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High-intensity non-invasive ventilation during exercise-training versus without in people with very severe COPD and chronic hypercapnic respiratory failure: a randomised controlled trial

Tessa Schneeberger ,[1,2] Clancy John Dennis,[3,4] Inga Jarosch ,[1,2] Daniela Leitl,[1,2] Antje Stegemann,[2] Rainer Gloeckl,[1,2] Wolfgang Hitzl,[5,6,7] Maximilian Leidinger,[2] Ursula Schoenheit-Kenn,[2] Carl-Peter Criée,[8] Andreas Rembert Koczulla,[1,2,9] Klaus Kenn[1,2]

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For numbered affiliations see end of article.

Correspondence to
Tessa Schneeberger;
tessa.schneeberger@staff.uni-marburg.de

ABSTRACT

Background People with very severe chronic obstructive pulmonary disease (COPD) using nocturnal non-invasive ventilation (NIV) for chronic hypercapnic respiratory failure (CHRF) experience reduced exercise capacity and severe dyspnoea during exercise training (ET). The use of NIV during ET can personalise training during pulmonary rehabilitation (PR) but whether high-intensity NIV (HI-NIV) during exercise is accepted and improves outcomes in these extremely physically limited patients is unknown. The aim of this trial was to determine if ET with HI-NIV during PR was more effective than without at improving exercise capacity and reducing dyspnoea during exercise.

Methods Patients with COPD, CHRF and nocturnal-NIV were randomised to supervised cycle-ET as part of PR with HI-NIV or without (control). Primary outcome was change in cycle endurance time (ΔCET_{time}), while secondary outcomes were dyspnoea at isotime during the cycle endurance test and during ET-sessions and for the HI-NIV group, post-trial preferred exercising method.

Results Twenty-six participants (forced expiratory volume in 1 s 22±7%pred, $PaCO_2$ 51±7 mm Hg) completed the trial (HI-NIV: n=13, ET: IPAP 26±3/EPAP 6±1 cm H_2O; control n=13). At completion of a 3 week ET-programme, no significant between-group differences in ΔCET_{time} were seen (HI-NIV-control: Δ105 s 95% CI (−92 to 302), p=0.608). Within-group ΔCET_{time} was significant (HI-NIV: +246 s 95% CI (61 to 432); control: +141 s 95% CI (60 to 222); all p<0.05). The number of responders (Δ>minimal important difference $(MID)_{101\,s}$: n=53.8%) was the same in both groups for absolute ΔCET_{time} and 69.2% of control and 76.9% of the HI-NIV group had a %change>$MID_{33\%}$. Compared with control, the HI-NIV group reported less isotime dyspnoea (Δ−2.0 pts. 95% CI (−3.2 to −0.8), p=0.005) and during ET (Δ−3.2 pts. 95% CI (−4.6 to −1.9), p<0.001). Most of the HI-NIV group (n=12/13) preferred exercising with NIV.

Conclusion In this small group of patients with very severe COPD requiring nocturnal NIV, participation in an ET-programme during PR significantly improved exercise capacity irrespective of HI-NIV use. Reported dyspnoea was in favour of HI-NIV.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ High-intensity non-invasive ventilation (HI-NIV) during a single exercise session has been shown to temporarily reduce carbon dioxide-levels (CO_2) and dyspnoea, while improving oxygenation and exercise capacity compared with oxygen (O_2) alone in people with chronic obstructive pulmonary disease (COPD) and chronic hypercapnic respiratory failure (CHRF). However, no study has investigated the effects of using HI-NIV during an exercise training (ET)-programme on changes in exercise capacity over the course of a pulmonary rehabilitation (PR)-programme. While systematic reviews did not find strong evidence for using NIV during ET in people with COPD, the inclusion criteria and range of NIV-modes were broad. Whether people with COPD, CHRF and nocturnal NIV experience, tolerate and accept HI-NIV during exercise and if they prefer exercising with HI-NIV compared with without during PR is also unknown.

