



# Acute effects of supplemental oxygen therapy using different nasal cannulas on walking capacity in patients with idiopathic pulmonary fibrosis: a randomised crossover trial

To the Editor:

Patients with idiopathic pulmonary fibrosis (IPF) and concurrent hypoxaemia should be treated with oxygen therapy [1]. Oxygen therapy is commonly given by conventional nasal cannulas (CNC), but can also be delivered by other less conventional cannulas such as the Oxyimizer. The Oxyimizer is a nasal cannula with an internal pendant reservoir incorporated in the lumen at the patient end which has the potential to provide increased oxygenation while using the same oxygen setting as one would with CNC [2].

It was previously shown that the use of the Oxyimizer compared to CNC leads to improvements in cycle endurance time and oxygen saturation albeit in interstitial lung disease [3]. The acute effects of supplemental oxygen therapy (SOT) delivered by the Oxyimizer in comparison to CNC during daily activities like walking in patients with IPF have not yet been investigated.

The aims of this trial were to determine, in people with IPF, whether SOT with the Oxyimizer was more effective than SOT with CNC at improving endurance walking capacity (primary outcome), oxygenation ( $S_{pO_2}$ ), heart rate, transcutaneous carbon dioxide ( $P_{tcCO_2}$ ) and dyspnoea. We hypothesised that the Oxyimizer would be superior to CNC at increasing walking exercise capacity with better oxygenation.

This single-centre study was a prospective, randomised controlled crossover trial with concealed sequence allocation generated by an independent person prior to the study.

Participants with a high-resolution computed tomography-confirmed diagnosis of IPF (usual interstitial pneumonia pattern; diagnosis performed prior to PR by patients pneumologist) with hypoxaemia (oxygen tension  $<55$  mmHg at rest or during exercise or  $S_{pO_2} <88\%$  during exercise) and an indication for oxygen during exercise were recruited. Excluded were those with a resting carbon dioxide tension  $>45$  mmHg or participants who had cardiovascular or orthopaedic conditions limiting the ability to perform the walking tests. All participants were recruited and tested within an inpatient pulmonary rehabilitation programme over 12 months between January 2018 and 2019 (Schoen Klinik Berchtesgadener Land, Germany). The study was approved by an Ethic Committee (Philipps-University of Marburg) and registered with ClinicalTrials.gov: NCT03411876. Informed written consent was obtained from all participants.

After an initial incremental shuttle walk test, participants performed, on consecutive days, two endurance shuttle walk tests (ESWTs) at 85% of maximum pace – one with the Oxyimizer Pendant and one with a CNC in a randomised order [4]. For both tests, oxygen was set at participants prescribed flow rate during exercise.



@ERSpublications

**Something simple, like changing a nasal cannula for a technologically superior one, can improve exercise capacity and oxygenation in patients with IPF. There is a need to develop improved cannulas for comfort and patient acceptance.** <https://bit.ly/2NelacE>

**Cite this article as:** Schneeberger T, Leidl D, Gloeckl R, *et al.* Acute effects of supplemental oxygen therapy using different nasal cannulas on walking capacity in patients with idiopathic pulmonary fibrosis: a randomised crossover trial. *ERJ Open Res* 2020; 6: 00197-2020 [<https://doi.org/10.1183/23120541.00197-2020>].

Copyright ©ERS 2020. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.



The primary outcome was the change of endurance walking capacity measured by the ESWT. Secondary outcomes were  $S_{pO_2}$ ,  $P_{tCO_2}$ , heart rate (all measured *via* an ear lobe sensor; SenTec Switzerland; the monitor was carried in a bag by the investigator with the display not visible by participants), time to desaturation, breathing frequency (measured *via* pressure signal to a NoxT3; Nox Medical USA) and sensation of dyspnoea (10-point Borg-scale).

Each participant completed a short questionnaire with the investigator at the end of each ESWT. Participants were asked two questions to rate perceived comfort and suitability for use in the daily life of the nasal cannula on a standardised Likert scale. After all tests, participants were asked which nasal cannula they preferred. All questions are provided in table 1.

Data were analysed for outliers and for normality. A crossover design was used to analyse continuously distributed data to test for significant differences, possible period or carry-over effects. 95% confidence intervals were computed for means for treatment effects, *i.e.* difference of means. For the crossover, period and carry-over effect, the  $\alpha$ -level was set to 5%. All statistical analyses in this report were performed by use of NCSS (NCSS 10, NCSS, LLC, Kaysville, UT).

