--- ONLINE SUPPLEMENT ---

Automatic oxygen titration vs. constant oxygen flow rates during walking in COPD – a randomized controlled, double-blind, crossover trial

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Oxygen flow rate titration for use during exercise

Every patient performed a standardized 6-minute walk test[1] starting with their current prescribed oxygen flow rate for exercise. Exercise capacity, desaturation during exercise (SpO_2 ≤90%) and time till desaturation was determined to assess whether the flow rate during exercise needed to be adjusted.
In patients desaturating during exercise, the test was repeated with an increased oxygen flow rate. Capillary blood gases were taken pre and post 6MWT. This process was repeated until the following criteria was met:
2 out of 3 of the indicators are required to show that the patient benefits from oxygen during exercise[2]:

- SpO_2 ≥ 90% throughout[2]
- ≥10% increase in walking distance from baseline[2]
- Improvement in BORG dyspnoea of at least 1 point from baseline[2]

Figure S1. FreeO_2 (OxyNov, Canada) device and oxygen cylinder on a cart

Termination criterion – Endurance Shuttle Walk Test

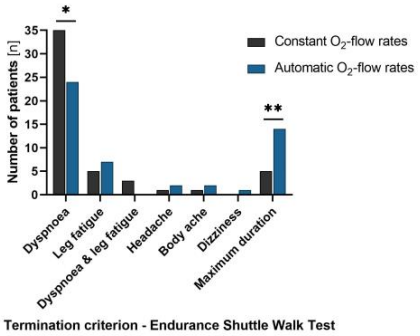


Figure S2. Termination criterion – Endurance Shuttle Walk Test. At the end of each endurance shuttle walk test, participants were asked for their main reason for stopping (p=0.001; marginal homogeneity test based on Monte Carlo simulation; *p=0.02 McNemar Test; **p=0.008 McNemar Test).

Table S1. Correlation matrix of patient characteristics for change in Dyspnoea (Δ) and Dyspnoea post endurance shuttle walk test

	ΔDyspnoea [points]		**Dyspnoea, post-walk** [points]	
	$ESWT_{constant}$	$ESWT_{automatic}$	$ESWT_{constant}$	$ESWT_{automatic}$
ESWT duration, sec	**-0.40 p=0.004**	-0.29 p=3.904E-02	-0.33 p=0.02	**-0.42 p=2.611E-03**
FRC_{pleth}, %/pred	0.28 p=4.921E-02	0.26 p=0.07	0.29 p=4.700E-02	0.33 p=2.214E-02
RV%/TLC, %/pred	0.34 p=1.625E-02	0.31 p=3.103E-02	**0.43 p=2.009E-03**	**0.40 p=4.264E-03**
RV, L	0.21 p=0.16	0.25 p=0.09	0.29 p=4.569E-02	0.33 p=2.208E-02
RV, %	0.30 p=3.611E-02	0.31 p=3.367E-02	0.35 p=1.609E-02	0.33 p=2.324E-02
Age, years	-0.31 p=2.763E-02	-0.22 p=0.11	-0.32 p=2.351E-02	-0.28 p=4.861E-02
Waist-hip ratio	0.25 p=0.09	0.19 p=0.19	0.31 p=3.082E-02	0.32 p=2.571E-02
Waist circumference	0.21 p=0.16	0.21 p=0.16	0.31 p=3.411E-02	0.31 p=3.220E-02
LTOT duration, month	**0.41 p=3.864E-03**	**0.48 p=5.101E-04**	**0.42 p=3.297E-03**	**0.41 p=3.997E-03**

ESWT: endurance shuttle walk test; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; LTOT: long-term oxygen therapy. Correlations with p-values <0.01 are presented in bold; P-values were calculated via Spearman rank-order correlations. P-values are unadjusted for multiple comparisons.

