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Automatic Oxygen Titration During Walking in Subjects With COPD: A Randomized Crossover Controlled Study

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BACKGROUND: Arterial oxygen desaturation frequently occurs in patients with COPD during daily activities at home. Oxygen flow is usually set at fixed and low rates for ambulatory patients. We evaluated an innovative closed-loop system ($FreeO_2$) that automatically adjusts the oxygen flow to the patient's needs in subjects with COPD during walking followed by recovery time, such as during ambulatory conditions. METHODS: Patients with COPD who exhibited oxygen desaturation on exertion were included in the study. Subjects performed endurance shuttle walk tests followed by 10 min of recovery. The tests were conducted in a random order and in crossover with the 3 following conditions: subjects breathing (1) air at 2 L/min, (2) oxygen at 2 L/min, or (3) $FreeO_2$ (variable oxygen flow). S_{pO2}, pulse rate, P_{ETCO_2}, breathing frequency, and oxygen flow were continuously recorded during the 3 conditions. The primary outcome was the percentage of time within the S_{pO2} target of 92–96%. Secondary outcomes included the endurance shuttle walk test time and distance. RESULTS: Sixteen subjects with COPD were recruited. The percentage of time with S_{pO_2} in the target range (92–96%) was higher while using the $FreeO_2$, and time with severe oxygen desaturation (S_{pO_2} <88%) was lower with $FreeO_2$ in comparison with constant-flow oxygen and air testing conditions (0.6% vs 23.9% vs 52.2%, $P < .001$). In comparison with air, walking distance was increased by 35% with oxygen ($P = .045$) and by 63% with $FreeO_2$ ($P < .001$). The walking distance was increased by 17% with $FreeO_2$ in comparison with constant oxygen, but the difference was not statistically significant ($P = .22$). CONCLUSIONS: Automatic titration of oxygen flow during walking to maintain oxygen saturation in a specified range improves oxygenation and may improve exercise tolerance during daily activity, such as walking, in patients with COPD in comparison with room air and fixed oxygen administration. (ClinicalTrials.gov registration: NCT02150434.) *Key words: oxygen inhalation therapy; technological innovations; hypoxia; hyperoxia; exercise; COPD.* [Respir Care 2016;61(11):1456–1464. © 2016 Daedalus Enterprises]

Introduction

Hypoxemia has physiological consequences, including reduction in exercise tolerance, which is one of the symptoms experienced by patients with COPD.[1] The potential of oxygen supplementation to improve exercise endurance has been long appreciated.[2] Oxygen therapy provided during exercise reduces ventilation and dynamic hyperinflation. In turn, this leads to improved peak exercise capacity, increased tolerance to constant work rate exercise, and

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Supplementary material related to this paper is available at http://www.rcjournal.com.

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reduced dyspnea.[3-5] In laboratory settings, acute oxygen supplementation improves exercise tolerance of patients receiving long-term oxygen therapy (LTOT)[6] as well as in those without LTOT, irrespective of whether they desaturate during exercise.[7,8] However, oxygen therapy applied in an ambulatory context, outside the exercise laboratory, has not consistently demonstrated efficacy to enhance exercise tolerance or quality of life of patients with COPD.[9-11] This discrepancy may be related to the insufficient correction of hypoxemia during exercise in the home setting, considering that patients receiving LTOT at home typically receive low oxygen flows (usually between 1 and 3 L/min) and may remain hypoxemic during some daytime activities and/or at night.[12-15] Despite this observation, self-adjustment of oxygen flows is not recommended to avoid hyperoxia-related adverse effects, including worsened hypercapnia in patients with severe disease.[16-18]

Closed loop adjustment of oxygen administration based on oxygen saturation measured via pulse oximetry (S_{pO_2}) may help to optimize oxygen therapy and improve patients' safety.[19] The $FreeO_2$ system is a newly developed device which automatically adjusts the oxygen flows administered to spontaneously breathing patients, with the aim of maintaining a predefined S_{pO_2} target.[20] The aim of the current study was to evaluate the effect of using this system in subjects with moderate or severe COPD during exercise. We hypothesized that continuous automatic adjustment of the oxygen flows during exercise would better maintain subjects within the designated oxygenation target, reduce episodes of desaturation and hyperoxia, and improve walking exercise tolerance in comparison with fixed levels of low-flow continuous oxygen or air.

QUICK LOOK

Current knowledge

Oxygen supplementation improves exercise tolerance of patients with COPD when oxygen flow is adjusted under clinical supervision to avoid hypoxemia. Applied in an ambulatory context, oxygen therapy has not consistently demonstrated efficacy to enhance exercise tolerance, and this discrepancy may be related to the insufficient correction of hypoxemia during exercise with limited oxygen flows. $FreeO_2$, a new device that adjusts oxygen flow every second to maintain stable S_{pO_2}, has been developed.

