. There is evidence that this form of oxygen supply is not only functional during rest but also during mild physical strain or overnight's sleep. Low noise, energy- and overhead-costs are particular advantages of this technology.

Key words: COPD, LTOT, oxygen, saturation, electrolysis, fuel cell

Introduction

Long-term oxygen-therapy (LTOT) is an accepted therapeutic approach in conditions with sustained respiratory failure, particularly for patients with chronic obstructive pulmonary disease (COPD) [1-3]. Guidelines for the prescription of LTOT in hypoxemic COPD patients are based on two landmark studies in which survival was the primary outcome [4, 5]. Although indications for LTOT are largely based on mortality data, there is increasing evidence for improvements in other outcome measures, including depression, cognitive function, quality of life, frequency of hospitalisation or rehabilitation [6-10].

To provide patients with continuous oxygen in different settings (e.g., stationary, ambulatory) several options for oxygen delivery have been developed. For the use at home, oxygen concentrating devices are most frequently prescribed, which are notable for their robust, user friendly design and large service intervals. However, the draw back is that those tools are bulky, heavy and noisy due to built-in compressors. To circumvent some of the inborn problems of oxygen concentrators and to provide mobile oxygen supply, liquid oxygen has been introduced to medical treatment although the provision is only accomplished at the expense of high cost [11, 12]. This has in part been compensated by the introduction of oxygen sparing devices. The principle of those valves is to synchronize the oxygen flow with patients respiratory manoeuvres. Oxygen release is triggered by inspiration of the patient, which can reduce oxygen consumption substantially [13, 14].

LTOT at home, however, remains an inconvenient and expensive intervention and patients compliance ranges from moderate to poor [15-17]. Concerted efforts were made to develop new methods of oxygen delivery which will maintain adequate arterial oxygenation, but at the same time reduce cost of oxygen administration, provide patients with prolonged oxygen availability and to improve equipment convenience [18].

Recently, a new technology for de-novo synthesis of oxygen with high purity for medical use was developed (Oxy-Gen lite, Linde Medical Devices GmbH, Aschau im Chiemgau, Germany). Oxy-Gen lite separates oxygen and protons from distilled water by electrolysis. The protons are re-utilised by a combined fuel cell chamber, resulting in generation of electricity and water, which both are recycled into the system. The oxy-

gen generated is delivered via a newly developed electronically controlled pulse valve, allowing the patient to trigger a bolus application of oxygen during early inspiration.

In the present study, we aimed to test the clinical applicability and safety of Oxy-Gen lite technology for a first time in patients with chronic respiratory failure that require LTOT. Therefore, we conducted a controlled, randomized, multicenter clinical trial and compared the equipotency of Oxy-Gen lite to the standard way of continuous oxygen supply for patients at seated-rest, during mild physical strain and overnight's sleep.

Methods

Patients and Hospitals

To test the feasibility of the newly developed device in a clinical setting, we selected adult patients with stable chronic obstructive pulmonary disease (COPD) and sustained respiratory failure. Arterial partial pressure of oxygen (paO_2) had to be between 40 - 60 mmHg at rest, awake and breathing room air. Measurements were taken at two independent visits by capillary blood analysis. All Patients included in the study had to be on LTOT (>3 month) by oxygen concentrator with a continuous flow rate not exceeding 2 litre per minute (L/min) for at least 12 hours per day. Clinical stability was demonstrated by no exacerbation for ≥ 4 weeks before enrolment.

The trial took place between September 2005 and June 2006 at four different respiratory care facilities in Germany. Following initial screening, a total of 54 patients were found eligible to enter the trial. The study was performed according to GCP requirements and monitoring was done by a professional contract research organisation (CRO). Of all 32 subjects enrolled, 27 completed at least two parts of the study (measurements of continuous oxygen and Oxy-Gen lite measurements at seated-rest and speaking out loud). The third part of the study (measurements during sleep) was completed by 20 patients. One patient died after enrolment without having actually participated in the study; one patient underwent lung transplantation after having been on the waiting list for the previous two years. All other drop-outs were related to lack of compliance on the patient side.