TABLE 1 Comparison of supplemental oxygen therapy effects by using the Oxymizer (OXY) or conventional nasal cannula (CNC)

	OXY <sup>#</sup>	CNC <sup>#</sup>	Difference (95% CI) OXY–CNC	p-value
<b>Supplemental oxygen</b>				
O <sub>2</sub> during ESWT L·min <sup>-1</sup>	5±2	5±2		
<b>Exercise capacity</b>				
ESWT time s	<b>523±372</b>	<b>419±333</b>	<b>104 (11–197)</b>	<b>0.031</b>
ESWT distance m	<b>545±377</b>	<b>430±443</b>	<b>115 (12–219)</b>	<b>0.031</b>
<b>Oxygen saturation</b>				
S <sub>pO<sub>2</sub></sub> baseline %	97.8±2.1	97.4±1.9	0.4 [–0.4–1.2]	0.28
S <sub>pO<sub>2</sub></sub> isotime %	<b>81.6±8.3</b>	<b>78.4±9.2</b>	<b>3.1 (1.4–4.9)</b>	<b>0.001</b>
S <sub>pO<sub>2</sub></sub> minimum %	78.1±8.0	77.9±19.2	0.2 [–9.0–8.6]	0.97
Reached S <sub>pO<sub>2</sub></sub> <90%	<b>18 (82%)</b>	<b>22 (100%)</b>	<b>4 (18%)</b>	<b>&lt;0.001</b>
Time to S <sub>pO<sub>2</sub></sub> <90% s	<b>106±50</b>	<b>50±24</b>	<b>56 (25–87)</b>	<b>0.003</b>
Reached S <sub>pO<sub>2</sub></sub> <85%	<b>11 (50%)</b>	<b>18 (82%)</b>	<b>7 (32%)</b>	<b>0.033</b>
Time to S <sub>pO<sub>2</sub></sub> <85% s	<b>114±65</b>	<b>77±43</b>	<b>37 (13–61)</b>	<b>0.007</b>
Reached S <sub>pO<sub>2</sub></sub> <80%	7 (32%)	9 (41%)	2 (9%)	0.75
Time to S <sub>pO<sub>2</sub></sub> <80% s	148±203	99±99	48 [–24–121]	0.15
<b>Heart rate</b>				
Baseline beats per min	81.0±12.9	82.6±12.0	–1.6 [–5.3–2.1]	0.37
Isotime beats per min	<b>112.3±16.3</b>	<b>118.0±12.7</b>	<b>–5.7 [–8.9–2.5]</b>	<b>0.002</b>
<b>Breathing frequency</b>				
Baseline L·min <sup>-1</sup>	30.9±8.0	31.7±11.6	–0.8 [–2.2–3.8]	0.59
Isotime L·min <sup>-1</sup>	<b>38.7±9.6</b>	<b>41.4±9.6</b>	<b>–2.7 [–4.1–1.4]</b>	<b>&lt;0.001</b>
<b>P<sub>tCO<sub>2</sub></sub></b>				
Baseline mmHg	38.8±5.5	38.6±6.2	0.2 [–1.1–1.6]	0.71
Isotime mmHg	38.5±11.5	39.2±9.0	–0.7 [–5.5–4.2]	0.78
<b>Dyspnoea</b>				
Baseline points	2.0 (0.3–3.0) <sup>¶</sup>	2.0 (1.0–3.0) <sup>¶</sup>	0.0 (0.0–0.0) <sup>¶</sup>	0.31
End-exercise points	5.5 (4.0–7.0) <sup>¶</sup>	6.0 (5.0–7.0) <sup>¶</sup>	–0.5 [–0.8–0.8] <sup>¶</sup>	0.87
<b>Interview about cannulas</b>				
Question: comfort <sup>†</sup>				
Disagree	<b>10 (45.5%)</b>	<b>2 (9.1%)</b>	<b>8 (36.1%)</b>	<b>0.026</b>
Neutral	3 (13.6%)	1 (4.5%)	2 (9.1%)	0.50
Agree	<b>9 (40.9%)</b>	<b>19 (86.4%)</b>	<b>–10 [–45.5%]</b>	<b>0.009</b>
Question: suitability for daily life <sup>§</sup>				
Disagree	<b>9 (40.9%)</b>	<b>1 (4.5%)</b>	<b>8 (36.4%)</b>	<b>0.013</b>
Neutral	3 (13.6%)	1 (4.5%)	2 (9.1%)	0.48
Agree	<b>10 (45.5%)</b>	<b>20 (91.0%)</b>	<b>–10 [–45.5%]</b>	<b>0.004</b>
Question: preference <sup>f</sup>	8 (36.4%)	14 (63.4%)	–6 [–27%]	0.52

Data are presented as mean±sd or n (%), unless otherwise stated. ESWT: endurance shuttle walk test; S<sub>pO<sub>2</sub></sub>: oxygen saturation measured by pulse oximetry; isotime: end of shortest test; P<sub>tCO<sub>2</sub></sub>: transcutaneous carbon dioxide tension. #: n=22; ¶: median (interquartile range); †: standardised interview question after each ESWT, “was the nasal cannula comfortable to wear?”; §: standardised interview question after each ESWT, “could you imagine wearing the nasal cannula during daily life?”; f: after all study-related measurements, “if you could choose, which nasal cannula would you prefer to wear?”. Statistically significant differences (p<0.05) are presented in bold.