Table S2. Correlation matrix of patient characteristics for change in PCO_2 (Δ) and PCO_2 post endurance shuttle walk test

	ΔPCO_2 [mmHg]		**PCO_2, post-walk** [mmHg]	
	$ESWT_{CFOS}$	$ESWT_{ATOS}$	$ESWT_{CFOS}$	$ESWT_{ATOS}$
FEV_1, %/pred	0.10 p=0.5	0.08 p=0.6	-0.12 p=0.39	-0.24 p=0.09
Body fat, kg	0.32 p=2.979E-02	0.29 p=0.05	0.10 p=0.52	0.09 p=0.54
Respiratory rate pre ESWT, n	-0.27 p=0.07	-0.26 p=0.07	0.10 p=0.5	-0.03 p=0.85
FRC_{pleth}, %/pred	-0.07 p=0.6	-0.25 p=0.08	0.35 p=1.464E-02	0.22 p=0.13
RV, %/pred	0.01 p=0.94	-0.14 p=0.33	0.33 p=2.384E-02	0.25 p=0.09
TLC, %/pred	0.04 p=0.8	-0.21 p=0.14	0.35 p=1.383E-02	0.25 p=0.09
sR_{tot}, %/pred	0.05 p=0.7	-0.26 p=0.07	**0.38** **p=6.140E-03**	0.29 p=4.382E-02
pH, pre ESWT	0.29 p=3.876E-02	0.28 p=4.852E-02	-0.31 p=0.03	**-0.37** **p=8.985E-03**
PCO_2, pre ESWT	-0.35 p=1.210E-02	**-0.41** **p=2.739E-03**	**0.59** **p=6.181E-06**	**0.61** **p=2.909E-06**
Waist-hip ratio	-0.07 p=0.6	0.01 p=0.9	-0.16 p=0.28	-0.25 p=0.09
Waist circumference, cm	0.01 p=0.92	0.10 p=0.5	-0.15 p=0.3	-0.27 p=0.06
BMI, kg/m^2	0.23 p=0.11	0.21 p=0.15	0.09 p=0.5	-0.03 p=0.8

FEV_1: forced expiratory volume in 1second; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; sR_{tot}: total specific airway resistance; pH: potential of hydrogen; PCO_2: partial pressure of carbon dioxide; BMI: body mass index; Correlations with p-values <0.01 are presented in bold; P-values were calculated via Spearman rank-order correlations. P-values are unadjusted for multiple comparisons.

