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Original research

Automatic oxygen titration versus constant oxygen flow rates during walking in COPD: a randomised controlled, double-blind, crossover trial

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ABSTRACT

Rationale In patients with COPD, oxygen (O_2)-supplementation via a constant flow oxygen system (CFOS) can result in insufficient oxygen saturation (SpO_2 <90%) during exercise. An automatically titrating O_2-system (ATOS) has been shown to be beneficial compared with an untitrated CFOS, however, it is unknown if ATOS is superior to CFOS, titrated during exercise as stipulated by guidelines. The aim was to investigate the effects of ATOS compared with titrated CFOS on walking capacity in people with hypoxaemic COPD.

Methods Fifty participants completed this prospective randomised controlled, double-blind, crossover trial. Participants performed two endurance shuttle walk tests (ESWTs) with: (1) exercise titrated CFOS ($ESWT_{CFOS}$) and (2) ATOS targeting an SpO_2 of 92% ($ESWT_{ATOS}$). Primary outcome measure was walking time. Secondary measures were SpO_2, transcutaneous-PCO_2 ($TcPCO_2$), respiratory rate (RR), heart rate (HR) at isotime (end of shortest ESWT) with blood gases and dyspnoea at rest and end exercise.

Results Participants (median (IQR): age 66 (59, 70) years, FEV_1 28.8 (24.8, 35.1) % predicted, PO_2 54.7 (51.0, 57.7) mm Hg, PCO_2 44.2 (38.2, 47.8) mm Hg) walked significantly longer with $ESWT_{ATOS}$ in comparison to $ESWT_{CFOS}$ (median effect (95% CI) +144.5 (54 to 241.5) s, p<0.001). At isotime, SpO_2 was significantly higher (+3 (95% CI 1 to 4) %, p<0.001) with ATOS while $TcPCO_2$, RR and HR were comparable. End exercise, PO_2 (+8.85 (95% CI 6.35 to 11.9) mm Hg) and dyspnoea (−0.5 (95% CI −1.0 to −0.5) points) differed significantly in favour of ATOS (each p<0.001) while PCO_2 was comparable.

Conclusion In patients with hypoxaemia with severe COPD the use of ATOS leads to significant, clinically relevant improvements in walking endurance time, SpO_2, PO_2 and dyspnoea with no impact on PCO_2.

Trial registration number NCT03803384.

Key messages

What is the key question?

► Does an automatic oxygen flow system perform better than a constant flow system with flows titrated for exercise as recommended by guidelines and is there an effect on carbon dioxide (CO_2) retention?

What is the bottom line?

► In patients with hypoxaemia with severe COPD the use of an automatic oxygen flow system leads to an increase in walking endurance time over the minimal important difference and despite higher oxygen (O_2)-flows, has no impact on PCO_2.

Why read on?

► We show that during walking exercise, despite constant flows being titrated according to guidelines, an automatically titrating oxygen system provides more O_2, maintains saturation and results in greatly improved walking durations and lower dyspnoea without adversely affecting CO_2.

INTRODUCTION

Oxygen (O_2) therapy is commonly used to treat people with hypoxic chronic obstructive pulmonary disease (COPD).[1] During exercise O_2 can increase O_2-transport,[2] delay muscle fatigue,[2] alter breathing mechanics,[3] reduce dyspnoea[3] and improve exercise endurance.[3] To be effective, prescribed flows are recommended to be titrated to an oxygen saturation (SpO_2) of ≥90%.[4] However, during demanding situations like exercise, titration of O_2-flow to maintain adequate SpO_2 is challenging.

In practice, contrary to guidelines suggesting titration via walking test,[2 5] exercise O_2-flows are frequently titrated at rest or prescribed as a fixed addition to the titrated resting flow.[6]

Given this, it is common to see continuous O_2-flows, while physically active, which are inadequate for varying physiological demands.[7 8] Further, in the study setting it has been seen that a single fixed flow is insufficient in keeping adequate oxygenation in some patients with COPD.[9]

In clinical practice there are concerns that providing excessive O_2 in patients with COPD may induce a reduction in minute ventilation and thus lead to potentially dangerous hypercapnia.[10] Possibly this thinking carries over to exercise where there is a fear that using high flow rates and therefore high O_2-levels in people with severe to very severe COPD may have a deleterious effect on already elevated carbon dioxide (CO_2) levels. For

this reason it is recommended that in all patients, especially those with baseline hypercapnia, blood gases should be checked after each titration of flow for signs of respiratory acidosis and worsening hypercapnia.[2 5]

To overcome the challenge of varying metabolic demands during exercise and physical activity an automatically titrating oxygen system (ATOS), which regulates O_2 flow to maintain a predefined SpO_2-target, has been proposed as a solution to optimise the effects of O_2-therapy.[1] To date, only two studies have examined walking-exercise with ATOS in patients with COPD. These studies have shown that ATOS is better at maintaining oxygenation compared with a constant flow oxygen system (CFOS) during exercise. In general, hypoxaemia as well as hyperoxia occurred less with longer walking durations when using ATOS. These trials however had small sample sizes and were potentially biased towards ATOS as they had inappropriate CFOS O_2-flow rates as a control comparison, and high SpO_2-targets.[6 11]

Considering that ATOS can provide flows above what is normally used by patients during exercise, ATOS may exacerbate any underlying hypercapnic tendencies. Since constant blood gas monitoring in exercise is impractical, the continuous monitoring of transcutaneous carbon-dioxide partial pressure ($TcPCO_2$) is logical. However, to date, $TcPCO_2$ during exercise with ATOS has not been examined. Overall, stronger evidence to support or refute the use of ATOS during exercise for people with COPD is needed. Given this, the aims of this trial were to determine, in people with COPD who were hypoxaemic at rest and/or during exercise, whether an ATOS was more effective than individually titrated CFOS at: improving endurance exercise capacity (primary outcome), oxygenation, respiratory rate, heart rate and reducing dyspnoea/leg fatigue. Additionally, CO_2-levels were monitored for potential side effects of using ATOS during walking exercise.