What this paper contributes to our knowledge

We evaluated $FreeO_2$ during exercise in subjects with COPD known to desaturate at efforts. Automated adjustment of oxygen flow with $FreeO_2$ allowed maintenance of a better oxygenation within a prespecified S_{pO_2} target, with less desaturation in comparison with constant oxygen flow and compressed air. Along with better oxygenation, exercise tolerance was improved (increased walking time and distance) with continuous oxygen and automated oxygen titration in comparison with compressed air. Despite the use of oxygen flows that were higher than typically used in daily life with $FreeO_2$ (up to 10 L/min during exercise), hypercapnia was not induced during the study, perhaps due to limited exposure time to hyperoxia with $FreeO_2$.

Methods

A detailed description of the methods is provided in the online supplementary materials at http://www.rcjournal.com.

Subjects

We conducted a randomized controlled blinded crossover study in 16 subjects with moderate to severe COPD to compare administration of air, oxygen at a fixed constant low flow, and oxygen at variable flows automatically adjusted during exercise.

Subjects older than 40 y with moderate to severe COPD[21] who did not require oxygen supplementation at rest were included in the study. Subjects were also selected on the basis of known (end-exercise S_{pO_2} <90% on a previous exercise test) or suspected (S_{pO_2} <95% at rest) desaturation during exercise. The exclusion criteria were an episode of exacerbation within last 4 weeks and a current medical condition, other than COPD, that could influence exercise tolerance. The study was approved by the institutional ethics committee, and a signed consent was obtained from each participating subject (approval number 20444).

Evaluated Device

The $FreeO_2$ system automatically adjusts the administered oxygen flow using a closed-loop algorithm based on S_{pO_2} and provides continuous monitoring of respiratory parameters in spontaneously breathing patients.[20] The system was developed by the authors (FL and ELH) in collaboration with the Department of Electronic and Informatics Engineering at Laval University, Québec.

Protocol; See Supplemental Figure E1

The study consisted of 2 preliminary and 3 study visits. During the first preliminary visit, demographic characteristics, spirometry, and arterial blood gases were collected, and an incremental shuttle walk test was performed in all

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subjects to determine peak $\dot{V}_{O_2}$ as described previously.[22] In addition, a first endurance shuttle walk test was performed for familiarization, as routinely performed in our laboratory and described previously.[23] During the second preliminary visit, a second shuttle walk test was performed for familiarization. Both familiarization walk tests were conducted without oxygen.

These preliminary visits were followed by 3 study visits completed on different days separated by ≥48 h. Each study visit consisted of an endurance shuttle walk test performed at 85% peak $\dot{V}_{O_2}$ while participants breathed: (1) compressed air delivered at a fixed flow of 2 L/min, (2) oxygen delivered at a fixed flow of 2 L/min, or (3) oxygen at a variable flows delivered by the FreeO_2 system in a random order. The gases were delivered through nasal cannulas (Softech Bi-Flo Cannula, Teleflex, Wayne, Pennsylvania). During the shuttle walk tests, the subjects were followed by a research assistant with a trolley containing one air tank and one oxygen tank (only one was connected to the nasal cannulas as per randomization), and the FreeO_2 system was set in titration mode (oxygen at variable flow visit) or recording mode only (continuous oxygen and continuous air visits). After each endurance shuttle walk test, physiologic data were recorded during 10 min of recovery. Subjects, investigators, and one research assistant were blinded to the testing condition. One research assistant who was in charge of the randomization and preparation of the experimental setting was not blinded but was not involved in subject supervision during exercise or data analysis.

Measurements

The primary outcome of the study was the percentage of time during which subjects were kept within the S_{pO_2} target of 92–96% to avoid hypoxemia, severe hypoxemia, and hyperoxia (defined as S_{pO_2} <92%, S_{pO_2} <88%, and S_{pO_2} >96%, respectively).[20] Secondary outcomes included the endurance shuttle walk test time and distance, blood gases, and dyspnea. Before each shuttle walk test, tests of respiratory function and arterial blood gases were performed to demonstrate subjects' clinical stability. In addition to the parameters continuously collected by the system FreeO_2, capillary blood gases were made at the beginning of and after the walk test and at the end the recovery phase. The Borg scale was used to assess dyspnea every minute during each walk test and during the recovery time.

