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 Oxymer. The Oxymer 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 Oxymer 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 Oxymer 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 Oxymer was more effective than SOT with CNC at improving endurance walking capacity (primary outcome), oxygenation (S_{pO_2}), heart rate, transcutaneous carbon dioxide (P_{tCO_2}) and dyspnoea. We hypothesised that the Oxymer 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 Berchtesgader 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 Oxymer Pendant and one with a CNC in a randomised order [4]. For both tests, oxygen was set at participants prescribed flow rate during exercise.

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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>

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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 α -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 [#]	CNC [#]	Difference [95% CI] OXY–CNC	p-value
Supplemental oxygen				
O ₂ during ESWT L·min ⁻¹	5±2	5±2		
Exercise capacity				
ESWT time s	523±372	419±333	104 (11–197)	0.031
ESWT distance m	545±377	430±443	115 (12–219)	0.031
Oxygen saturation				
S _{pO₂} baseline %	97.8±2.1	97.4±1.9	0.4 (–0.4–1.2)	0.28
S _{pO₂} isotime %	81.6±8.3	78.4±9.2	3.1 (1.4–4.9)	0.001
S _{pO₂} minimum %	78.1±8.0	77.9±19.2	0.2 (–9.0–8.6)	0.97
Reached S _{pO₂} <90%	18 (82%)	22 (100%)	4 (18%)	<0.001
Time to S _{pO₂} <90% s	106±50	50±24	56 (25–87)	0.003
Reached S _{pO₂} <85%	11 (50%)	18 (82%)	7 (32%)	0.033
Time to S _{pO₂} <85% s	114±65	77±43	37 (13–61)	0.007
Reached S _{pO₂} <80%	7 (32%)	9 (41%)	2 (9%)	0.75
Time to S _{pO₂} <80% s	148±203	99±99	48 (–24–121)	0.15
Heart rate				
Baseline beats per min	81.0±12.9	82.6±12.0	–1.6 (–5.3–2.1)	0.37
Isotime beats per min	112.3±16.3	118.0±12.7	–5.7 (–8.9–2.5)	0.002
Breathing frequency				
Baseline L·min ⁻¹	30.9±8.0	31.7±11.6	–0.8 (–2.2–3.8)	0.59
Isotime L·min ⁻¹	38.7±9.6	41.4±9.6	–2.7 (–4.1–1.4)	<0.001
P_{tCO₂}				
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
Dyspnoea				
Baseline points	2.0 (0.3–3.0) [¶]	2.0 (1.0–3.0) [¶]	0.0 (0.0–0.0) [¶]	0.31
End-exercise points	5.5 (4.0–7.0) [¶]	6.0 (5.0–7.0) [¶]	–0.5 (–0.8–0.8) [¶]	0.87
Interview about cannulas				
Question: comfort ⁺				
Disagree	10 (45.5%)	2 (9.1%)	8 (36.1%)	0.026
Neutral	3 (13.6%)	1 (4.5%)	2 (9.1%)	0.50
Agree	9 (40.9%)	19 (86.4%)	–10 (–45.5%)	0.009
Question: suitability for daily life [§]				
Disagree	9 (40.9%)	1 (4.5%)	8 (36.4%)	0.013
Neutral	3 (13.6%)	1 (4.5%)	2 (9.1%)	0.48
Agree	10 (45.5%)	20 (91.0%)	–10 (–45.5%)	0.004
Question: preference ^f	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_{pO₂}: oxygen saturation measured by pulse oximetry; isotime: end of shortest test; P_{tCO₂}: 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 ± 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 ± 12.3 mmHg). The mean oxygen flow rate during exercise was 5 ± 2 L·min⁻¹. 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.

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Author contributions: K. Kenn, D. Leidl, R. Gloeckl and T. Schneeberger designed the study. D. Leidl, 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. Leidl, 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.

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