We hypothesised that ATOS would be superior to CFOS at increasing walking exercise capacity, but with higher CO_2-levels.

METHODS

This study was a prospective, single centre, randomised controlled crossover trial with blinding of participants, investigators and statistician. Randomisation of test order was achieved by an independent person prior to the study using a computer-generated random sequence. Test order was concealed in sequentially numbered sealed opaque envelopes. Participants between 40 and 80 years with a confirmed diagnosis of severe or very severe COPD (GOLD stage III to IV) with hypoxaemia or an indication for O_2-therapy during exercise (PO_2 <55 mm Hg at rest or during exercise or nadir SpO_2 <88% during exercise) were recruited. Excluded were participants with an acute exacerbation of COPD or those who had cardiovascular medical conditions or orthopaedic restrictions limiting the ability to perform walking tests.

All participants were recruited and tested within an inpatient pulmonary rehabilitation programme over a period of 11 months (Schoen Klinik Berchtesgadener Land, Germany).

Informed written consent was obtained from all participants.

After an initial incremental shuttle walk test, participants performed on consecutive days (24-hour wash-out period), in a randomised order, two endurance shuttle walk tests (ESWTs) at 85% of maximum pace with[12]: (1) individually titrated constant oxygen-flow rates ($ESWT_{CFOS}$) and (2) automatically titrated oxygen-flow rates ($ESWT_{ATOS}$). The $FreeO_2$ (OxyNov, Canada), is a device which uses physiological data (primarily SpO_2) in a closed loop algorithm to control an O_2-flow from 0 to 20 L/min (flow accuracy ±0.1 L/min) to maintain SpO_2 to a predefined target.[13 14] The $FreeO_2$ can also provide a constant flow. Therefore, to blind participants and investigators, the $FreeO_2$ device was used for both ESWTs with the display of the device covered and an independent person other than the study investigator configured the settings before the test. The $FreeO_2$ device, including the O_2-cylinder was attached to a cart (online supplemental figure S1) and pushed by the investigator.

For the $ESWT_{ATOS}$, SpO_2-target was set at 92% to maintain participants SpO_2 ≥90%. For the $ESWT_{CFOS}$ an individually exercise titrated O_2-flow was used (see online supplemental for more information about O_2-flow rate titration).

Outcome measures

Primary outcome was change in endurance exercise capacity as measured by ESWT. Secondary outcomes were time to SpO_2 <90% and differences in SpO_2, $TcPCO_2$, heart rate (measured continuously via ear lobe sensor; SenTec, Switzerland), breathing frequency (measured continuously by respiratory inductance plethysmography; ApneaLink, ResMed, Australia) at rest, end exercise and 25%, 50%, 75% and 100% of isotime (end of shortest ESWT). O_2-partial pressure, CO_2-partial pressure, pH, base excess, hydrogen carbonate, lactate (measured by blood gas analysis; RAPIDPoint, Siemens, Germany) and sensation of dyspnoea and leg fatigue (10-point Borg scale[15]) were taken at rest and at the end of ESWTs. Blood gas samples were taken after 10 min at rest breathing with CFOS or ATOS and immediately at ESWT termination by an independent person.

At the end of each test, participants were asked to rate their perception of oxygenation, comfort of O_2-delivery and possibility of using the O_2-supplementation in everyday life on a standardised Likert-scale. Finally, after all tests, participants were asked to rate their preferred O_2-system.

Statistical methods

Sample size calculation

In a retrospective study (n=12 patients with COPD) at our clinic, mean ESWT duration (primary endpoint) was compared in a CFOS and ATOS group. The mean difference in ESWT duration between both groups was 234.9 s and a SD of 392 s. To achieve a power of 90% at a significance level of 5% in a 2×2 crossover design for testing the effect one-sided, a sample size of 50 subjects was calculated. Assuming a drop-out rate of 10%, 55 subjects were enrolled in this study.

Data analysis

Data was checked for consistency and normality. Spearman's and Pearson's correlation coefficients were computed to analyse relations between variables. Data deviated from normality and hence non-parametric 2×2 crossover models were applied, 95% CI for medians and median effects were computed. No carry-over effects were found in the primary outcome. Two multivariable regression models with forward and backward variable selection algorithms were set up and tested to find models with high prediction accuracy, one model to predict the PCO_2 post walk in the ATOS group and another for the CFOS group. Multiple R, coefficients of determination were computed, regression coefficients were tested and residuals were analysed for normality. Observed versus predicted values were illustrated.

All reported tests were two-sided, and p values<0.05 were considered statistically significant. NCSS (NCSS 10,