Statistical Analysis

Data were expressed using mean ± SD to summarize characteristics of subjects. Continuous variables were analyzed using a mixed model. The statistical models were fitted to compare heterogeneous variances among conditions (air, Free O_2, and constant O_2), and we tested whether the models could be reduced to a mixed model with the same variance across the factor levels. The univariate normality assumption was verified with the Shapiro-Wilk tests on the error distribution from the statistical model after a Cholesky factorization. The Brown and Forsythe variation of the Levene test statistic was used to verify the homogeneity of variances. When appropriate, some variables analyzed were using a log transformation to fulfill the model assumptions, and reported *P* values are based on these transformations. When these assumptions were not fulfilled after a log transformation, an alternative procedure that does not depend on these assumptions was performed. The statistical approach used was to replace the observations by their rank within subjects, called rank transformation, and apply the ordinary F test from the mixed model. This technique is an approximate procedure that results in good statistical properties when compared with exact tests. Posteriori comparisons were performed using the Tukey comparison. O_2 flow analyses were performed using a Student *t* test and compared with 2 constant values, 0 and 2. The estimated probability to perform the walk test was analyzed using a shared frailty model for clustered data (subjects), an extension of the Cox regression model with a log-normal distribution. The results were considered significant when *P* values were ≤.05. All analyses were conducted using the statistical packages R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Sixteen subjects with COPD were enrolled in the study; of these, 15 completed the study. One subject performed the first study visit but was not able to complete the study due to deterioration of his clinical condition (not related to the testing). Thirteen subjects were male (81%), the mean age of the subjects was 69 ± 9 y, and none received LTOT. All subjects had oxygen desaturation during the familiarization endurance shuttle walk tests conducted without oxygen administration (mean S_{pO_2} ± SD = 83.5 ± 4.0%, range 73–89%). Baseline physiologic characteristics of the subjects are presented in the Table 1. Tracings of S_{pO_2} values and oxygen flows during the walk test and recovery during the 3 tested conditions for one typical subject are shown in supplemental Figure E2.

Oxygenation

The percentage of time with S_{pO_2} in the predefined target range (92–96%) was significantly higher during walking while using FreeO_2 in comparison with walking while

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Table 1. Physiological Characteristics and Resting Blood Gases of Study-Participating Subjects at Baseline

Subject No.	BMI (kg/m^2)	FEV_1 (L)	FEV_1 (% predicted)	FEV_1/FVC	$\dot{V}_{O_2}$ peak (L/min)	pH	P_{aCO_2} (mm Hg)	HCO_3^- (mmol/L)	P_{aO_2} (mm Hg)	S_{aO_2} (%)
1	22	1.17	43	0.38	1.21	7.40	40	25	78	95
2	22	0.82	38	0.29	0.86	7.41	47	30	65	93
3	31	1.15	50	0.43	0.80	7.42	40	25	65	92
4	25	1.78	68	0.50	1.32	7.45	35	24	87	97
5	22	1.12	56	0.40	0.80	7.41	36	22	60	91
6	29	1.5	68	0.43	1.50	7.43	41	26	77	96
7	25	0.69	21	0.28	NA	7.46	33	23	66	94
8	21	0.78	56	0.34	0.62	7.43	45	29	57	90
9	29	1.46	44	0.35	1.58	7.42	41	26	83	96
10	28	0.79	28	0.30	1.48	7.41	48	29	91	97
11	27	1.09	38	0.35	1.01	7.40	52	32	61	91
12	24	1.2	48	0.34	1.62	7.43	39	25	62	92
13	22	1.05	40	0.25	1.04	7.41	41	26	84	96
14	20	0.55	23	0.30	0.51	7.42	43	27	68	93
15	23	1.01	44	0.37	1.04	7.44	39	26	72	95
16	20	0.85	30	0.29	1.17	7.45	40	27	70	95
Mean	24	1.06	43	0.35	1.10	7.42	41	26	72	94
SD	3	0.32	15	0.07	0.35	0.02	5	2	10	2

BMI = body mass index
$\dot{V}_{O_2}$ peak = peak oxygen uptake
NA = not applicable

breathing compressed air or fixed constant flow oxygen (60.3 ± 26.7% vs 18.3 ± 20.2% vs 43.9 ± 34.3%, $P < .001$) The difference was also statistically significant between constant oxygen and $FreeO_2$ ($P = .045$). The percentage of time spent with S_{pO_2} <88% was reduced with $FreeO_2$ in comparison with compressed air and constant low-flow oxygen (0.6 ± 1.1% vs 52.2 ± 32.6% vs 23.9 ± 32.7%, $P < .001$). The difference was also statistically significant between constant oxygen and $FreeO_2$ ($P = .033$) (Fig. 1 and Table 2).