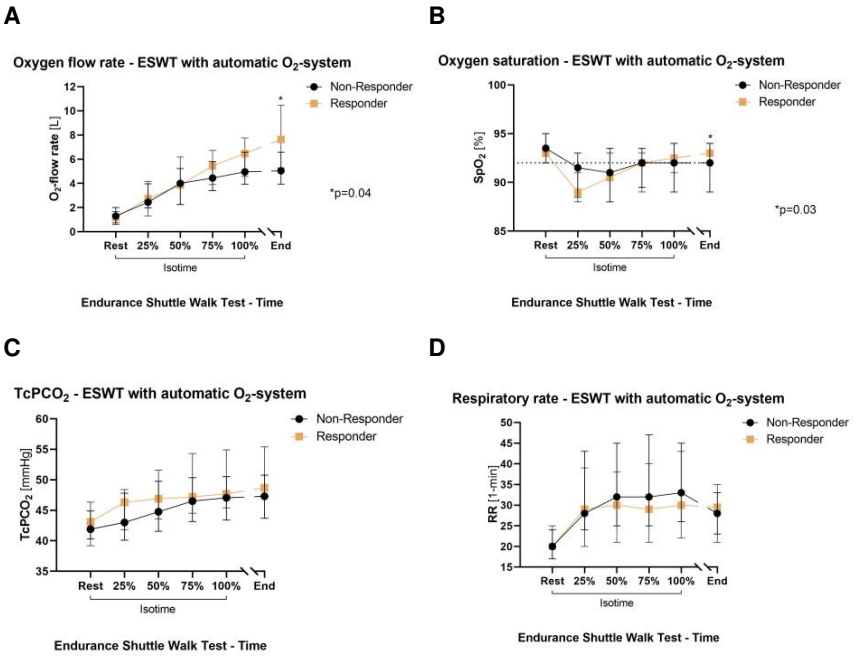


Figure S3. A) Oxygen flow rates during the endurance shuttle walk test (ESWT) automatic divided by automatically titrating O_2-system (ATOS) responder and ATOS non-responder. **B)** Oxygen saturation (SpO_2) during ESWT divided by ATOS responder and ATOS non-responder. Dashed line at 92% SpO_2. **C)** Transcutaneous carbon dioxide (TcPCO2) during ESWT divided by ATOS responder and ATOS non-responder. **D)** Respiratory rate (RR) during ESWT divided by ATOS responder and ATOS non-responder. Data is presented as median; error bars: interquartile range. Responder: "participants walking ≥ minimal important difference (65s) during $ESWT_{ATOS}$ in comparison to $ESWT_{CFOS}$". Non-Responder: "participants walking less than 65s during the $ESWT_{ATOS}$ compared to $ESWT_{CFOS}$"; P-values were calculated via Mann-Whitney-U-Test. P-values are unadjusted for multiple comparisons.

Table S3. Subgroup analyses (normocapnic participants vs. hypercapnic participants) - results. Data presented as median (interquartile range)

	Hypercapnia n=23	**Normocapnia** n=27	**p-value[x)]**
Walking capacity			
Time, sec			
ESWT$_{CFOS}$	277.0 (195.0, 480.0)	440.0 (260.0, 768.0)	4.184E-02
ESWT$_{ATOS}$	322.0 (249.0, 794.0)	855.0 (393.0, 1200.0)	0.07
Distance, m			
ESWT$_{CFOS}$	**230.0 (140.0, 410.0)**	**330.0 (240.0, 860.0)**	**6.998E-03**
ESWT$_{ATOS}$	260.0 (160.0, 670.0)	700.0 (330.0, 1210.0)	1.572E-02
Blood gas analysis			
PO_{2rest}, mmHg			
ESWT$_{CFOS}$	77.3 (71.7, 90.4)	80.4 (73.1, 91.0)	0.63
ESWT$_{ATOS}$	65.0 (61.9, 67.2)	65.6 (62.7, 70.4)	0.22
PO_{2post}, mmHg			
ESWT$_{CFOS}$	60.9 (53.8, 64.5)	61.8 (55.7, 68.9)	0.53
ESWT$_{ATOS}$	70.3 (62.5, 75.1)	73.0 (67.0, 77.0)	0.23
PCO_{2rest}, mmHg			
ESWT$_{CFOS}$	**46.1 (42.5, 49.8)**	**40.6 (36.7, 42.6)**	**4.724E-05**
ESWT$_{ATOS}$	**46.3 (40.4, 50.7)**	**40.1 (35.7, 42.2)**	**1.256E-04**
PCO_{2post}, mmHg			
ESWT$_{CFOS}$	**52.5 (49.2, 55.6)**	**49.4 (45.1, 51.2)**	**4.483E-03**
ESWT$_{ATOS}$	**52.9 (50.1, 55.6)**	**47.6 (44.8, 52.7)**	**7.013E-03**
Ph_{rest}			
ESWT$_{CFOS}$	**7.40 (7.38, 7.41)**	**7.42 (7.41, 7.44)**	**1.709E-03**
ESWT$_{ATOS}$	**7.40 (7.38, 7.42)**	**7.43 (7.41, 7.44)**	**9.323E-03**
Ph_{post}			
ESWT$_{CFOS}$	7.34 (7.31, 7.37)	7.37 (7.33, 7.38)	3.456E-02
ESWT$_{ATOS}$	7.34 (7.32, 7.37)	7.35 (7.31, 7.39)	0.23

ESWT: endurance shuttle walk test; CFOS: constant flow oxygen-system; ATOS: automatically titrating oxygen-system; PO_2: partial pressure of oxygen; PCO_2: partial pressure of carbon dioxide; pH: potential of hydrogen. Differences with p-values <0.01 are presented in bold; [x)]Mann-Whitney-U-Test. P-values are unadjusted for multiple comparisons.

Participants´ Preference

After each endurance shuttle walk test (ESWT), participants have been asked three standardized questions to objectify their sensations regarding oxygenation, comfort, and possible usage in everyday life. Both, investigator and participant were blinded and did not know via which method oxygen was supplied

(continuous vs. automatic) during ESWT (see Figure S4a, S4b, S4c). At the end of the trial, participants were asked which kind of oxygen flow device they would prefer to use (see Figure S4d).