WHAT THIS STUDY ADDS

⇒ This study shows that HI-NIV could be a useful addition to ET during a PR-programme in people with very severe COPD, CHRF and nocturnal NIV as participants completed the programme with less dyspnoea and similar significant increases in exercise capacity. All participants who used HI-NIV during exercise reported that it made breathing easier and 12 out of 13 participants stated that they would prefer to continue exercising with NIV rather than oxygen alone.

Trial registration number NCT03803358.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease[1] that can lead to chronic hypercapnic respiratory

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ As modern PR offers greater personalisation and individualisation of programmes, adjuncts such as HI-NIV during exercise are of increasing importance and can help clinicians and therapists to provide the right treatment (HI-NIV), to the right people (very severe COPD with CHRF and nocturnal NIV), at the right moment (ET), for the right outcomes (dyspnoea) and make a difference for patients with severe, end-stage lung disease. People comfortable managing and using nocturnal NIV should be offered the chance to use it within PR during appropriate exercise if they experience severe exertional dyspnoea.

failure (CHRF).[2] Chronically elevated levels of arterial carbon dioxide ($PaCO_2$) can cause symptoms such as dyspnoea, reduced quality of life (QoL) and an increased risk of hospitalisation or death.[3] Chronic hypercapnia, defined as a $PaCO_2$ of more than 45 mm Hg,[4] is prevalent in 25% of people with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage III or IV COPD.[5] Nocturnal non-invasive ventilation (NIV), when set to reduce chronically elevated $PaCO_2$, known as high-intensity NIV (HI-NIV), can delay the need for hospital readmission[6] and improve survival[2] in CHRF. However, even with nocturnal NIV, people with CHRF may have a reduced exercise capacity,[7] an increased $PaCO_2$ and severe dyspnoea during exercise.[8] These symptoms can make exercise training (ET) uncomfortable leading to physical activity avoidance and may hinder the physiological and clinical benefits of ET.[9 10]

To personalise ET for people with COPD and CHRF during pulmonary rehabilitation (PR), NIV during exercise may offer increased exercise tolerance and superior outcomes compared with standardised methods.[7 9] HI-NIV during a single exercise session has been shown to temporarily reduce $PaCO_2$ and dyspnoea, while improving oxygenation and exercise capacity compared with oxygen (O_2) alone in people with COPD and CHRF.[7 8] However, no study has investigated the effects of using HI-NIV during ET on changes in exercise capacity within a PR-programme. While two systematic reviews[11 12] did not find strong evidence for using NIV during ET in people with COPD, the inclusion criteria and range of NIV modes were broad. Furthermore, included trials involved participants lacking an indication for nocturnal NIV[13] and used only low to moderate levels of ventilatory support. A more recent trial in CHRF and nocturnal NIV found promising results using NIV during ET.[14]

The high number of dropouts in a previous ET trial was attributed to NIV-intolerance during exercise;[15] however, other acute trials which included NIV-naïve patients found relatively good tolerance after a short acclimatisation.[16 17] Whether people with COPD, CHRF and nocturnal NIV experience, tolerate and accept HI-NIV during exercise and if they prefer exercising with HI-NIV compared with without is also unknown. There is a need for more evidence to support or refute the use of HI-NIV during ET as a personalised adjunct within PR.

The purpose of this study was to determine whether ET with HI-NIV is more effective than ET without NIV as part of a PR-programme in improving exercise capacity and reducing dyspnoea in people with very severe COPD and CHRF who use nocturnal NIV. We also aimed to determine whether these individuals preferred using HI-NIV during exercise to oxygen alone. We hypothesised that ET with HI-NIV would be more effective at increasing exercise capacity and reducing dyspnoea compared with ET without NIV and that people would prefer to exercise with HI-NIV.