Continuous Oxygen

All patients included in this study used oxygen concentrators with continuous flow at home. However, different brands and technologies of concentrators were used, which differ in terms of flow rates and effective oxygen concentrations (Table 1). To ensure identical conditions in this study, we used the central oxygen systems of each hospital as a source of continuous oxygen flow. Oxygen (99% purity independent of flow rate) was drawn from calibrated airflow meters that allowed to adjust flow rates in L/min. All patients were supplied with the same type and brand of oxygen cannula with double nasal prongs (Dahlhausen Medical Technologies, Germany).

Oxy-Gen Lite

The construction of the patented device is schematically depicted in Figure 1, the systems characteristics are given in Table 1. The principle element consists of an electrolyser unit to separate protons and oxygen from distilled water, coupled to a fuel cell generating electricity from the hydrogen protons. On the electrolyser side, the oxygen is first spitted from the water. Next, the protons are lead through the fuel cell Proton Exchange Membrane (PEM) and re-combined with oxygen from room air, gaining back water and energy. The summarized chemical reaction and a flow sheet for key processes of Oxy-Gen lite technology are shown in Figure 2. Because Oxy-Gen lite is separating oxygen via electrolysis from deionized water, without direct contact to the ambient air, the generated oxygen has a very high purity (> 99,9% when dried). The generated oxygen is humidified by the electrolyser cell itself, with a resulting relative humidity of 85%, making an external humidifier dispensable.

Table 1. Technical characteristics of the oxygen generating and delivering device (Oxy-Gen lite) and oxygen concentrators frequently prescribed in Germany.

Manufacturer	**Linde Medical Devices**	**Köber**	**Devilbiss**	**Weinmann**
Model	Oxy-Gen lite	Köber O_2	Compact 5	Oxymat 3
Size (height, width,depth)	49 x 26 x 28 cm	53 x 20 x 52 cm	70 x 41 x 36 cm	40 x 70 x 35 cm
Weight	10.0 kg	19.8 kg	24.5 kg	20.0 kg
Power consumption	130 Watt	350 Watt	365 Watt	360 Watt
Max. oxygen output	0.56 L/min*	6 L/min	5 L/min	5L/min
O_2 concentration	>99.9%	1-4 L/min 95 - 3%	1-5 L/min 93 ± 3%	1-4 L/min 95 ± 3%
		4-5 L/min 85 ± 3%		4-5 L/min 90 ± 3%
		5-6 L/min 75 ± 3%		
Noise level	35 dB (A)	35 dB (A)	45 dB (A)	40 dB (A)