51 IPF patients were screened for eligibility with 25 patients excluded by either the inclusion criteria (n=22) or declining to participate (n=3). Four participants dropped out during the trial (n=1 external injury; n=1 acute infection; n=1 early discharge; n=1 withdrawn consent). Twenty-two participants completed all tests and were considered for final analyses (age:  $70\pm 7$  years; sex (female/male): n=8/15; inspiratory vital capacity:  $54\pm 15\%$  predicted; arterial oxygen tension at rest breathing room air:  $59.1\pm 12.3$  mmHg). The mean oxygen flow rate during exercise was  $5\pm 2$  L·min<sup>-1</sup>. In ESWTs, walking capacity was significantly greater with the Oxymizer compared to CNC (table 1). The longest ESWT was with the Oxymizer in 74% of participants (n=16), with CNC in 13% (n=3) and 13% (n=3) had matched durations.

At isotime (end of the shortest ESWT),  $S_{pO_2}$  was significantly higher, while heart rate and breathing rate were significantly lower when using the Oxymizer compared to CNC. Time until  $S_{pO_2} < 90\%$  and  $S_{pO_2} < 80\%$  were significantly shorter with CNC (table 1).

Overall, a significantly smaller number of participants desaturated ( $S_{pO_2} < 90\%$  and  $S_{pO_2} < 80\%$ ) with the Oxymizer in comparison to CNC (table 1).

No statistical differences were seen for  $P_{tCO_2}$  and dyspnoea levels between the Oxymizer and CNC.

A higher number of participants did not agree that the delivery of SOT by an Oxymizer was comfortable in comparison to a CNC. Further, more participants could not imagine wearing the Oxymizer during daily life (table 1). After all study-related measurements, 63.6% (n=14) of the participants prefer SOT with a CNC over the Oxymizer.

This study shows that in people with IPF using oxygen during exercise, the simple change from CNC to a nasal cannula incorporating an internal reservoir leads to a significantly improved walking capacity, higher oxygen saturation and is associated with a lower heart rate and breathing frequency.

Of the participants who walked longest with the Oxymizer, 56% (n=9) walked beyond the minimal important difference (MID) of 65 s for an ESWT [4]. With CNC, only one reached this MID. Previously published studies of the Oxymizer used cycling exercise and did not reach clinical significance [3, 5]. In the Edvardsen study [3], participant pathologies were diverse and not specific to IPF. Further, in the Edvardsen [3] and the Gloeckl [5] study, cycle exercise was used which is not as demanding on oxygenation as walking and therefore could have limited improvements in exercise performance.

In line with these studies, the difference in oxygen saturation at  $ESWT_{isotime}$  was significantly in favour of the Oxymizer ( $\Delta=3.1\%$ , 95% CI [1.4–4.9],  $p=0.001$ ) preventing a decline in saturation in the range of that presented as a meaningful drop of 2–5% [6]. Additionally, a significantly smaller number of participants showed severe desaturations. In those participants who did desaturate during ESWTs while using the Oxymizer, time until  $S_{pO_2}$  dropped below 90% and below 85% was increased by 112% and 48%, respectively. This can be interpreted as an Oxymizer-related significant and potentially clinically relevant increase in oxygenation.

Even with longer walking duration and better oxygenation, however, only 36% of participants would prefer the Oxymizer – mainly due to the stiff, inflexible material of the cannula being uncomfortable, a fact that was already described in prior research [7–9].

There are some limitations to the current study: 1) it was not possible to blind the participants nor the investigator for the nasal cannulas; however, the statistician was blinded. 2) Due to a lack of data, a sample size estimation was performed based on previous studies using the Oxymizer. However, these studies were not in walking IPF patients. Ultimately, the primary endpoint effect was proven to be statistically significant and the risk of a false decision only limited by the significance level of 5%.