METHODS

This study was a prospective, randomised controlled trial (RCT) with blinded outcome assessors and statistician. Groups were allocated via computer-based block randomisation which was performed by an independent person and concealed in sequentially numbered opaque envelopes. The study was conducted at the Schoen Klinik Berchtesgadener Land, Germany from January 2019 to July 2021 and included participants aged 40–80 with very severe COPD (GOLD IV), CHRF and with a prescription of nocturnal NIV(confirmed according to guidelines[18] at study inclusion). All participants took part in a 3 week inpatient PR-programme. Participants were excluded if they had a body-mass index greater than 35 kg/m^2 or cardiovascular/orthopaedic/neurological restriction that would limit their ability to perform ET. After written informed consent, participants were randomised into groups that received cycle-ET with HI-NIV during exercise ($HI\text{-}NIV_{group}$) or without (control-group). Otherwise, all participants received the same PR-content (described elsewhere[19]) and nocturnal NIV and O_2-therapy were continued independently of group-assignment.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. However, prior to initiating the study, we engaged in conversations with the patient group under consideration to understand the need for such a trial.

Exercise training

Endurance-ET for both groups initially consisted of 10 min of stationary cycling at 60% of the individual's peak work rate (PWR), which was determined via incremental cycle test. Training took place 5 days/week over a 3 week period. Exercise duration was gradually increased to a total of 30 min (online supplemental table 1).[20] A respiratory therapist specialised in providing NIV during exercise, supervised ET-sessions. Throughout the ET-programme, work rate was increased based on symptoms, with the goal of achieving a 'somewhat severe' to 'severe' level of dyspnoea or rate of perceived exertion (4–6 on

the 10-point Borg scale)[21] during or at the end of the ET sessions.

Non-invasive ventilation during exercise training

All participants had nocturnal NIV for management of CHRF. Nocturnal settings for inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP), respiratory rate (RR) and inspiratory time (TI) were titrated to decrease $PaCO_2$ via HI-NIV methodology.[2] Nocturnal NIV settings were used as baseline settings for exercise and adjusted as needed for comfort and support. To maximise the reduction in $PaCO_2$ and work of breathing, TI and RR were adjusted to minimise the number of spontaneously triggered breaths and maximise the number of ventilator-controlled breaths during exercise. The respiratory therapist used two guiding questions to adjust NIV setting: 'are you getting enough air?' and 'would you like to breathe quicker?' aiming to alter IPAP and TI to maximise comfort. If a participant reported expiratory discomfort, EPAP was adjusted. Prior to ET, a single-test session was conducted to familiarise participants with HI-NIV. For ET, all participants used the same ventilator (prisma VENT40, Loewenstein Medical, Germany) and HI-NIV was applied via a full-face mask with single limb circuit and a passive expiratory vent. Supplemental O_2 was provided as prescribed via the ventilator.

Outcome measures

The primary outcome of this study was change in endurance exercise capacity from pre-PR to post-PR, as measured by a cycle endurance test (CET) at 75% of the PWR. Exercise tests ceased if the participant felt too breathless, could not maintain pedal cadence, or reached the maximum test duration (20 min). The CET was performed without NIV but with supplemental O_2 as prescribed.

Secondary outcomes included differences in sensation of dyspnoea, the perception of respiratory effort and leg fatigue (measured via the 10-point Borg scale), differences in physiological measures ($PaCO_2$, pH, oxygenation, lactate, blood pressure) during the CET and changes in measures of QoL from pre-PR to post-PR. Transcutaneous carbon dioxide ($TcPCO_2$), oxygen saturation (SpO_2) and heart rate were continuously recorded using earlobe sensor (SenTec, Switzerland), while RR was continuously measured using respiratory inductance plethysmography (ApneaLink, ResMed, Australia). Arterialised earlobe capillary blood gas, blood pressure, dyspnoea, respiratory effort and leg fatigue were measured at rest before the CET and at isotime (the end of the shortest CET (pre-PR or post-PR)). QoL measures (Chronic Respiratory Questionnaire (CRQ); Severe Respiratory Insufficiency scale (SRI); Hospital Anxiety and Depression Scale (HADS)), the 6 Min Walk Distance (6MWD) and maximal voluntary muscle force of the quadriceps femoris (microFET, Hoggan Scientific, USA) were taken at pre-PR and post-PR. From each ET session, postexercise dyspnoea, respiratory effort, leg fatigue as well as achieved training duration, watts and breaks were documented. $TcPCO_2$, SpO_2 and heart rate were recorded weekly during an ET session.

