Automated O_2 titration improves exercise capacity in patients with hypercapnic Chronic Obstructive Pulmonary Disease

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Supplementary Material

METHODS

Trial design and participants

We conducted a randomized, double-blinded crossover controlled study. Twelve patients older than 40 years with severe COPD (Gold III-IV), hypercapnia (resting $PaCO_2$ > 45mmHg) and requiring long-term oxygen therapy were included in the study from outpatient (4/12) and inpatient (8/12) rehabilitation clinics. Recruitment took place at the Grenoble University Hospital (Grenoble, France) and at the rehabilitation centre "Les Rieux" (Nyons, France). Exclusion criteria were exacerbation within four weeks before inclusion or current medical condition, other than COPD, that constitute a limitation to walk (orthopaedic or rheumatologic disorders). The study was approved by the institutional ethics committee and a signed consent was obtained from each participant (CPP Sud Est V, 11-AGIR-01). The clinical trials registration number is NCT01575327. A consort flowchart is shown on Figure E1.

Randomization and blinding

Following baseline assessment, patients were randomly assigned (1:1) by a blinded statistician using a computer-generated allocation sequence to use either adjusted O_2 flows or constant O_2 flows during the first endurance walking test. Then, the other O_2 supplementation strategy was applied for the second test. Patients, investigators and research assistants were all blinded for testing conditions. One research assistant oversaw the randomization (computer generated) and the experimental setting. The research assistant was not otherwise involved in patient supervision during exercise or data analysis.

Procedure/ Interventions

Automatically-adjusted O_2 flow rates device

In the present study, we used the FreeO_2 system that automatically adjusts every second oxygen flow using a closed-loop algorithm based on measured versus targeted SpO_2. It provides continuous monitoring of cardio-respiratory parameters in spontaneously breathing patients (SpO_2, O_2 flow rate, heart rate)[23,24]. This system can deliver from 0 to 20L/min, with 0.1L/min incremental or decremental steps, on a per second basis.

Protocol (Figure E2)

The study consisted in two preliminary visits and two experimental visits for the cross over comparison. During the first preliminary visit, demographics, spirometry and arterial blood gases were collected and an incremental shuttle walking test was performed to determine peak walking speed, as previously described [26]. This test was performed while patients received their usual O_2 supplementation during exercise (resting flow + ~1L/min). During the second preliminary visit, a first endurance shuttle walking test was performed for familiarization purposes [27]. These visits were followed by the two experimental visits completed in a random order, on different days and separated by at least 48 hours (washout period = 4.0 ± 4.6 days). Each experimental visit consisted in an endurance shuttle walking test (ESWT) performed at 85 % estimated peak VO_2 [28] during which participants breathed: (i) oxygen delivered at the usual fixed flow, ~1L/min above the resting flow rate as recommended [14] (constant O_2 flow), or (ii) oxygen at variable flows (FreeO_2) set at SpO_2 > 94%. The oxygen was delivered through nasal cannulas (Softech Bi-Flo Cannula, Teleflex). During both ESWTs, the FreeO_2 system was used,

either in the titration mode during which O_2 flows were variable or in the recording mode during which O_2 flow was constant. After each ESWT, physiologic data were recorded during 10 minutes of recovery. Before each ESWT, a spirometry was performed to confirm patients' clinical stability.

Outcomes

The primary outcome of the study was the walking endurance time (and the corresponding walking distance). Secondary outcomes included time spent within pre-specify SpO_2 targets (< 88% and between 92 and 96%), capillary blood gases (PcO_2, $PcCO_2$), heart rate (HR), dyspnea and leg fatigue. In addition to the parameters continuously collected by the system FreeO_2 (SpO_2 and HR), earlobe capillary blood gases were obtained before, at the end, and 10 min post exercise. A modified Borg scale was used to assess dyspnea and leg-fatigue scores at one-minute intervals during exercise and at the end of exercise. Isotime exercise was assessed for HR, dyspnea and leg fatigue. It corresponded to the longest time duration reached during the ESWT in both conditions (automatically-adjusted O_2 flow and constant O_2 flow). Warm-up was included in the calculation of the endurance time.

Statistical Analysis

Sample size calculation

The sample size calculation was based on preliminary data from the work of Lellouche et al. [29]. In this study, walking endurance time in patients with severe COPD averaged 264 ± 102 sec and was increased by 43 % with FreeO_2, as compared to constant O_2 flow [29]. Based on this

dataset and on the hypothesis that FreeO_2 would have a similar exercise-enhancing effect in patients with severe COPD and chronic respiratory failure, we calculated that 12 completed patients would be necessary in a cross-over trial to provide a statistical power of 80% at the 0.05 level.