*with COIS oxygen demand system equivalent to 3L/min

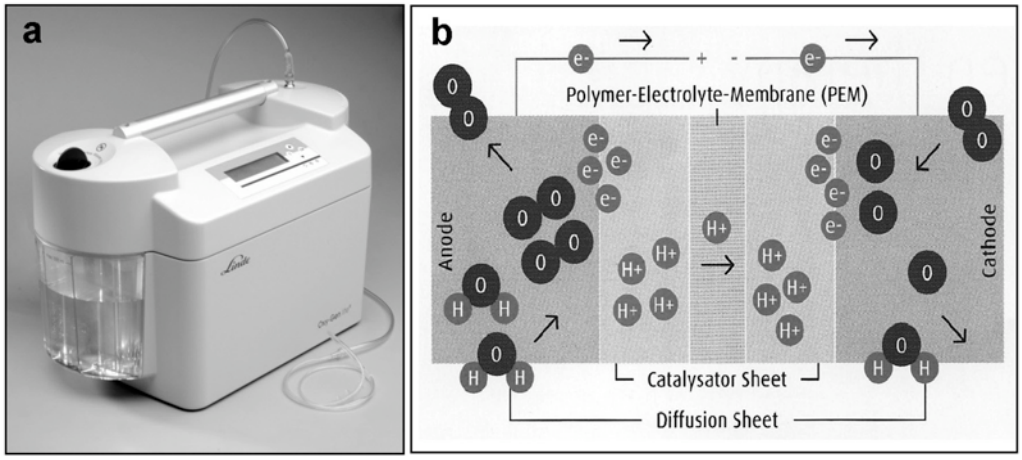

*Fig. 1. (*a) Photograph of oxygen generating and delivering device Oxy-Gen-lite. The system consists of the bi-functional electrolysis/fuel cell and the proprietary oxygen delivering device (COIS). (b) Schematic drawing of the partial electrolysis of water and the fuel cell technology used by Oxy-Gen lite device.

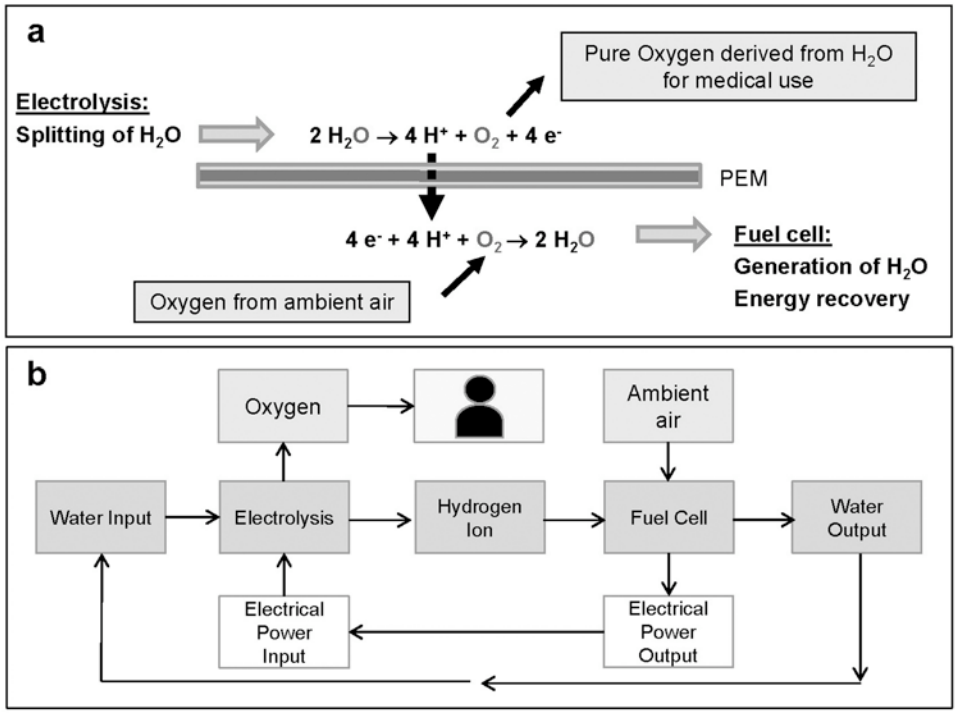

Fig. 2. Simplified chemical formula (a) and flow sheet (b) for key processes of Oxy-Gen lite technology.

The device was coupled to an oxygen demand system (COIS, Controlled Oxygen Insufflation System) that liberates preset doses of oxygen at the early phase of inspiration. In an extensive pre-study development phase with varying flow profiles, maximal flow settings, inspiratory delays and triggering sensitivities, a best fitting algorithm was derived and implemented in the system. Using these settings, the maximal oxygen delivery rate of Oxy-Gen lite (0.56 L/min) was shown to be equivalent to a conventional continuous flow rate of approximately 3L/min, which represents a 5-fold reduction in oxygen consumption. Due to the regain of energy in the fuel cell and the integrated COIS system, the net energy consumption values approximately 130 Watts in average and 180 Watts at maximal oxygen delivery. The electric current is proportional to the generated oxygen following the Faraday law.