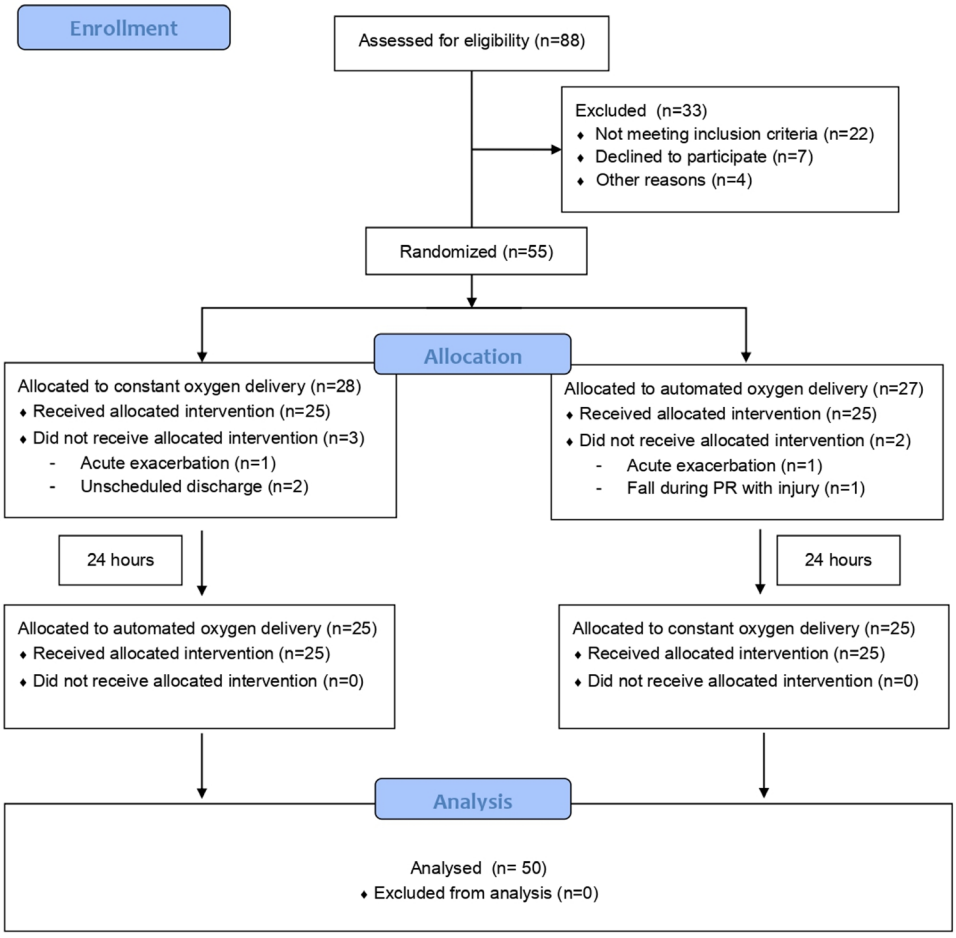

Figure 1 Consolidated Standards of Reporting Trials—flow diagram. PR, pulmonary rehabilitation.

NCSS, Kaysville, Utah, USA) and STATISTICA 13 (Hill, T. & Lewicki, P. Statistics: Methods and Applications, StatSoft, Tulsa, Oklahoma, USA) were used to analyse data descriptively, for testing crosstabulations tables, all two-sample tests and were also used to test and illustrate multiple regression models. StatXact (2013), V.10.0.0, Cytel Software Corporation (Cambridge, Massachusetts, USA) was used for sample size computations and for testing treatment and carry-over effects in non-parametric crossover analyses. P values were computed based on Monte-Carlo simulation methods instead of using asymptotic p values.

PASW 24 (IBM SPSS Statistics for Windows, V.21.0.) was used to compute correlations as well as descriptive analyses.

RESULTS

Trial flow and participant characteristics

Fifty-five participants were recruited with five participants not completing the study (figure 1). All had severe to very severe COPD and were hypoxaemic (table 1). The median (IQR) pace for the ESWTs was 3.1 (2.6, 4.2) km/hour. $ESWT_{CFOS}$ was performed with a median O_2-flow of 3 L/min while $ESWT_{ATOS}$ resulted in a median flow of 4.5 L/min (table 2, figure 2A).

Primary outcome

Participants walked significantly ($p<0.001$) longer in $ESWT_{ATOS}$ compared with $ESWT_{CFOS}$ (table 2); 68% (n=34) of participants walked longer in $ESWT_{ATOS}$, 20% (n=10) walked longer in $ESWT_{CFOS}$ and 12% (n=6) walked equally. A longer duration than the minimal important difference (MID) of 65 s for an ESWT[12] was achieved by 76.5% (n=26/34) of participants walking longer in $ESWT_{ATOS}$ and 50% (n=5/10) of those in $ESWT_{CFOS}$.

Reasons for ESWT termination significantly differed between the two tests (p=0.001). Dyspnoea was reported as the main reason for stopping the ESWT in 70% (n=35/50) of participants with CFOS while only 48% (n=24/50) of the participants stopped due to breathlessness with ATOS (p=0.02). Participants with a higher residual volume /total lung capacity per cent predicted showed a greater rest to end exercise change in dyspnoea during walking ($ESWT_{CFOS}$: r=0.34, p=0.01; $ESWT_{ATOS}$: r=0.31, p=0.03) and more breathlessness at end exercise ($ESWT_{CFOS}$: r=0.43, p=0.002; $ESWT_{ATOS}$: r=0.40, p=0.004) (online supplemental figure S2 and table S1).

As a subgroup analysis, the cohort was divided into two groups: (1) ATOS responders ('participants walking ≥MID (65 s) during $ESWT_{ATOS}$ in comparison to $ESWT_{CFOS}$') and (2) ATOS non-responders (participants walking less than 65 s during the $ESWT_{ATOS}$ compared with $ESWT_{CFOS}$'). Baseline characteristics were comparable. ATOS responders showed a significantly higher oxygenation and felt less breathlessness in comparison to ATOS non-responders at the end of $ESWT_{ATOS}$ and received a significantly higher mean O_2-flow rate during $ESWT_{ATOS}$ (table 3, online supplemental figure S3A,B). Respiratory rate and $TcPCO_2$ during $ESWT_{ATOS}$ were comparable at each time point (online supplemental figure S3C,D), however mean $TcPCO_2$ over the complete $ESWT_{ATOS}$ duration was significantly different between

Table 1 Participant characteristics

Variable	COPD, n=50
Age, years	66 (59, 70)
Gender, female/male, n	23/27
BMI, kg/m^2	23.9 (21.3, 27.0)
Waist–hip ratio	
Females	0.89 (0.83, 0.94)
Males	1.0 (0.94, 1.04)
Pulmonary function	
FEV_1, L	0.78 (0.59, 1.0)
FEV_1, % predicted	28.8 (24.8, 35.1)
FVC, L	1.69 (1.19, 2.28)
FVC, % predicted	50.1 (41.6, 63.7)
FEV_1/FVC, %	45.8 (40.8, 53.7)
TLC, L	7.7 (7.0, 9.1)
TLC, % predicted	137.0 (121.8, 154.8)
FRC_{pleth}, L	6.8 (5.9, 7.6)
FRC_{pleth}, % predicted	213.6 (182.0, 251.8)
RV, L	5.9 (5.0, 7.0)
RV, % predicted	269.9 (218.1, 335.6)
RV/TLC, %	77.1 (68.6, 82.7)
RV/TLC, % predicted	188.5 (172.1, 206.9)
Raw, kPa s L^{-1}	0.87 (0.63, 1.10)
Raw, % predicted	289.6 (209.6, 367.3)
sRaw, kPa s	6.0 (4.4, 8.9)
sRaw, % predicted	575.8 (397.4, 844.0)
GOLD grade	
III, n	23 (46)
IV, n	27 (54)
Blood gases, room air—rest	
pH	7.41 (7.39, 7.42)
PO_2, mm Hg	54.7 (51.0, 57.7)
PCO_2, mm Hg	44.2 (38.2, 47.8)
Exercise capacity	
6-minute walk distance, m	303.5 (245.0, 371.5)
6-minute walk distance, % predicted	48.4 (38.5, 59.5)
Incremental shuttle walk test, m	205.0 (130.0, 325.0)
Long-term oxygen therapy	
Period of application, months	47 (18, 79)
O_2-flow rates, L	
Rest	1.75 (1.0, 2.9)
Night	2.0 (1.0, 2.9)