After study completion, participants in the $HI\text{-}NIV_{group}$ completed a 5-point Likert scale questionnaire[17] concerning perception of using HI-NIV during ET. Finally, each participant in the $HI\text{-}NIV_{group}$ was asked if they would prefer exercising with or without NIV in the future.

Statistical methods

Sample size calculation: the study had 90% power to detect a mean difference of 101 s or more in the primary outcome between the two groups, with a sample size of n1=n2=13 in each group. The type I error was set at 5% and the SD for the primary outcome was assumed to be 83.9 s, based on data from a previous study (online supplemental file[14]). We assumed variance homogeneity, normal data and two dropouts in each group. Under these assumptions, the final sample size was n1=n2=15, with a total sample size of 30 participants in the study.

Analyses: data were checked for consistency and normality. Fisher's Exact test or Pearson's test were used to analyse cross tabulations. Independent and dependent t-tests were used for normally distributed data, and bootstrap-t tests were used for non-normally distributed data; 95% CIs were computed for differences. All tests were two-sided, and p-values<0.05 were considered statistically significant. All statistical analyses were performed using NCSS (NCSS V.10, NCSS, LLC. Kaysville, UT) and STATISTICA V.13 (Hill & Lewicki. Statistics: Methods and Applications. StatSoft, Tulsa, OK).

RESULTS

Trial flow and participant characteristics

A total of 30 participants were recruited (mean±SD forced expiratory volume in 1 s (FEV_1) 22±7%pred), with four not completing the trial. Detailed patient enrolment information is presented in figure 1. All participants had nocturnal HI-NIV (duration 29±28 months, IPAP 24.3±3.8 cm H_2O, EPAP 6.1±1.4 cm H_2O) for CHRF ($PaCO_2$ 50.9±7 mm Hg at rest) and 42.3% of participants were on the lung transplantation wait list (table 1). During the 3 week PR programme, participants completed an average of 12±2 training sessions.

Pre-PR and post-PR values of all outcomes for both groups are reported in online supplemental table 2.

Primary outcome

There was no statistically significant difference between groups in the change in exercise capacity (CET duration) from pre-PR to post-PR (Δ105 s 95% CI (−92 to 302); table 2, online supplemental figure 1). Within-group ΔCET_{time} absolute and percentage increase from pre-PR

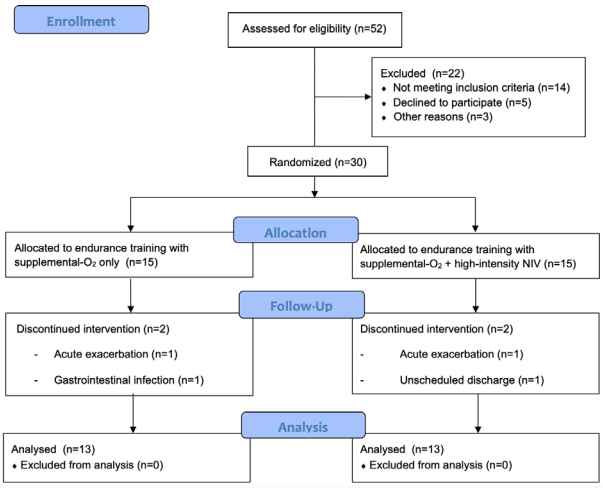

Figure 1 Consolidated Standards of Reporting Trials—flow diagram. O_2, oxygen; NIV, non-invasive ventilation.

to post-PR were significant in both groups, exceeding the minimal important difference (MID) of 101 s/ 33%[22] for constant power exercise duration changes in COPD following a PR-programme (table 2, online supplemental figure 2). The number of responders (ΔCET_{time}>101 s: n=53.8%) was the same in both groups and 69.2% of control and 76.9% of the HI-NIV group had a percentage change in cycle endurance time>33%.