1. **Did you have the feeling that you have been provided with sufficient oxygen while walking?**

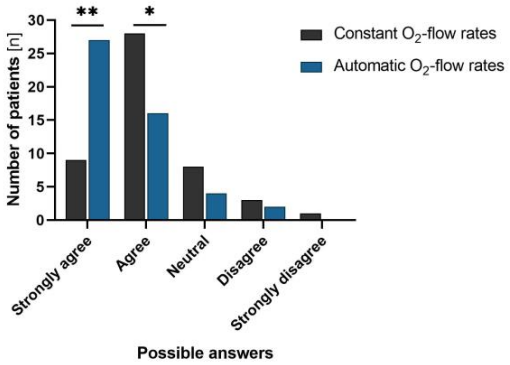


Figure S4a. Participants' preference – oxygenation (p=0.0009; marginal homogeneity test based on Monte Carlo simulation; *p=0.031McNemar Test; **p=0.0005 McNemar Test).

2. **Was the administration of oxygen comfortable?**

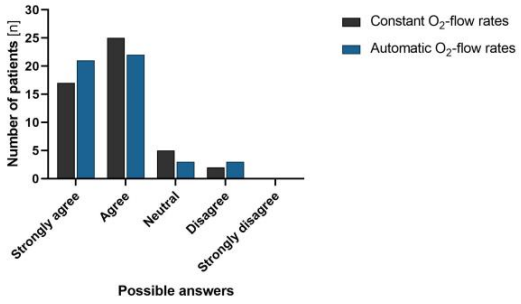
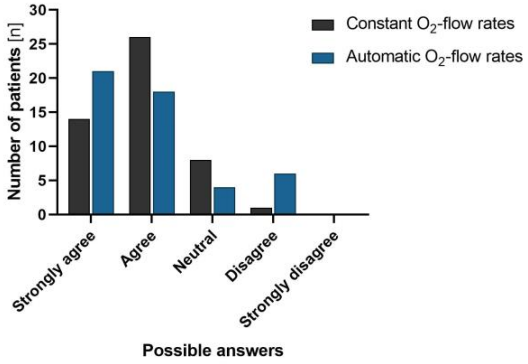


Figure S4b. Participants' preference – comfort (p=0.52; marginal homogeneity test based on Monte Carlo simulation).

3. **Could you imagine using the oxygen flow device in your everyday life?**



This question was followed by asking during what activities would you consider using each device?

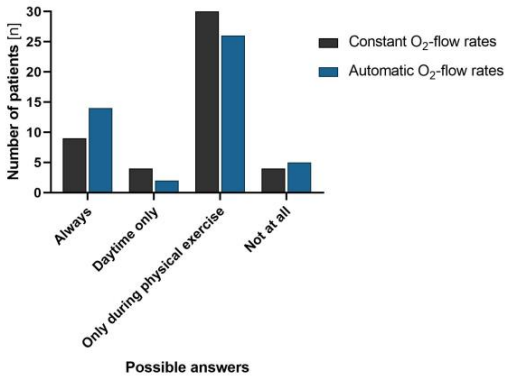


Figure S4c. Participants' preference – possible usage in everyday life (p=0.73 and p=0.23; marginal homogeneity test based on Monte Carlo simulation).

4. **If you could choose – which kind of oxygen flow system (constant vs. automatic) would you prefer?**

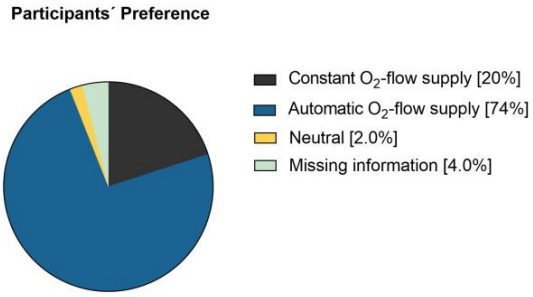


Figure S4d. Participants' preference – oxygen supplementation (p<0.0001; one sample, chi-Quadrat Test).

Literature

1 Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease: Eur Respiratory Soc, 2014

2 Hardinge M, Annandale J, Bourne S, et al. British Thoracic Society guidelines for home oxygen use in adults. Thorax 2015; 70 Suppl 1:i1-43