Data presented as median (interquartile range (IQR)) or number.
%, per cent; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; kg, kilograms; kg/m^2, kilograms per metre squared; L, litre; m, metres; mm Hg, millimetres of mercury; n, number; PCO_2, partial pressure of carbon dioxide; pH, potential of hydrogen; PO_2, partial pressure of oxygen; Raw, airway resistance; RV, residual volume; sRaw, specific airway resistance; TLC, total lung capacity.

ATOS responders and non-responders: $TcPCO_{2mean}$, mm Hg 47.1 (45.3, 52.7) versus 45.0 (41.6, 48.8); median effect (95% CI) 3.5 mm Hg (0.1 to 7.1), p=0.037.

Secondary outcomes

SpO_2 was significantly higher at rest and 25% isotime with CFOS compared with ATOS, whereas at 100% isotime and at end exercise the reverse was seen (figure 2B). Time to SpO_2 <90% was significantly shorter with ATOS (table 2).

In line with this, PO_2 was significantly higher with CFOS at rest and significantly higher at end exercise with ATOS. Except for lactate, there was no statistical difference in pH, base excess, hydrogen carbonate and PCO_2 between the two interventions at rest and end exercise (table 2). The magnitude of change (Δ) in PCO_2 from rest to end exercise varied in both tests ($ESWT_{CFOS}$: range, −3.7 to 20.3 mm Hg; $ESWT_{ATOS}$: range, −1.7 to 19.6 mmHg). 62% of the participants had a comparable PCO_2 response between the two ESWTs.

There was a weak to medium correlation between the mean O_2-flow and the change in PCO_2 (ΔPCO_2) during $ESWT_{CFOS}$ and $ESWT_{ATOS}$, independent of O_2-system ($ESWT_{CFOS}$: r=0.29, p=0.04; $ESWT_{ATOS}$: r=0.39, p=0.007; online supplemental table S2).

A multivariable regression model for PCO_2 post each ESWT, based on pre walking measures, achieved a multiple correlation coefficient of R=0.78, R2=0.60 ($ESWT_{CFOS}$) and R=0.72, R2=0.52 ($ESWT_{ATOS}$). The relation between observed and predicted variables is illustrated in figure 3A,B.

No differences were found for $TcPCO_2$ at any time point between the $ESWT_{CFOS}$ and $ESWT_{ATOS}$ (table 2, figure 2C). Heart rate was statistically, significantly different between the two interventions at rest, 25%, 50% isotime and end exercise (table 2, figure 2D). Respiratory rate differed significantly at rest and dyspnoea differed at end exercise while leg fatigue showed no difference at any time point (table 2).

When questioned, a significantly (p=0.0005) higher number of participants strongly agreed that perceived oxygenation was 'satisfactory' while using ATOS (n=28) in comparison to CFOS (n=9). After completion of all study-related measurements a significantly (p<0.0001) higher number of participants (n=37) preferred ATOS over a CFOS. No other question differed significantly (online supplemental figure S4A–D).

DISCUSSION

An automatically titrating O_2-system used during walking resulted in a significantly improved exercise capacity and was associated with better oxygenation and less dyspnoea at end exercise compared with a constant flow O_2-system. The change in both $TcPCO_2$ and PCO_2 during walking was comparable between systems. However, significant correlations between the change in PCO_2 and the mean O_2-flow, independent of delivery system, were observed.

Comparison to other trials

Our results augment the data supporting the use of ATOS compared with CFOS in walking exercise by applying methodological rigour to the study design, using a robust sample size calculation, a more realistic SpO_2 target for ATOS (92% vs 94%[6 11] SpO_2) and a constant flow titration during exercise (as recommended by clinical guidelines)[2 5] instead of a resting titration or standardised constant O_2-flow (eg, resting O_2-flow+1 L/min[6]; 2 L/min O_2[11]). This is also the first trial to measure CO_2-levels continuously during exercise with ATOS and the first to present an independent measurement of the partial pressure of oxygen after walking exercise. Further, this is the first time a comparison of isotime measures during the ESWT have been shown and this is also the first study to report