Data analysis

Data were expressed using mean +/- SD to summarize subjects' characteristics. Continuous variables were analysed using a mixed model. The statistical models were fitted to compare heterogeneous variances among conditions and were 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's variation of Levene's test statistic was used to verify the homogeneity of variances. When appropriate, some variables (including number of shuttles; endurance time; walking distance and isotime-exercise dyspnoea borg score) were log-transformed to fulfil 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 applying the ordinary F test from the mixed model. This technique is an approximate procedure results and has good statistical properties when compared to exact tests. Correlation between changes in endurance time and pulmonary function were assessed using Pearson (when normality passed) or Spearman correlation coefficient (when Normality failed). The results were considered

significant when p-values were < 0.05. All analyses were conducted using the statistical packages R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria.) and SAS v9.4 (SAS Institute Inc, Cary, NC, U.S.A.).

Table E1: patients' characteristics

Gender (M/F)	5/7
Age	65 ± 10
BMI, kg/m^2	25 ± 7
GOLD stages & smoking history	
Pack-years smoking	43 ± 22
Current smokers	3 (25%)
Number of exacerbation / year	1.3 ± 0.5
OLD since	7.5 ± 5.0
Lung function	
FEV_1, L	0.70 ± 0.25
FEV_1, % pred.	30 ± 9
FVC, L	1.64 ± 0.74
FVC, % pred.	44 ± 7
FEV_1 / FVC, % pred.	50 ± 15
TLC, L.	6.53 ± 1.19
TLC, % pred.	124 ± 25
IC, L	1.42 ± 0.50
FRC, L	5.09 ± 1.28
RV, L	4.73 ± 1.26
RV, % pred.	225 ± 76
VR/CPT %	71 ± 7
DLCO %	32 ± 18
Physiological parameters	
PaO_2, mmHg	62.0 ± 6.4
$PaCO_2$, mmHg	48.7 ± 3.0
pH	7.42 ± 0.03
$HCO3^-$	31.5 ± 3.8
Functional capacity	
6MWD (m)	352 ± 52
Mean SaO_2 during 6MWD	89 ± 2.5
MRC score	3.0 ± 0.6
Cardiovascular comorbidities	
Treated hypertension	6 (50%)
Cardiac failure	4 (33%)

Obesity / Type 2 diabetes	4 (33%)
Medication	
Short-acting beta agonist	11 (92%)
Long-acting beta agonist	6 (50%)
Corticosteroids	6 (50%)
Anticholinergic	8 (66%)

Table E2: unexpected event report

Patient	Unexpected event	Timing	Dropped out
#3	Patient stopped after the VO_2 max test – He felt too weak to continue the study	Visit #1	Yes

Figure Legend

Figure E1: Study Flowchart

Figure E2: Study design

Figure E3: Individual data of lowest O_2 saturation during the ESWT when using constant O_2 flows or automatically titrated O_2 flows (FreeO_2). Average lowest O_2 saturation was 83.6 ± 7.0 % with constant O_2 flow vs. 89.5 ± 3.9 % with FreeO_2 ($p < 0.001$).