Study Protocol

The study protocol was approved by the ethics committee of the University Hospital Frankfurt, Germany. After informed consent and signature, patients were enrolled into the study and randomly assigned to one of two arms starting with continuous oxygen or Oxy-Gen lite therapy, respectively (Fig. 3).

The reference oxygen saturation at seated-rest was determined for each individual patient after a wash-in period with standard continuous oxygen therapy at a L/min-setting familiar to the patient. After 30 minutes, the oxygen saturation was documented as reference saturation. Next, the bolus size of the Oxy-Gen lite device that corresponds to the individual L/min-setting under standard therapy was determined for each patient. Therefore, the bolus size of Oxy-Gen lite was

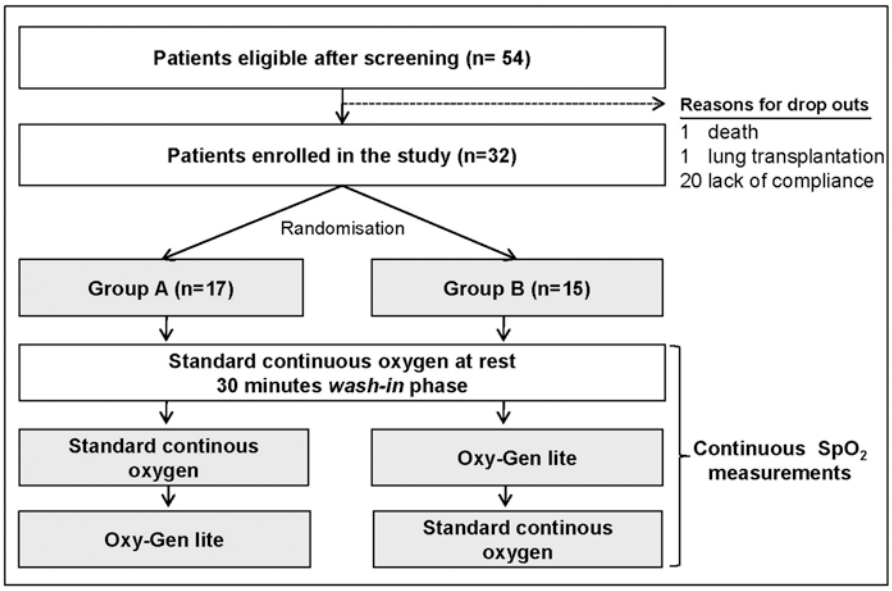

Fig. 3. Trial design.

titrated until a stable oxygen saturation was achieved at rest that was identical to the reference saturation under standard care. Those instrument settings (L/min or bolus size) were kept constant for each patient throughout the different trial phases (rest, speaking, sleeping) and no further adjustments were allowed.

For the studies at seated-rest, patients underwent oxygen therapy by either standard or Oxy-Gen lite approach for 30 minutes and the resulting oxygen saturations were documented every minute. For the speaking-trial, patients were advised to read out loud newspaper clippings with familiar wording for a continuous 10 minutes period either under standard continuous oxygen or Oxy-Gen lite therapy.

During the sleeping-trial, patients spent one night with oxygen therapy by either standard or Oxy-Gen lite approach. All measurements were done by automated recording systems like Porti V (Fenyves & Gut, Hechingen, Germany) or similar. The device was programmed to continuously record patients oxygen saturation (mean, max, min) and measurements were started at night after the patient went to bed.

Data Management and Statistical Analysis

The complete study was monitored by a professional CRO, which also holds responsible for patient randomisation, query management and data storage. After clarification of the data, the central data bank was closed and forwarded for statistical analysis (SAS software, Version 8, SAS Institute Inc, Cary, USA). As a primary hypothesis of this trial Oxy-Gen lite therapy will be considered equivalent to the standard treatment (continuous oxygen supply) if it can be shown to be no more than 2.5% inferior on mean oxygen saturation at seated-rest. Based on our pre-study data (not shown), we estimated n = 25 as the minimal number of patients in the analysis to show one-sided equivalence with a = 0.05 and a power of 80%. Oxygen saturation during speaking out loud and night's sleep were considered as secondary variables. The individual differences of mean oxygen saturation values proved sufficient normal distributed to assess the equivalence of mean oxygen saturation under continuous oxygen vs. Oxy-Gen lite therapy by 95% CI, respectively.