Table 2 Results

	Constant O_2-flow, CFOS, n=50	Automatic O_2-flow, ATOS, n=50	P value[x)]	Median effect (95% CI) automatic—constant
Primary outcome				
ESWT Time, s	**333.50 (214, 581)**	**522.5 (277, 1200)**	**1.203E^{-04}**	**144.5 (54 to 241.5)**
Secondary outcomes				
ESWT Distance, m	**310 (200, 620)**	**465 (200, 1030)**	**2.602E^{-04}**	**150 (60 to 31)**
Oxygen Mean O_2-flow rate	**3.0 (3.0, 4.0)**	**4.5 (3.2, 6.1)**	**1.000E^{-05}**	**1.34 (0.68 to 2.14)**
Blood gas analyses				
PO_{2rest}, mm Hg	**80.2 (73.1, 90.6)**	**65.35 (62.6, 68.1)**	**1.582E^{-14}**	**–17.8 (–22.1 to –13.8)**
PO_{2post}, mm Hg	**61.35 (55.0, 64.5)**	**71.5 (64.2, 75.8)**	**3.304E^{-08}**	**8.85 (6.35 to 11.9)**
PCO_{2rest}, mm Hg	42.5 (39.8, 46.1)	40.85 (39.2, 48.2)	0.87	
PCO_{2post}, mm Hg	50.45 (46.7, 54.0)	50.45 (46.8, 54.8)	0.41	
Ph_{rest}	7.41 (7.39, 7.43)	7.42 (7.40, 7.43)	0.64	
Ph_{post}	7.35 (7.32, 7.38)	7.34 (7.32, 7.37)	0.19	
BE_{rest}, mmol/L	1.75 (0.30, 3.20)	1.20 (0.10, 3.60)	0.68	
BE_{post}, mmol/L	0.80 (–0.80, 2.10)	0.50 (–1.10, 2.40)	0.52	
HCO_{3rest}, mmol/L	26.0 (24.70, 27.30)	25.4 (24.50, 27,60)	0.97	
HCO_{3post}, mmol/L	25.0 (23.60, 26.10)	24.80 (23.40, 26.50)	0.78	
S_aO_{2rest}, %	**95.0 (94.60, 96.60)**	**93.08 (91.70, 93.50)**	**1.582E^{-14}**	**-3.0 (-3.45 to -2.6)**
S_aO_{2post}, %	**89.19 (86.50, 91.30)**	**92.75 (91.30, 94.04)**	**1.450E^{-08}**	**3.17 (2.15 to 4.37)**
$Lactate_{rest}$, mmol/L	1.19 (0.99, 1.67)	1.09 (0.88, 1.45)	0.23	
$Lactate_{post}$, mmol/L	1.90 (1.50, 2.62)	1.85 (1.14, 2.40)	4.134E^{-02}	–0.135 (–0.29 to –0.005)
SenTec digital monitor				
SpO_{2rest}, %	**96.0 (95.0, 98.0)**	**93.0 (93.0, 95.0)**	**2.286E^{-11}**	**–3 (–3.5 to –2.5)**
$SpO_{2isotime\_100\%}$, %	**89.0 (86.0, 93.0)**	**92.0 (90.0, 94.0)**	**5.275E^{-04}**	**3 (1 to 4)**
SpO_{2post}, %	**89.0 (86.0, 93.0)**	**93.0 (92.0, 94.0)**	**1.758E^{-04}**	**3 (1.5 to 5)**
SpO_{2min}, %	88 .0 (85, 91)	87.5 (83.0, 89.0)	0.05	
SpO_{2max}, %	**97.0 (96.0, 99.0)**	**95.0 (94.0, 96.0)**	**1.122E^{-09}**	**–2 (–2.5 to –1.5)**
SpO_{2mean}, %	92.0 (89.0, 94.0)	92.0 (91.0, 93.0)	0.77	
Time to SpO_2 <90%, s	**n=32** **102.0 (73.0, 158.0)**	**n=39** **55.0 (19.0, 74.0)**	**6.937E^{-06}**	**–71.8 (–101 to –47)**
Time to SpO_2 <85%, s	n=11 152.0 (112.0, 194.0)	n=16 81.5 (61.0, 137.5)	0.11	
$TcPCO_{2rest}$, mm Hg	43.0 (39.8, 46.1)	42.6 (39.4, 46.3)	0.19	
$TcPCO_{2isotime\_100\%}$, mm Hg	47.7 (45.4, 50.9)	47.7 (44.6, 53.7)	0.93	
$TcPCO_{2post}$, mm Hg	47.75 (45.4, 50.9)	48.0 (45.5, 53.6)	0.57	
$TcPCO_{2max}$, mm Hg	48.9 (45.8, 51.75)	49.2 (46.4, 55.2)	0.42	
$Heart\ rate_{rest}$, b/min	83.0 (78.0, 88.0)	84.0 (79.0, 93.0)	3.859E^{-02}	2 (0 to 4.5)
$Heart\ rate_{isotime\_100\%}$, b/min	100.5 (95.0, 106.0)	100.5 (95.0, 108.0)	0.17	
$Heart\ rate_{post}$, b/min	**101.0 (95.0, 107.0)**	**103.0 (96.0, 112.0)**	**4.381E^{-03}**	**3.5 (1 to 5.5)**
$Heart\ rate_{max}$, b/min	104.5 (99.0, 116.0)	106.0 (99.0, 117.0)	0.06	
Respiratory rate				
$Respiratory\ rate_{rest}$, 1 /min	**18.0 (14.0, 24.0)**	**20 (17.0, 24.0)**	**1.079E^{-03}**	**2 (1 to 3.5)**
$Respiratory\ rate_{isotime\_100\%}$, 1 /min	31.0 (24.0, 45.5)	31.0 (23.5, 44.0)	0.25	
$Respiratory\ rate_{post}$, 1 /min	29.0 (24.0, 34.0)	29.0 (21.0, 34.0)	0.40	
Borg scale				
$Dyspnoea_{rest}$, points	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.96	
$Dyspnoea_{post}$, points	**6.0 (5.0, 7.0)**	**5.0 (4.0, 7.0)**	**1.914E^{-04}**	**–0.5 (–1 to –0.5)**
$Leg\ fatigue_{rest}$, points	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.79	
$Leg\ fatigue_{post}$, points	4.0 (3.0, 6.0)	4.0 (3.0, 5.0)	0.10	

Differences with p values<0.01 are presented in bold.
Note: Median effects are not necessarily medians of differences; [x)]non-parametric 2×2 crossover models based on Monte Carlo simulations using Wilcoxon (mid rank) test. P-values are unadjusted for multiple comparisons.
Data presented as median (IQR).
ATOS, automatically titrating oxygen system; BE, base excess; CFOS, constant flow oxygen system; ESWT, endurance shuttle walk test; HCO_3, hydrogen carbonate; O_2, oxygen; PCO_2, partial pressure of carbon dioxide; pH, potential of hydrogen; PO_2, partial pressure of oxygen; SaO_2, oxygen saturation measured by blood gas analyses; SpO_2, oxygen saturation; $TcPCO_2$, transcutaneous carbon dioxide.