With $FreeO_2$, mean and maximum oxygen flow during the endurance shuttle walk test was 2.9 ± 1.7 and 6.3 ± 2.2 L/min, both being significantly different from constant oxygen at 2 L/min. Eleven subjects (73%) required >5 L/min with $FreeO_2$ during the endurance shuttle walk test, with one subject requiring 11.3 L/min.

Endurance Time and Distance

The walking endurance time was significantly different between air, constant oxygen, and $FreeO_2$ (400 ± 212 vs 577 ± 323 vs 674 ± 376 s, $P < .001$). In the pairwise comparisons, the difference between the endurance shuttle walk test performed while breathing compressed air and variable oxygen with $FreeO_2$ was statistically significant ($P < .001$), as was the difference between compressed air and constant oxygen ($P = .009$). However, the difference between constant oxygen and $FreeO_2$ did not reach statistical significance ($P = .25$).

The walking distance was also significantly different between air, constant oxygen, and $FreeO_2$ (501 ± 233 m vs 676 ± 284 m vs 819 ± 441 m, $P < .001$). However, the difference between constant oxygen and $FreeO_2$ did not reach statistical significance ($P = .22$) (Figs. 2 and 3).

None of the subjects attained the maximum 20-min duration of the endurance shuttle walk test with air, whereas 4 subjects with $FreeO_2$ and 2 with constant low-flow O_2 reached this duration (Fig. 2). During each endurance shuttle walk test, the distance walked was better with $FreeO_2$ in 9 subjects, better with O_2 at constant flow in 4 subjects, and identical between $FreeO_2$ and constant O_2 in 2 subjects; no subject performed better with air ($P = .03$). The main reason to stop the walk test was dyspnea in 14 subjects with air, 11 subjects with constant O_2, and 9 subjects with $FreeO_2$ ($P = .12$). The other reason to stop the walk test was muscular weakness.

Physiologic Response

There was no significant difference in P_{aCO_2} between tested conditions at the end of the endurance shuttle walk test, even when it was conducted with high oxygen flow ($FreeO_2$). Capillary blood gases and dyspnea scores at base-

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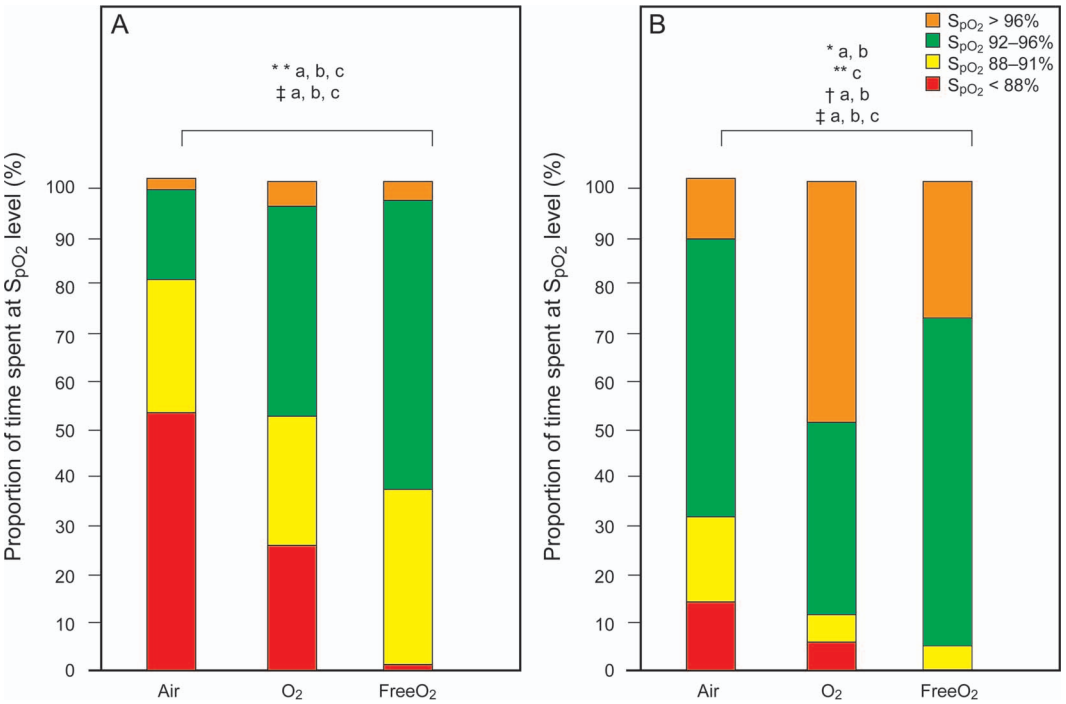