Therapeutical equivalence was assessed by one-sided lower 95% CI [19]:

$$Lower\ 95\%CI < \overline{P}_{cont} - \overline{P}_{Oxy\text{-}Gen} + t_{(n-1;\ 1-a)} * SD_{(P\ cont\ -\ P\ Oxy\text{-}Gen)} / \sqrt{n} < 2.5\%$$

where $\overline{P}_{cont}$, $\overline{P}_{Oxy\text{-}Gen}$ = means of oxygen saturation

$SD_{(P\ cont\ -\ P\ Oxy\text{-}Gen)}$ = standard deviation of individual differences

Data are presented by tables, histograms or boxplots with median, Q1,Q3 and mean ± SD, where appropriate. Statistical significance was predefined at the level of a = 0.05. Empirically found p-values are given descriptively.

Results

Recruitment was closed after sufficient patients (n=32) were enrolled to test the primary hypothesis of this trial, i.e. the equality of oxygen saturation at seated-rest during standard oxygen therapy vs. Oxy-Gen lite therapy under the conditions described by the protocol.

Baseline Patient Data

There were no significant differences between the two treatment arms of the study in respect to anthropometric measurements, standard laboratory parameters as well as pulmonary function data. Some of the most important data are summarized in Table 2.

Measurements at Rest

The mean reference saturation (oxygen saturation after 30 min at seated-rest under standard therapy) in

Table 2. Baseline patient data.

	All patients (n=32)	Randomisation Group A* (n=17)	Randomisation Group B* (n=15)
Age [years, (+/- SD)]	58.3 (+/- 16.1)	59.4 (+/- 16.5)	57.0 (+/- 16.1)
Sex [male/female]	16/16	8/9	8/7
Size [cm]	169 ± 11	167 ± 9	171±12
Weight [kg]	67.3 ± 17	63.8 ± 16	71.2 ± 17
Heart rate [bpm]	88 ± 12	89 ± 11	88 ± 13
Blood pressure [mmHg]	128/77	129/78	127/75
Haemoglobin [g/dL]	13.7 ± 2.3	13.4 ± 2.7	14.0 ± 1.4
Vital capacity [L]	2.3 ± 0.7	2.4 ± 0.7	2.3 ± 0.7
FEV1 [L/sec]	1.04 ± 0.5	1.01 ± 0.5	1.07 ± 0.5
pO_2 [mm Hg]	53.3 ± 9	54.6 ± 5	51.9 ± 11
pCO_2 [mm Hg]	41.7 ± 7	42.3 ± 8	41.0 ± 5
Oxygen saturation [%]	89.4 ±3	89.8 ± 2	89.1 ± 3

* differences between groups A and B were statistically not significant (p >0.05)