Secondary outcomes

Participants in the HI-NIV_{group} reported feeling significantly less dyspnoeic at isotime in the post-PR CET compared with the control-group. While the HI-NIV_{group} showed significant improvements in $PaCO_2$ and pH, there were no between-group differences (online supplemental table 3).

Both groups showed significant and clinically relevant improvements in 6MWD, but there was no difference between the groups (table 2). There was also no between-group difference in the change in knee extension force; however, within the HI-NIV_{group}, the change was significant. The HI-NIV_{group} had significantly greater improvements in the total CRQ score and emotional function score compared with the control-group. Within only the HI-NIV_{group}, there were significant improvements in all CRQ domains and the anxiety domain of the HADS, exceeding the MID of 0.5 points[23] and 1.5 points.[24] There were no between-group differences in the change in HADS-score and SRI-score (table 2).

Exercise training

No adverse events were reported. Both groups followed the ET-protocol, with similar increases in ET-duration. There was no difference in ET-intensity between groups (table 3). The number of breaks during cycling-ET was similar, but average duration was significantly shorter in the HI-NIV_{group}. Dyspnoea and respiratory effort were significantly higher in the control-group compared

Table 1 Participant characteristics

	Control-group	HI-NIV group
Subjects	13	13
Age, years	63±7	59±5
Female/male	6/7	9/4
BMI, kg/m^2	23±5	25±4
Waist-hip ratio	0.96±0.1	0.93±0.1
Pulmonary function		
FEV_1, L	0.6±0.2	0.6±0.2
FEV_1, % pred	22±8	22±6
FEV_1/FVC, %	46±13	45±9
TLC, L	9.3±1.6	8.7±1.3
TLC, % pred	159±31	157±26
RV, L	7.7±1.8	7.2±1.2
RV, % pred	352±79	351±66
RV/TLC, % pred	220±45	214±18
Raw, kPa s L^{-1}	1.1±0.3	1.3±0.4
Blood gas (rest)		
ph	Room air	Room air
	n=10	n=12
	7.40±0.02	7.39±0.03
	With oxygen*	With oxygen*
	n=3	n=1
	7.36±0.05	7.32
$PaCO_2$, mm Hg	Room air	Room air
	n=10	n=12
	50.6±7.0	49.1±6.3
	With oxygen*	With oxygen*
	n=3	n=1
	53.5±7.1	68.9
PaO_2, mm Hg	Room air	Room air
	n=10	n=12
	52.8±7.9	52.3±7.7
	With oxygen*	With oxygen*
	n=3	n=1
	76.9±15.9	90.5
Oxygen therapy (flows)		
Exercise, L min^{-1}	3.3±0.9	3.1±1.0
Night, L min^{-1}	1.9±0.7	1.7±0.8
Rest, L min^{-1}	1.7±1.1	1.6±0.8
Nocturnal non-invasive ventilation		
Since months	21±29	37±24
Mean usage time, h	8.0±1.5	8.3±3.8
IPAP, cm H_2O	24.2±3.9	24.4±4.0
EPAP, cm H_2O	6.1±1.7	6.1±1.3
RR, breaths/min^{-1}	14.5±2.2	15.9±2.2
Exercise capacity		

Continued

Table 1 Continued

	Control-group	HI-NIV group
PWR-test, watt	44±17	44±17
CET, watt	32±13	32±13

Data presented as mean and SD or number. Baseline characteristics were comparable between groups (all p>0.05).
*Patient did not tolerate breathing without oxygen.
BMI, body mass index; CET, cycle endurance test; EPAP, expiratory positive airway pressure; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IPAP, inspiratory positive airway pressure; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; pH, potential of hydrogen; PWR, peak work rate; Raw, airway resistance; RR, respiratory rate; RV, residual volume; TLC, total lung capacity.

with the $HI\text{-}NIV_{group}$. Mean $TcPCO_2$ was significantly lower and mean SpO_2 was significantly higher in the $HI\text{-}NIV_{group}$ (table 3, figure 2). ET-settings and ET-measurements of HI-NIV are presented in online supplemental table 4.