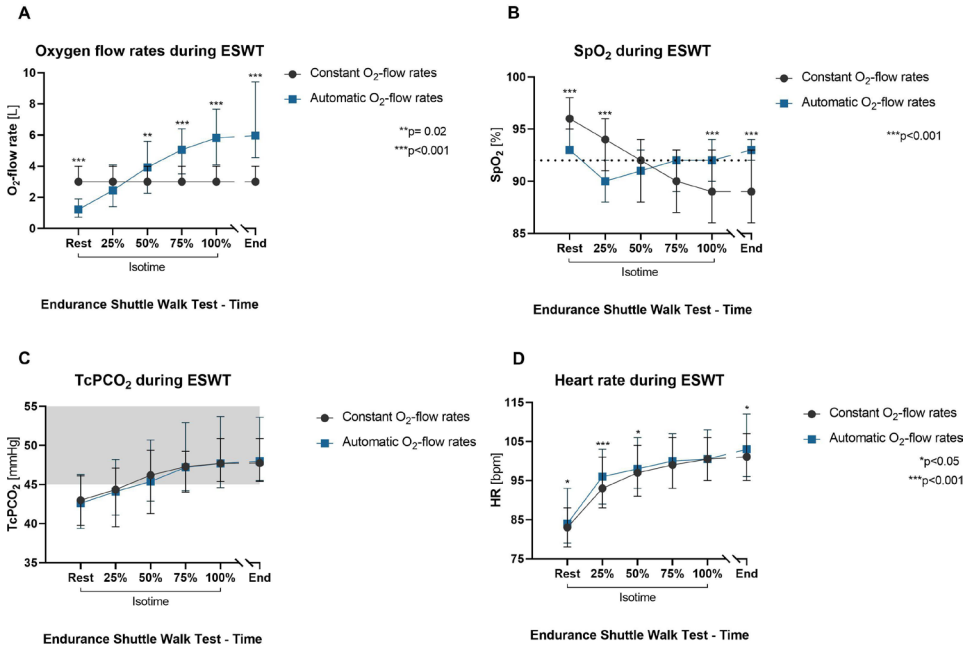

Figure 2 (A) Oxygen flow rates during the endurance shuttle walk test (ESWT). (B) Oxygen saturation (SpO_2) during ESWT. Dashed line at 92% SpO_2. (C) Transcutaneous carbon dioxide ($TcPCO_2$) during ESWT. Shaded area in grey between 45 and 55 mm Hg. (D) Heart rate (HR) during ESWT. Data is presented as median; error bars: IQR; p values were calculated via non-parametric 2×2 cross-over models based on Monte Carlo simulations using Wilcoxon (mid rank) test. P values are unadjusted for multiple comparisons.

participants perception and preference due to the O_2-delivery systems during walking exercise.

Exercise capacity

Even using individually exercise titrated CFOS, the increase in walking distance with ATOS was comparable or even greater to that seen in previous studies with a resting-titrated or standardised CFOS (change in walking duration: 43% vs 33%[6] and 17%[11]). This may be due to the greater number of participants in our study as well more being hypoxaemic at rest (PO_2: 54.7 vs 62[6] and 72[11] mm Hg) making the effects of supplemental oxygen potentially more consistent.[16]

No differences in lung function or anthropometric parameters were found between ATOS responders (change in walking duration >MID) and non-responders. In our study, ATOS responders tended to have lower lactate values as well as less leg fatigue at $ESWT_{ATOS}$ end compared with non-responders (table 3). Further, while responders walked a significantly longer duration and reported less dyspnoea, a significantly higher average O_2-flow rate with ATOS was used. We might assume that the higher airflow may have contributed to a reduced sensation of breathlessness,[17] however, no correlation between O_2-flow rates and dyspnoea was found.

In addition to an increased walking capacity in 68% of the study cohort, significantly fewer participants had to stop $ESWT_{ATOS}$ due to dyspnoea. Possibly this could be due to a better correction of hypoxaemia during the later stages (from 100% isotime) of the ESWT with ATOS. It has been shown that acute O_2-supplementation improves exercise performance by reducing ventilation, dynamic hyperinflation and the perception of dyspnoea[3 18] and those effects were potentially greater with ATOS. Somfay *et al* showed that supplemental oxygen during exercise induced a dose-dependent improvement in endurance capacity and symptom perception, which they attributed to decreased hyperinflation and slower breathing pattern.[19] Participants in our trial were also given increasing doses of oxygen as SpO_2 declined during exercise, so we might expect similar changes, however, when comparing ATOS to CFOS, we saw similar 100% isotime and end exercise respiratory rate. As inspiratory capacity was not measured in our study, we cannot report if a reduction in dynamic hyperinflation occurred.

Oxygenation

Oxygen saturation was superior at 100% isotime (Δ3%) and at end exercise (Δ3%) with ATOS compared with CFOS by a statistically and clinically relevant amount.[20] Vivodtzev *et al* reported that minimum SpO_2-values occurred with CFOS (CFOS: 83.6% vs ATOS: 89.5%; $p<0.001$)[6] which is contrary to the present study where minimum SpO_2-values during walking were comparable although a greater number of patients desaturated and the time to desaturation (SpO_2 <90%) was significantly shorter with ATOS. Compared with Lellouche *et al* and Vivodtzev *et al*, individually titrated CFOS may have been better suited to the participants physiological needs during exercise[6 11] However, as CFOS was exercise titrated in the present study, flows may have been greater than needed at rest which is confirmed by SpO_2-profiles where a significantly higher SpO_2 at rest and ESWT 25% isotime with CFOS was seen compared with ATOS (figure 2). The decline in SpO_2 at the beginning of walking with ATOS could indicate that the automatic increase in O_2-flows were slower than the physiological decrease during early exercise. The lower SpO_2-target used in the current trial (92% vs 94%[6 11]) may have also slowed the response of ATOS compared with previous trials.