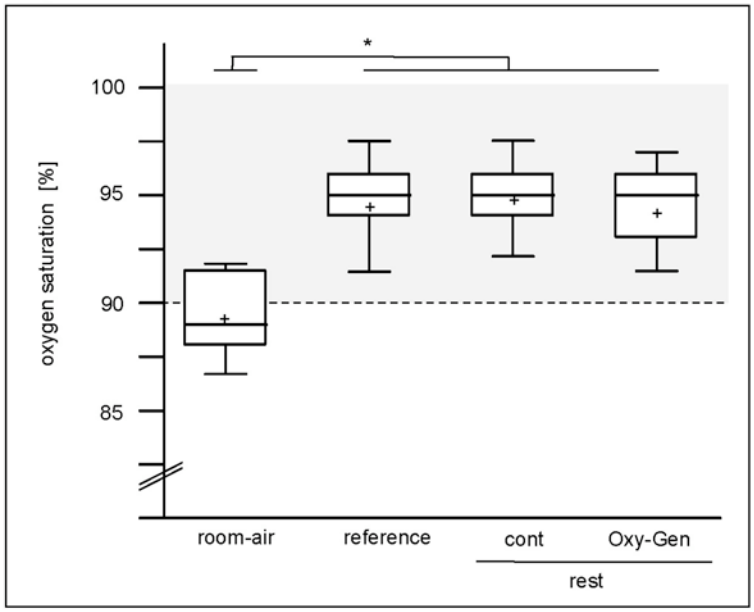

Fig. 4. Box plots (median, Q1,Q3 and mean ± SD) for oxygen saturation at seated-rest (room-air, baseline saturation without supplemental oxygen; reference, reference saturation; cont, continuous oxygen supply; Oxy-Gen, oxygen supply by Oxy-Gen lite). * indicates p < 0.001 for differences between room-air and different conditions of oxygen supply. Greyed-out area represents the upper plateau of the sigmoid oxyhaemoglobin dissociation curve [20].

this study was 94.5 ± 3.0%. Patients required on average 1.66 ± 0.4 (range 1.0 – 2.0) L/min of continuous oxygen and the corresponding bolus size under Oxy-Gen lite therapy was 47.4 ± 21.2 (range 15-70) ml/Bolus. Both methods of oxygen supply established an oxygen saturation within the normal range (i.e., upper plateau of the sigmoid oxyhaemoglobin dissociation curve) compared to room air (p <0.001) [20]. Mean ± SD of oxygen saturation at rest under standard oxygen therapy vs. Oxy-Gen lite therapy was 94.9 ± 2.7% vs. 94.2 ± 2.7%, respectively (Fig. 4). Measurements at seated-rest did reveal equivalence between both treatments. The mean difference of oxygen saturation between continuous and Oxy-Gen lite therapy proved within a lower one-sided 95% CI of 1.04% relating to the reference saturation (p <0.05).

Measurements during Physical Strain or Sleeping

When speaking out loud, oxygen saturation under continuous oxygen and Oxy-Gen lite therapy was 94.5 ± 2.7 % and 93.4 ± 3.2 %, respectively. For the sleeping-trial, oxygen saturation under continuous oxygen and Oxy-Gen lite therapy was 93.2 ± 4.0 % and 91.9 ± 3.3 %, respectively (Fig. 5). There was a trend for lower oxygen saturation during physical strain and night's sleep compared to measurements at seated-rest. However, decrease of oxygen saturation was comparable under both systems of oxygen supply and oxygen saturation remained in the normal range. Again, during speaking as well as sleeping, the mean differences of oxygen saturation between both methods of oxygen supply proved equivalent within a 95% CI of 1.78% and 2.36%, respectively (p <0.05).