Fig. 1. Percentage of time spent within the predefined S_{pO_2} ranges during the 3 tested conditions (compressed air, constant low-flow oxygen [O_2], and $FreeO_2$), during the endurance shuttle walk test (A) and during the 10-min recovery period (B). The percentage of time within the oxygenation target (S_{pO_2} = 92–96%) was significantly higher with $FreeO_2$. The percentage of time with S_{pO_2} <88% was significantly lower with $FreeO_2$. The percentage of time with hyperoxia (S_{pO_2} >96%) was higher with constant oxygen flow. * $P < .05$ between groups for S_{pO_2} >96%, ** $P < .05$ between groups for S_{pO_2} 92–96%, † $P < .05$ between groups for S_{pO_2} 88–91%, ‡ $P < .05$ between groups for S_{pO_2} < 88%, a = $P < .05$ between Air and O_2, b = $P < .05$ between Air and $FreeO_2$, and c = $P < .05$ between O_2 and $FreeO_2$.

line and during the experiment are provided in the supplementary material.

Discussion

Although oxygen therapy is typically provided via constant low flow (usually 1–3 L/min) for patients with COPD, continuous S_{pO_2} monitoring reveals episodes of desaturation during various activities.[13-15] This observation suggests that oxygen flows should be tailored to patients' needs to avoid hypoxemia.[24] This study is the first clinical evaluation of the $FreeO_2$ system, a new device that automatically titrates oxygen flow to maintain stable oxygenation monitored by pulse oximetry. In a group of subjects with COPD exhibiting exercise-induced O_2 desaturation, automated adjustment of oxygen with $FreeO_2$ allowed maintenance of a better oxygenation within a prespecified target, with less desaturation in comparison with constant low-flow oxygen at 2 L/min and compressed air. Along with better oxygenation, exercise tolerance was improved (increased walking time and distance) with continuous oxygen and automated oxygen titration in comparison with compressed air. Interestingly, despite the use of oxygen flows that were higher than typically used in daily life, hypercapnia was not induced during the study, perhaps due to limited exposure time to hyperoxia with $FreeO_2$.

Previous Studies on Automated Oxygen Titration

Several automated systems to adjust oxygen flow in spontaneously breathing patients have been proposed.[19,20,25,26] We previously conducted a proof-of-concept study in healthy subjects in whom hypoxemia was induced.[20] In that study, fluctuating subjects' oxygen needs (using hypoxic challenge with increased and then decreased needs), we demonstrated that automated oxygen titration could improve oxygenation in comparison with constant oxygen flows.[20] In the present study, we reproduced a similar pattern of fluctuating oxygen needs, increased during exercise and decreased during recovery. Consistent with our experimentation in healthy subjects, both hypoxemia and hyperoxia were reduced with the automated system, in comparison with compressed air and constant low-flow oxygen in persons with moderate to severe COPD.

In a pilot study, Cirio and Nava[25] compared automated oxygen regulation with manual O_2 regulation in subjects with COPD during 15-min bouts of constant load cycling exercise. They reported that S_{pO_2} was significantly higher

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Table 2. Main Oxygenation Parameters During the Whole Test, During Endurance Shuttle Walk Test, and During the Recovery Time for the Three Tested Conditions: Constant Air, Constant Oxygen Flow, and $FreeO_2$