CO_2

In clinical practice, increasing O_2-flows in patients with hypercapnia has ongoing concerns due to the risk of hyperoxia-induced hypercapnia and is therefore regularly avoided.[21 22] However, in agreement with PCO_2 results observed by Lellouche *et al*,[11] carbon dioxide levels measured via blood gas sample and transcutaneously were comparable between the two ESWTs, even

Table 3 Subgroup analyses (ATOS responders vs non-responders)—results. Data presented as median (IQR)

	Non-responder (n=24)	Responder (n=26)	P value[x)]	Median effect (95% CI) responder—non-responder
Baseline characteristics				
FEV_1, % predicted	29.4 (25.6, 36.9)	30.1 (24.1, 33.4)	0.67	
RV,/TLC, % predicted	182.8 (168.0, 203.0)	199.3 (178.7, 209.6)	0.18	
FRC, % predicted	207.7 (176.5, 240.3)	228.7 (188.5, 252.7)	0.42	
PO_2—rest with room air, mm Hg	53.6 (52.0, 57.2)	54.7 (50.4, 57.3)	0.86	
PCO_2—rest with room air, mm Hg	44.4 (39.5, 46.8)	44.6 (38.1, 48.6)	0.72	
O_2 flow rate—exercise, L/min	3.5 (3.0, 4.0)	3.0 (2.5, 4.0)	0.42	
Age, years	66.5 (61.0, 73.0)	62.0 (59.0, 68.0)	0.20	
BMI, kg/m^2	24.3 (21.3, 26.4)	23.7 (21.3, 26.1)	0.45	
Waist circumference, cm	96.5 (89.5, 107.0)	89.5 (83.0, 100.5)	0.13	
Waist–hip ratio	0.97 (0.89, 1.0)	0.91 (0.86, 0.98)	0.14	
$ESWT_{ATOS}$				
Mean O_2-flow rate, L	**3.9 (2.6, 4.7)**	**5.2 (3.9, 6.7)**	**8.768E^{-03}**	**1.6 (0.49 to 2.7)**
Time, s	**280.0 (199.0, 857.0)**	**751.5 (419.0, 1200.0)**	**2.664E^{-03}**	**268 (75 to 549)**
Distance, m	265.0 (155.0, 925.0)	675.0 (350.0, 1210.0)	1.287E^{-02}	225 (50 to 530)
Blood gas analyses				
PO_{2rest}, mm Hg	65.4 (62.7, 67.9)	65.1 (61.0, 68.6)	0.75	
PO_{2post}, mm Hg	**66.3 (60.7, 73.2)**	**74.1 (71.0, 76.6)**	**3.364E^{-03}**	**7.25 (2.4 to 11.6)**
SaO_{2rest}, mm Hg	93.1 (91.4, 93.7)	92.9 (91.7, 93.3)	0.62	
SaO_{2post}, mm Hg	91.8 (88.9, 93.7)	93.5 (92.0, 94.2)	4.141E^{-02}	1.24 (0.04 to 2.8)
PCO_{2rest}, mm Hg	40.8 (39.9, 47.0)	41.8 (39.0, 48.3)	0.74	
PCO_{2post}, mm Hg	48.3 (46.2, 53.6)	51.6 (48.6, 56.1)	0.23	
Ph_{rest}	7.41 (7.39, 7.43)	7.41 (7.40, 7.43)	0.68	
Ph_{post}	7.36 (7.33, 7.38)	7.34 (7.31, 7.36)	0.05	
$Lactate_{rest}$, mmol/L	1.2 (1.0, 1.6)	1.0 (0.8, 1.2)	0.14	
$Lactate_{post}$, mmol/L	1.9 (1.6, 2.4)	1.4 (1.0, 2.2)	0.08	
Borg scale				
$Dyspnoea_{post}$, points	6.0 (4.0, 7.5)	5.0 (4.0, 5.0)	1.107E^{-02}	–1 (–2 to 0)
ΔDyspnoea, points	**4.0 (3.0, 6.5)**	**3.0 (2.0, 4.0)**	**1.614E^{-03}**	**–1 (–2 to 0)**
$Leg\ fatigue_{post}$, points	6.0 (4.0, 7.5)	4.0 (3.0, 5.0)	0.35	
ΔLeg fatigue, points	4.0 (3.0, 6.5)	2.0 (1.0, 3.0)	0.58	

Differences with p values<0.01 are presented in bold. Note: Median effects are not necessarily medians of differences; [x)]Mann-Whitney U test. P values are unadjusted for multiple comparisons.
ATOS, automatically titrating oxygen system; BMI, body mass index; ESWT, endurance shuttle walk test; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; PCO_2, partial pressure of carbon dioxide; pH, potential of hydrogen; PO_2, partial pressure of oxygen; RV, residual volume; SaO_2, oxygen saturation measured by blood gas analyses; TLC, total lung capacity.

with higher O_2-flows from 50% isotime on with ATOS. When comparing ATOS-responders to non-responders, responders received on average 1.6 L/min more oxygen with ATOS and mean $TcPCO_2$ during walking was significantly higher. Overall, for both systems a significant correlation between change in PCO_2 and the mean O_2-flow was found.

Exercise-induced hypercapnia

Some patients with COPD, while normocapnic at rest, retain CO_2 during increased activity and may develop exercise-induced hypercapnia (EIH: defined as PCO_2 ≥45 mm Hg post ESWT).[23 24] To examine a possible difference in the effects between participants who were normocapnic at rest (PCO_2 <45 mm Hg breathing room air; n=27) and those who were hypercapnic at rest (PCO_2 ≥45 mm Hg breathing room air; n=23) a subgroup analysis was performed (online supplemental table S3). We found, in the normocapnic subgroup, signs of EIH in 77.8% (n=21/27) of the participants with CFOS and 74.1% (n=20/27) with ATOS. Development of EIH in both ESWTs was observed in 74.1% (n=20) of participants. This is greater than previously seen by Andrianopoulos *et al* where only 31% of participants developed EIH during a 6-minute walk test.[25] This could be explained by participants being less hypoxaemic at rest with better lung function and only 79% having a prescription of O_2 during exercise compared with 100% in the present study.[25]