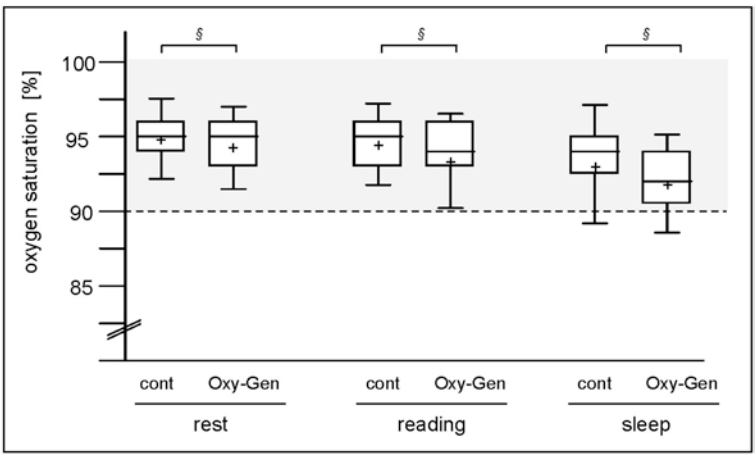

Fig. 5. Box plots (median, Q1,Q3 and mean ± SD) for oxygen saturation at seated-rest, speaking out loud or night's sleep, respectively (cont, continuous oxygen supply; Oxy-Gen, oxygen supply by Oxy-Gen-lite). § indicates statistical equivalence for both methods of oxygen supply ($p<0.05$). Greyed-out area represents the upper plateau of the sigmoid oxyhaemoglobin dissociation curve.

Discussion

Recent advances in electrolysis and fuel cell technology allowed construction of a device for efficient de-novo generation of oxygen from deionised-water. Equipped with an electronic pulsed dose oxygen conserving device, Oxy-Gen lite is now certified and available for everyday use in medicine. In this study, we aimed to compare the efficacy of the new system with that of standard continuous flow nasal oxygen during usual activities of daily life. Our results show that Oxy-Gen lite was equivalent to continuous flow oxygen in maintaining oxygen saturation at seated-rest, during mild physical strain (speaking out loud) and overnight's sleep in patients with COPD under the conditions of this study.

Although several previous studies have demonstrated the effectiveness of oxygen conservation devices at rest, there have been few studies of their performance during physical strain or sleep. Our rationale to test the performance of Oxy-Gen lite during speaking out loud was the observation that many patients with COPD desaturate with minimal activity (e.g., talking, eating). It seems likely that hypoxemia during activity may discourage exercise, promote deconditioning and thereby diminishes quality and potentially length of life [21]. Although mortality data for COPD are lacking, it is known that exercise desaturation in otherwise normoxic subjects with interstitial lung disease is associated with shorter survival [22]. On the other hand, it was previously shown that supplementation with oxygen improves exercise endurance in subjects with advanced COPD [23,24]. We found that Oxy-Gen lite technology can adequately oxygenate most patients during mild physical strain without clinically relevant differences for oxygen saturation between continuous vs. pulsed oxygen supplementation.

We also aimed to test administration of oxygen during night's sleep, because Patients with severe COPD may have episodes of sleep-disordered breathing associated with profound hypoxemia [25]. These episodes are associated with transient increases in pulmonary arterial pressure, and repeated episodes may well contribute to progressive sustained pulmonary hypertension and the genesis of cor pulmonale [26]. It was shown that supplemental oxygen prevents nocturnal desaturation [27] and data from one observational study suggest a survival benefit in COPD subjects that are normoxic at daytime [28]. It was postulated that reduced mortality under nocturnal oxygen therapy results from decreased physiologic stress of repeated hypoxemia. Additional benefits might result from improved quality and quantity of sleep [29]. Again, we found that both Oxy-Gen lite and standard continuous therapy adequately oxygenated COPD patients during night's sleep and there were no clinically relevant differences with regard to mean or lowest oxygen saturation or the number and duration of desaturations at night. Demonstration of Oxy-Gen lite efficacy during night's sleep is of particular importance because despite a sophisticated evolution of oxygen demand systems, there has been concern that those devices fail to sense inspiratory pressure swings at night, especially when sleeping patients breath with open mouths [30].

Today, two main regimens are available for domiciliary oxygen administration to patients with hypoxemia: Oxygen concentrators and liquid oxygen systems. Despite significant differences in operating expenses, no clear criteria exist for the use of traditional stationary vs. liquid oxygen. Of note, clinical cardiopulmonary status and blood gas levels do not seem to be the deciding factors [31,32]. From the institutional standpoint, the oxygen concentrator technology is by far the most cost effective of the various oxygen delivery systems [33]. However, mainly due to built-in compressors, conventional concentrators are floor-standing, heavy and bulky. The most frequent complaints patients make about concentrator treatment is that devices are noisy and make them feel tied down [34]. In contrast, Oxy-Gen light technology requires no compressor, which made it possible to construct a device with round half the size and weight of a conventional oxygen concentrator. Due to reduction of moving parts, the system operates free of vibrations and with low noise level (35dB). Another clinically relevant limitation for concentrators is the fact that they do not provide 100% of oxygen. Depending on the design, state of repair and how close flow is set to the maximum rate, the O_2 concentration can drop substantially [35,36]. In contrast, Oxy-Gen lite de-novo produces reagent-grade oxygen with a purity of >99.9% and, due to the active principle of electrolysis, the oxygen concentration is independent of the flow rate.