Parameter	Whole Test (Walk Test + Recovery)					Endurance Shuttle Walk Test					Recovery				
	Air (2 L/min)	Oxygen (2 L/min)	$FreeO_2$ (Variable Flow)	*P*	*P* ($FreeO_2$ vs Constant O_2)	Air (2 L/min)	Oxygen (2 L/min)	$FreeO_2$ (Variable Flow)	*P*	*P* ($FreeO_2$ vs Constant O_2)	Air (2 L/min)	Oxygen (2 L/min)	$FreeO_2$ (Variable Flow)	*P*	*P* ($FreeO_2$ vs Constant O_2)
% of time with S_{pO_2} >96%	6.9 ± 11	26.7 ± 21.4	14.4 ± 11.4	.008	.04	1.9 ± 4.0	5.2 ± 8.8	3.6 ± 6.8	.11	-	12.9 ± 17.6	50.4 ± 35.0	29.2 ± 20.3	.004	.08
% of time with S_{pO_2} 92–96%	41.6 ± 20.6	42.9 ± 16.4	62.3 ± 20.2	.001	.004	18.3 ± 20.2	43.9 ± 34.3	60.3 ± 26.7	<.001	.04	56.6 ± 25.8	39.6 ± 30.3	67.1 ± 22.3	.02	.02
% of time with S_{pO_2} 88–91%	21.4 ± 10.3	16.8 ± 15.9	21.0 ± 14.5	.55	-	27.5 ± 19.9	27.1 ± 26.9	35.5 ± 25.5	.56	-	18.0 ± 21.0	5.5 ± 4.3	3.4 ± 3.6	.006	.88
% of time with S_{pO_2} <88%	30.0 ± 20.8	13.6 ± 19.5	.4 ± .9	<.001	.001	52.2 ± 32.6	23.9 ± 32.7	.6 ± 1.1	<.001	.03	12.5 ± 9.7	4.4 ± 5.7	.2 ± .9	<.001	.006
Mean S_{pO_2}, %	90.2 ± 3.2	92.9 ± 3.0	93.8 ± .8	<.001	.39	87.2 ± 3.6	90.6 ± 4.0	92.2 ± 1.1	<.001	.06	92.7 ± 2.5	95.3 ± 1.8	95.3 ± 1.0	<.001	.36
Mean minimum S_{pO_2}, %	82.7 ± 3.6	86.3 ± 4.7	88.9 ± 1.4	<.001	.01	82.8 ± 4.2	86.3 ± 4.7	88.9 ± 1.4	<.001	.01	82.7 ± 3.6	87.7 ± 4.9	90.1 ± 1.6	<.001	.004
Minimum S_{pO_2}, %	74	75	87			74	75	87			75	77	88		
Mean oxygen flow, L/min	0	2.0 ± .0	2.9 ± 1.7	<.001	.06	0	2.0 ± .0	3.7 ± 1.7	<.001	.008	0	2.0 ± .0	2.3 ± 2.0	<.001	.55
Maximum oxygen flow, L/min	0	2.0 ± .0	6.3 ± 2.2	<.001	<.001	0	2.0 ± .0	6.3 ± 2.2	<.001	<.001	0	2.0 ± .0	5.6 ± 1.8	<.001	<.001

Results are mean ± SD. *P* values are provided for the variance analysis (comparison of the 3 tested conditions with mixed model analysis) and for pairwise comparison between $FreeO_2$ and constant O_2 (Tukey test for multiple comparisons).

(95 ± 2 vs 93 ± 3%, $P = .04$), and desaturations below S_{pO_2} target were less frequent (19 ± 21% vs 38 ± 24% of the time, $P < .001$) with automated O_2 regulation in comparison with manual regulation. In addition, the respiratory therapist spent less time adjusting oxygenation with automated regulation than with manual O_2 regulation (2.0 ± 0.1 min vs 5.6 ± 3.7 min, $P = .005$). Rice et al[26] also confirmed that an automated system adjusting oxygen flows based on oximetry data allowed better control of oxygenation in subjects receiving LTOT, in comparison with 2 non-automated systems. In this latter study, the percentage of time with S_{pO_2} <90% was not significantly different among the 3 oxygenation systems, but the percentage of time above the S_{pO_2} target was significantly less with automated oxygen titration. Moreover, the automated system allowed significant oxygen savings.[26] Automated oxygen regulation may also reduce the time spent by hospital staff to manually titrate the dose of oxygen delivered.[27] None of the previous studies on automated oxygen titration reported data on exercise tolerance.[25,26]

Oxygenation

In the present study, we used a constant oxygen flow rate of 2 L/min as used previously in a study evaluating ambulatory oxygen in subjects with COPD who were normoxic at rest.[11] Although increasing O_2 flows during supervised rehabilitative exercise can be easily done, this practice is often avoided in ambulatory patients, especially in severe patients with the presence of CO_2 retention where there is a risk of hyperoxia-induced hypercapnia.[28] The predefined S_{pO_2} target of 92–96% was achieved by setting the automated device at 94%. This window was selected on the following premise. There is an overall agreement that S_{aO_2} should be maintained >90% for peripheral oxygenation. To achieve this goal, we used a minimum S_{pO_2} level of 92%.[29-31] We have set the S_{pO_2} upper limit at 96%, considering the potential risks associated with hyperoxia in patients with COPD,[16-18] including the administration of low-flow oxygen,[28] as well as in various clinical situations[32-34] and the uselessness of maintaining high S_{pO_2} in most situations. The same S_{pO_2} range target (92–96%) was also chosen in one study involving subjects with COPD during their participation in pulmonary rehabilitation[25] and in 2 studies evaluating closed-loop devices adjusting the F_{IO_2} in intubated subjects.[27,35,36] Our finding that closed-loop oxygen titration was associated with better control of the oxygenation, with reduced episodes of desaturation and hyperoxia, is also in accordance with studies conducted in mechanically ventilated adults,[36] in infants,[35] and in subjects with COPD during pulmonary rehabilitation.[25] The frequency of S_{pO_2} < 88% was very low with automated oxygen titration, in comparison with low-dose constant oxygen flow and compressed air. This was true