In this study we developed a multivariable regression model to predict the PCO_2 post walking exercise. As exercise-induced changes in PCO_2 are highly dependent on several pathophysiological mechanisms in COPD[23] the ability to predict the PCO_2 post walking may help clinicians better select patients for ATOS. However, we suggest evaluating this in a larger sample in order to readjust the models and further improve accuracy. Of note,

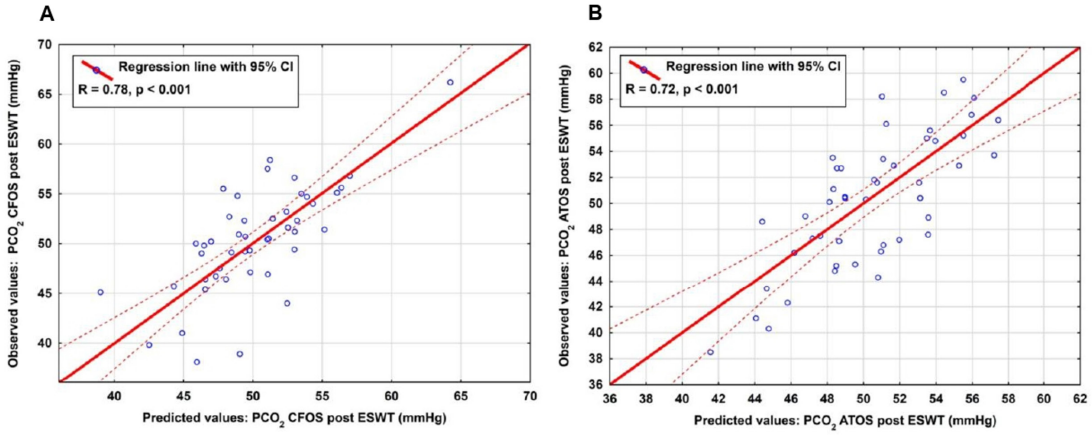

Figure 3 (A) Illustration of relation between observed and predicted PCO_2 values (mm Hg) post endurance shuttle walk test (ESWT) with constant oxygen flows of the regression model. The model based on body mass index (p=0.0002), waist circumference (p=0.00008), residual volume in litres (p=0.008) and PCO_2 at rest prior to walking test (p=0.00002). Multivariable regression model equation: *PCO_2 post walk predicted=22.358 + 1.325*Body Mass Index – 0.395*waist circumference + 1.382*residual volume + 0.574*PCO_2 pre walking test.* (B) Illustration of relation between observed and predicted PCO_2 values (mm Hg) post ESWT with automatic oxygen flows of the regression model. The model is based on body mass index (p=0.011), waist circumference (p=0.028) and PCO_2 in rest prior walking test (p=0.028). Multivariable regression model equation: *PCO_2 post walk predicted=26.462 + 0.628*PCO_2 pre walking test +0.693*Body Mass Index – 0.203*waist circumference*. ATOS, automatically titrating oxygen system; CFOS, constant flow oxygen system; PCO_2, partial pressure of carbon dioxide.

independent of O_2-system, PCO_2 was on average normocapnic pre-exercise (CFOS: 42.5 mm Hg; ATOS: 40.85 mm Hg) and was a median of 50.45 mm Hg post exercise. This is reinforced by a moderate negative correlation between resting PCO_2 and change in ESWT PCO_2 showing participants with a lower starting PCO_2 had the greatest changes during exercise. Simard *et al* found, that in some patients with COPD, EIH is a precursor to chronic hypercapnia.[26] The large number of participants with EIH in the current study might underline the importance of observing PCO_2-levels in patients with severe and very severe COPD during exercise to consider using other aids (eg, non-invasive ventilation).[27 28]

Limitations

Some limitations of the present study must be considered. Surprisingly, 14 patients reached the maximal exercise duration of 20 min with ATOS and 5 of those with CFOS also. Had this limit been longer, the effect size may have been different, however, given the present study reached an effect of statistical significance greater than the MID, the final outcome is unaffected. The ISWT was conducted once, but 90% of the participants did either not reach the maximum duration or reached it only in one test. We therefore assume, that in the majority of the study population the speed was appropriately chosen. Second the use of the 6-minute walk test to obtain an O_2-titration is not optimal for an ESWT, however it is the practice suggested in clinical guidelines and is superior to using the same O_2-flow for the entire group.

Further, this study demonstrates the immediate effects of O_2-therapy during walking exercise and might not reflect longer usage scenarios or during different exercise modalities. Also of note, no adjustment for multiple comparisons was done on the familywise error, however, p values with high precision (in scientific notation) are presented for use in a correction such as a Bonferroni-Holm. Finally, the regression models are based on learning samples only and the generalisability of the models should be evaluated in independent validation data sets.

Current generation ATOS devices are limited though as they are large, assume an infinite O_2-supply and rely completely on a finger sensor. Future studies should determine whether improved ATOS with faster O_2-flow regulation have the potential to improve results. They should also focus on medium-term and long-term effects of using ATOS in exercise training or daily life as well as economic factors like O_2-usage (eg, overall use during exercise training), device, maintenance and staff costs (eg, reduced number of O_2-titration assessments). Further, other pathologies, such as interstitial lung disease[29] or COVID-19[30] may desaturate in exercise and an ATOS could be a promising approach.

CONCLUSION

As shown by this randomised, double-blinded, crossover trial, we found that the use of an automatically titrating supplemental O_2-system, capable of adjusting O_2-flows during exercise in response to SpO_2, leads to significantly and clinically relevant improvements in walking endurance time, oxygenation and dyspnoea compared with an individually, exercise titrated constant O_2-flow system as commonly used in practice.

The clinical implications are that ATOS set to keep a SpO_2-target of 92% in patients with hypoxaemia with severe and very severe COPD has an immediate positive effect on exercise capacity with no difference in CO_2. This result disputes the 'one flow rate fits all' mentality for O_2-supplementation during exercise and suggests that automatic systems may be a promising method for improved, individually tailored treatment. Finally, participants preferred an automatic O_2-system over constant and future work should be invested in making a more portable version which reacts faster to changing O_2-levels.

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