The most convenient system for continuous oxygen supply at home as well as during extensive daily outdoor activities is liquid oxygen [37]. It is four times as concentrated as gas in a high–pressure cylinder and the containers are relatively small and light. For outdoor use, patients can easily refill a portable container from a stationary container. Liquid oxygen therapy, however, is handicapped by its high costs, mainly due to logistical expenditure. A typical cylinder with a filling capacity of 30 kg liquid oxygen (equivalent to a gas volume of 25.650 L) has an operating time of approx. 200 hours at continuous 2 l/min flow, thus requiring weekly changing/service intervals. A recent study that compared the charges for LTOT found mean total costs (including oxygen, rent, freight, medical technician and healthcare services) over a six month period of 4950 (+/-2340) US$ vs. 1310 (+/-650) US$ for liquid oxygen vs. concentrator therapy, respectively [38]. Another disadvantage is that liquid oxygen can only be kept for a short time because of significant evaporation rates (approx. 0,68 kg per day) and some countries do not provide area-wide distribution networks [39,40]. In the light of these limitations it seems an particular advantage of the Oxy-Gen lite technology that it is universally applicable with no logistics required and at the same time produces a virtually unlimited amount of oxygen at the expense of 2-3 L of deionized water (which can be purchased at a conventional drugstore) and electric power. Because of energy re-gain in the coupled fuel cell, the net energy consumption values approximately 130 Watts, which is less than half the energy consumption of an average oxygen concentrator (approx. 360 Watts). At a rate of 0,19 € per KWh, the average monthly operating cost for Oxy-Gen lite in Germany adds up to less than 25€ per month.

Another frequent concern with LTOT is that the humidity and temperature of supplemental oxygen, particularly from cryogenic sources, is outside the optimal physiologic range. Breathing cool, dry gases constitutes an osmotic challenge to mucosal cell function with deleterious effects such as nasal discomfort and bleeding, mucosal damage, reduced ciliary motility and decreased mucus production [41-43]. Conversely, some investigators have shown a protective effect from inhaling warm, humidified gas [44]. Optimal conditions are postulated when the inspired gas has 100% relative humidity and is at body temperature [45]. Therefore, humidifiers are commonly employed in patients who require ≥ 2 L/min of oxygen supplementation to prevent mucosal drying. However, conventional bubble humidifier are non-heated and result in a relative humidity of little more than 70% [46]. Moreover, multiple-use reservoirs are a potential source for contamination with pathogenic microorganisms [47,48] and bacterial carry-over by microaerosols poses a risk for pulmonary infection [49]. In contrast, by nature of oxygen generation from water by electrolysis, Oxy-Gen lite produces pre-warmed and humidified oxygen (85% relative humidity) without the need for external humidifiers. Finally, because oxygen humidification is achieved without the need for a bubble humidifier and the water content of the inhaled gas is limited to what can be carried in the vapor phase (without generation of microaerosols), Oxy-Gen lite technology might reduce the incidence of airborne infections related to LTOT equipment.

In conclusion, oxygen generation and application by Oxy-Gen lite is safe and similarly effective as standard continuous oxygen therapy in maintaining oxygen saturation at rest, during mild physical strain and overnight's sleep in patients with COPD, at least under the conditions of our study. Low noise and humidity of the gas are special advantages of the new technology.

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