This study revealed that something simple like using better oxygen cannulas can result in significant and clinically relevant benefits like improving walking duration and oxygen saturation in patients with IPF. However, only a minority would prefer to use the Oxymizer due to the cannula being uncomfortable. This shows an unmet need of combining superior technical aspects with an adequate level of comfort for the optimal nasal cannula. Attention should be brought to oxygen providers that besides the traditional requirements like how to store, transport or generate medical gases, the interface between oxygen supply and patients is of great importance.

**Tessa Schneeberger<sup>1,2</sup>, Daniela Leitl<sup>1,2</sup>, Rainer Gloeckl<sup>1,2</sup>, Inga Jarosch<sup>1,2</sup>, Daniela Reimann<sup>3</sup>, Wolfgang Hitzl<sup>4,5,6</sup>, Rembert Koczulla<sup>1,2,7</sup> and Klaus Kenn<sup>1,2</sup>**

<sup>1</sup>Dept of Pulmonary Rehabilitation, Philipps-University of Marburg, German Centre for Lung Research (DZL), Marburg, Germany. <sup>2</sup>Institute for Pulmonary Rehabilitation Research, Schoen Klinik Berchtesgadener Land, Schoenau am Koenigssee, Germany. <sup>3</sup>Dept of Internal Medicine, Philipps

University of Marburg, Marburg, Germany. <sup>4</sup>Research Office (Biostatistics), Paracelsus Medical University, Salzburg, Austria. <sup>5</sup>Dept of Ophthalmology and Optometry, Paracelsus Medical University, Salzburg, Austria. <sup>6</sup>Research Program Experimental Ophthalmology and Glaucoma Research, Paracelsus Medical University, Salzburg, Austria. <sup>7</sup>Teaching Hospital, Paracelsus Medical University, Salzburg, Austria.

Correspondence: Tessa Schneeberger, Philipps-University of Marburg, Department of Pulmonary Rehabilitation, Malterhoeh 1, 83471 Schoenau am Koenigssee, Germany. E-mail: tschneeberger@schoen-klinik.de

Received: 19 April 2020 | Accepted after revision: 15 June 2020

Acknowledgements: We thank Clancy J. Dennis for the linguistic review of this manuscript.

This study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) with identifier number NCT03411876. Because of a data privacy statement in the ethics proposal, raw data sharing is not permitted. The study protocol and informed consent form (German language) can be shared.

Author contributions: K. Kenn, D. Leitl, R. Gloeckl and T. Schneeberger designed the study. D. Leitl, D. Reimann and T. Schneeberger performed the study measurements. W. Hitzl and T. Schneeberger performed data analyses. T. Schneeberger prepared the first draft of the manuscript. K. Kenn, R. Koczulla, D. Leitl, R. Gloeckl, I. Jarosch and W. Hitzl critically revised the manuscript. All authors have read and approved the manuscript. T. Schneeberger takes the responsibility for the integrity of the data.

Conflict of interest: None declared.

Support statement: Consumable materials for the SenTec device were kindly supported by SenTec AG. SenTec AG had no influence on the study design, execution or analyses.

## References

- 1 Raghu G, Collard HR, Egan JJ, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788–824.
- 2 Tiep BL, Nicotra B, Carter R, *et al.* Evaluation of a low-flow oxygen-conserving nasal cannula. *Am Rev Respir Dis* 1984; 130: 500–502.
- 3 Edvardsen A, Jarosch I, Grongstad A, *et al.* A randomized cross-over trial on the direct effects of oxygen supplementation therapy using different devices on cycle endurance in hypoxemic patients with interstitial lung disease. *PLoS One* 2018; 13: e0209069.
- 4 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 Respir J* 2014; 44: 1447–1478.
- 5 Gloeckl R, Heinzlmann I, Matthaei M, *et al.* Benefits of an oxygen reservoir cannula versus a conventional nasal cannula during exercise in hypoxemic COPD patients: a crossover trial. *Respiration* 2014; 88: 399–405.
- 6 Stoller JK, Panos RJ, Krachman S, *et al.* Oxygen therapy for patients with COPD: current evidence and the long-term oxygen treatment trial. *Chest* 2010; 138: 179–187.
- 7 Claiborne RA, Paynter DE, Dutt AK, *et al.* Evaluation of the use of an oxygen conservation device in long-term oxygen therapy. *Am Rev Respir Dis* 1987; 136: 1095–1098.
- 8 Collard P, Wautelet F, Delwiche JP, *et al.* Improvement of oxygen delivery in severe hypoxaemia by a reservoir cannula. *Eur Respir J* 1989; 2: 778–781.
- 9 Gould G, Hayhurst MD, Scott W, *et al.* Clinical assessment of oxygen conserving devices in chronic bronchitis and emphysema. *Thorax* 1985; 40: 820–824.