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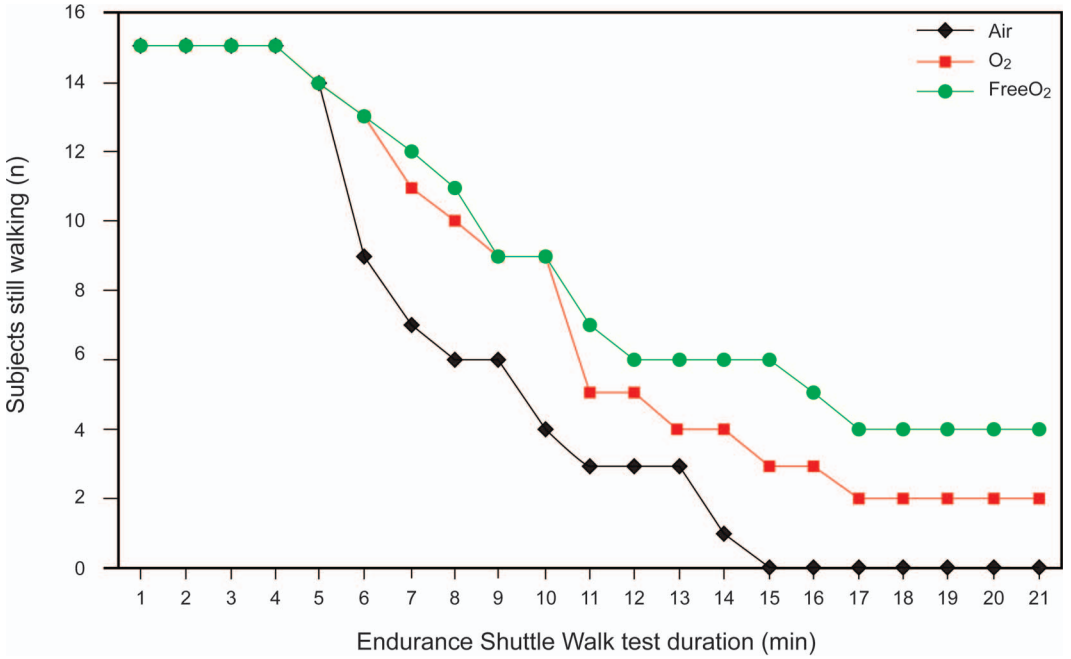

Fig. 2. Number of subjects still walking during the endurance shuttle walking test during the 3 tested conditions (compressed air, constant low-flow oxygen [O_2], and $FreeO_2$). The maximum duration of the endurance shuttle walk test (20 min) was reached by only 2 subjects breathing low-flow oxygen and 4 subjects breathing oxygen with $FreeO_2$. No subjects breathing compressed air could walk >15 min, whereas 3 with constant low-flow oxygen and 6 with $FreeO_2$ did so. A survival analysis (Cox model) determined $P < .001$ between the 3 tested conditions.

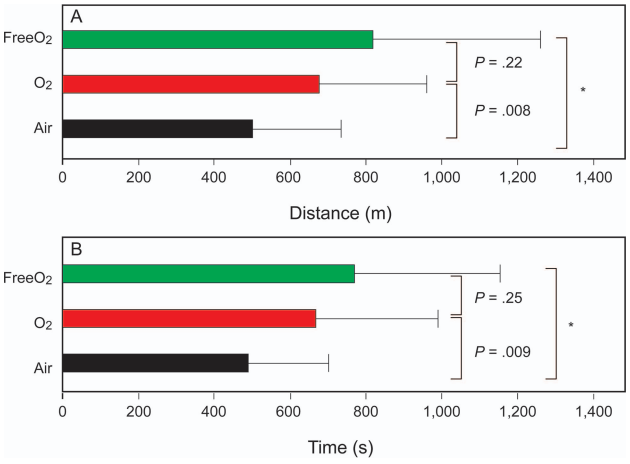

Fig. 3. Mean ± SD walk distance (A) and mean ± SD walk time (B) during the endurance shuttle walk test during the 3 tested conditions. For both walking distance and time, differences were statistically significant between compressed air and constant low-flow oxygen and between air and $FreeO_2$. Differences between constant oxygen and $FreeO_2$ did not reach statistical significance. * $P < .001$.