Figure E1: Study Flowchart

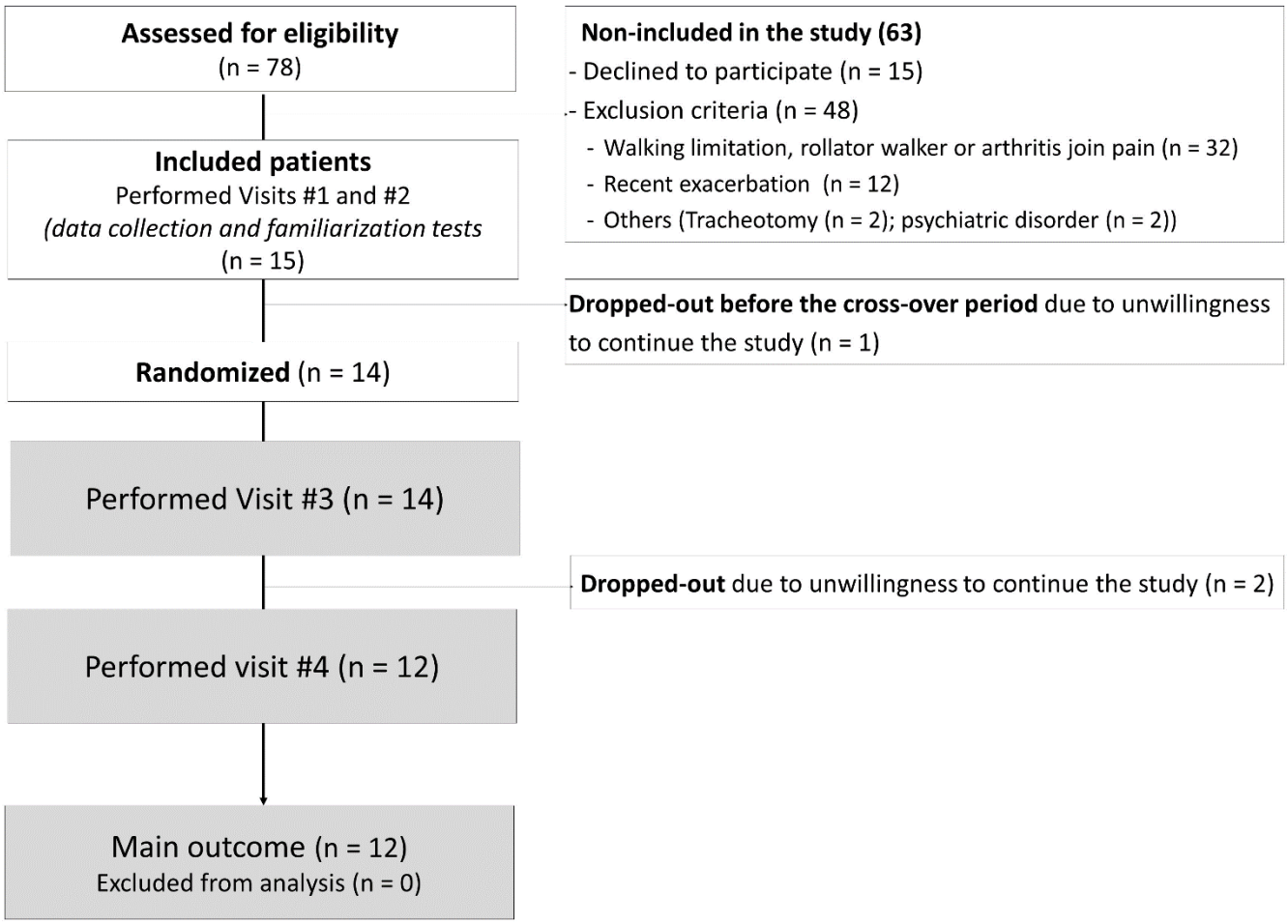


Figure E2

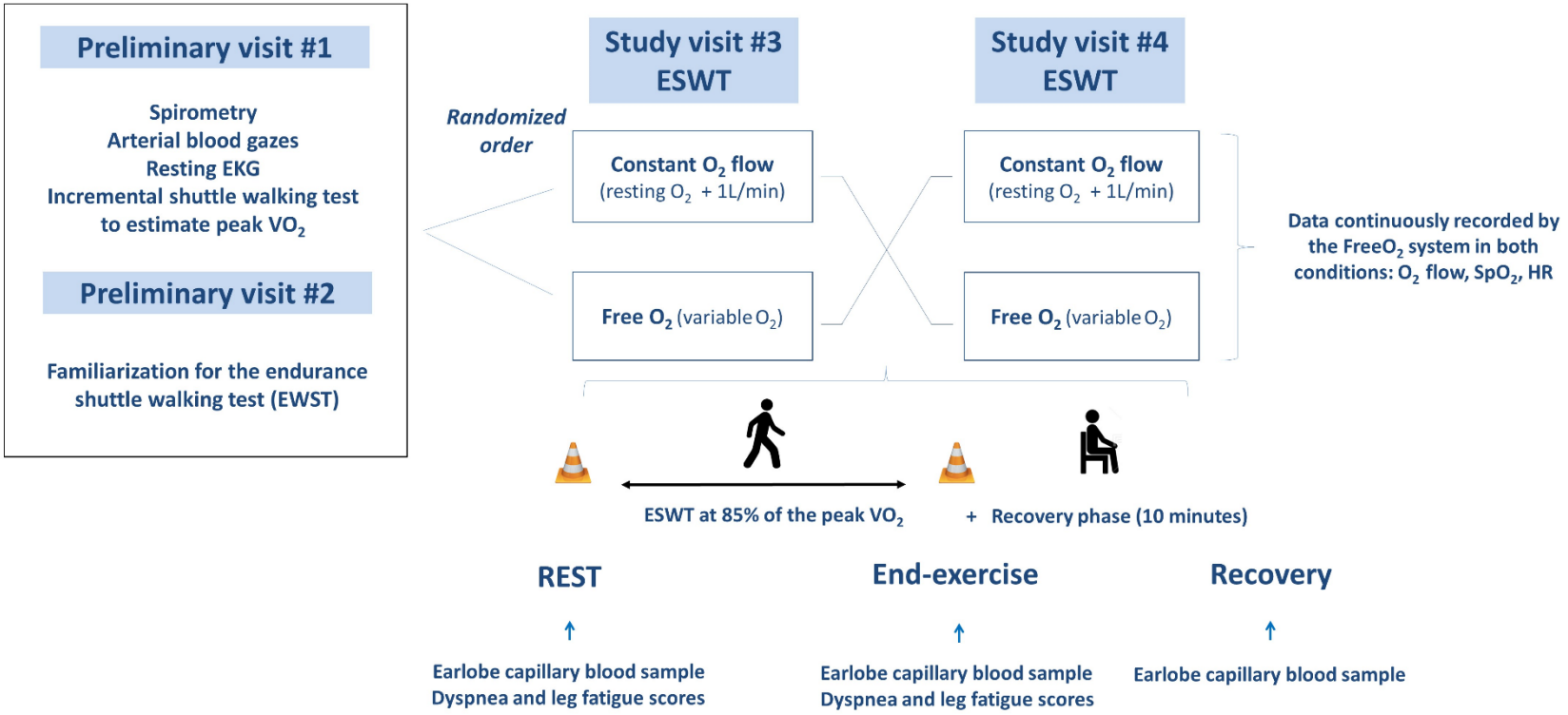
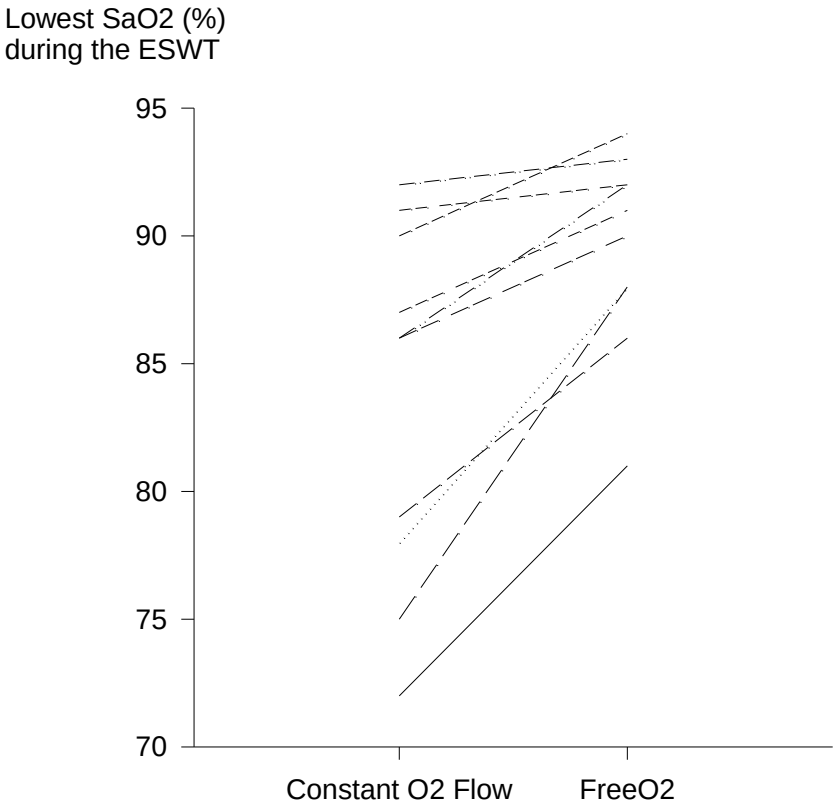

Preliminary visit #1
Spirometry
Arterial blood gazes
Resting EKG
Incremental shuttle walking test to estimate peak VO_2
Preliminary visit #2
Familiarization for the endurance shuttle walking test (EWST)
Study visit #3 ESWT
Study visit #4 ESWT
Randomized order
Constant O_2 flow (resting O_2 + 1L/min)
Free O_2 (variable O_2)
Constant O_2 flow (resting O_2 + 1L/min)
Free O_2 (variable O_2)
Data continuously recorded by the FreeO_2 system in both conditions: O_2 flow, SpO_2, HR
ESWT at 85% of the peak VO_2
+ Recovery phase (10 minutes)
REST
End-exercise
Recovery
Earlobe capillary blood sample
Dyspnea and leg fatigue scores
Earlobe capillary blood sample
Dyspnea and leg fatigue scores
Earlobe capillary blood sample

Figure E3


Lowest SaO2 (%)
during the ESWT
95
90
85
80
75
70
Constant O2 Flow
FreeO2