during walking and recovery and is consistent with previous findings in healthy subjects with experimentally induced hypoxemia.[20] The minimal S_{pO_2} values were reduced with the $FreeO_2$ system, also in concordance with findings in healthy subjects.[20]

Tolerance to Exercise

Several factors may account for the finding that the benefits of oxygen seen in the laboratory setting are not translated into routine daily life.[3-11,37] One factor might be that the set continuous oxygen flows used in the ambulatory context are insufficient to correct oxygen desaturation during exercise. Most patients with COPD who require LTOT increase the oxygen flow by 1 L/min during exercises as compared with at rest.[21] This may be insufficient to prevent severe desaturations during exercise. Strickland et al[38] compared 4 portable oxygen delivery systems in 39 subjects with severe COPD during a 6-min walk test and reported that the minimal S_{pO_2} varied from 70 to 76%, which is in line with our results.

In studies demonstrating an impact of oxygen on exercise tolerance, high oxygen flows were used,[3,39] and a dose-response effect is often demonstrated.[5] In the review of Bradley et al,[40] 29 of 31 studies evaluating the impact of oxygen on exercise tolerance used flows >2 L/min. Consistent with these reports, we showed that automated oxygen titration prevented profound oxygen desaturation (mean lowest S_{pO_2} during endurance shuttle walk test was 88.9% with $FreeO_2$), and in comparison with air, the endurance walking distance was significantly increased by 35% with constant oxygen and by 63% with $FreeO_2$. The walking distance was higher with $FreeO_2$ in comparison

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with constant oxygen, but the difference was not statistically significant (676 ± 284 m vs 819 ± 441 m, $P = .22$). To obtain these effects, >5 L/min of oxygen flow were required in most subjects (and up to 11.3 L/min in one subject). However, physicians may be reluctant to use high oxygen flows in severe COPD, with the potential risk of inducing hypercabia.[28] With automated titration oxygen based on patients' needs, this risk is reduced, as shown in the present study.

Clinical Application

After bronchodilation, a 65-s or 95-m improvement in the endurance shuttle walk test performance has been considered clinically relevant and likely to be perceived by the patients.[41] In the present study, compared with air, we demonstrated mean improvements of 175 m walking distance with oxygen alone and of 318 m with automated oxygen titration during exercise. An improvement in walking performance of this magnitude may be relevant during patients' daily lives and may also be important in relation to other clinical outcomes, such as mortality.[42]

Limitations of the Study

The study has potential limitations. One issue was that all investigators could not be blinded. After randomization, one research assistant had to set-up the system and connect the nasal cannulas to either compressed air, low-flow constant oxygen, or automated oxygen titration. Despite this, several precautions were taken to minimize any potential related bias. The remaining investigators who were in charge of supervising the exercise testing procedures and subjects were blinded to the conditions. Second, given that few subjects had chronic hypercapnia (P_{aCO_2} >45 mm Hg), we cannot exclude the possibility that high oxygen flows with use of the $FreeO_2$ system may induce or worsen hypercapnia for some patients. However, considering that CO_2 retention was not worsened with $FreeO_2$ in the 3 subjects with resting P_{aCO_2} >45 mm Hg and that episodes of hyperoxia (S_{pO_2} >96%) were also reduced with automated oxygen titration (particularly during recovery) in comparison with constant oxygen, we believe that automated oxygen titration is probably safe in patients with chronic hypercapnic respiratory failure. However, this is an area that requires further study.

Exercise tolerance might have been improved if the continuous oxygen flow had been set a higher level (4 or 5 L/min). However, this flow is not representative of the usual flow used by patients at home. In addition, with such high oxygen flows, the time with hyperoxia would increase a lot. This is a small study with a limited number of subjects, and results may not be generalizable to patients with a wider range of disease severity. One limitation is that the subjects did not have to wheel their own trolleys. It is possible that the weight of the device might have affected performances, but in the near future, smaller and lighter devices will be available. One last limitation was that compressed air and oxygen delivery through nasal cannulas prevented a detailed assessment of the ventilatory response during walking. This would have been instrumental in understanding the physiological mechanisms leading to improved exercise tolerance with automated oxygen titration.

Conclusions

This clinical evaluation of a novel device whose purpose is to automatically adjust oxygen flows ($FreeO_2$ system) demonstrates significant physiological impact during exercise in subjects with COPD. This system was able to better maintain subjects in the oxygenation target, avoid severe desaturation, and reduce the time with hyperoxia in comparison with constant low-flow oxygen and improved the endurance time during walking in comparison with air alone. Recent technological advancements should allow the utilization of oxygen therapy with better efficacy and safety by meeting physiological requirements that are constantly changing during daily living.

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