Perception of NIV-usage during exercise

Online supplemental figure 3 shows responses to the post ET perception questionnaire in the HI-NIV group.

All participants except one of the $HI\text{-}NIV_{group}$ (n=12/13) selected that they would like to continue ET with NIV.

DISCUSSION

The use of HI-NIV during cycle-ET within a 3 week inpatient PR-programme in people with very severe COPD and CHRF already established on nocturnal NIV, resulted in no statistically significant improvement in exercise capacity compared with exercising without HI-NIV. Both groups achieved significant and clinically relevant benefits with changes in exercise capacity of a magnitude expected from an effective PR-programme for people with COPD.[22] While not significant, between-group differences tended to be greater for constant-power cycle exercise duration in favour of HI-NIV.[22]

Most noticeably, the $HI\text{-}NIV_{group}$ perceived significantly less dyspnoea throughout ET and at isotime during the post-PR CET without NIV beyond the suggested MID

Table 2 Within-group and between-group statistical analyses

	Within-group difference from pre-PR (post-PR–pre-PR)		Between-group differences	
	Control-group	HI-NIV group	HI-NIV group–control-group	P value
Subjects	13	13		
CET				
Time, s	141 (60 to 222)*	246 (61 to 432)*	105 (–92 to 302)	0.608
Time, % change	56 (29 to 83)*	99 (22 to 175)*	43 (–35 to 120)	0.665
6MWT				
Distance, m	41 (15 to 67)*	50 (16 to 84)*	9 (–31 to 50)	0.645
HADS, pts				
Anxiety	–0.4 (–2.4 to 1.8)	–2.0 (–3.8 to –0.22)*	–1.6 (–4.3 to 0.9)	0.182
Depression	0.1 (–0.9 to 1.0)	–0.6 (–2.0 to 0.75)	–0.7 (–2.3 to 0.9)	0.361
CRQ, pts				
Total	0.4 (–0.8 to 0.9)	1.0 (0.7 to 1.4)*	0.6 (0.1 to 1.2)†	0.023
Dyspnoea	0.2 (–0.4 to 0.9)	0.8 (0.06 to 1.6)*	0.6 (–0.3 to 1.5)	0.134
Fatigue	0.4 (–0.1 to 1.0)	1.0 (0.5 to 1.7)*	0.6 (–0.1 to 1.4)	0.104
Emotional function	0.4 (–0.0 to 0.8)	1.2 (0.8 to 1.6)*	0.8 (0.2 to 1.3)†	0.011
Mastery	0.5 (–0.1 to 1.1)	1.0 (0.6 to 1.5)*	0.5 (–0.1 to 1.2)	0.091
SRI, pts				
Summary scale	0.6 (–3.4 to 4.6)	–3.4 (–8.2 to 1.2)	–4 (–9.9 to 1.7)	0.075
Knee extension peak force				
N	20 (–19 to 61)	26 (9 to 42)*	6 (–36 to 47)	0.621
% pred	8 (–4 to 21)	7 (2 to 13)*	–1(–14 to 12)	0.849

Data presented as mean (95% CI).
*Significant within-group difference from pre-PR.
†Significant between-group difference.
CET, Cycle Endurance Test; CRQ, Chronic Respiratory Disease questionnaire; HADS, Hospital Anxiety and Depression Scale; 6MWD, 6-Min Walk Test; NIV, nocturnal non-invasive ventilation; PR, pulmonary rehabilitation; SRI, Severe Respiratory Insufficiency questionnaire.

Table 3 Exercise training parameters (watt, duration and breaks) and $TcPCO_2$, SpO_2, HR, dyspnoea, respiratory effort and leg fatigue during cycle exercise training

	Control-group	HI-NIV group	Between-group differences HI-NIV group–CG	P value
Watt, %PWR	61±12	64±7	3 (–5 to 10)	0.49
Target duration, % pred	91±14	95±15	4 (–8 to 16)	0.476
Breaks, n	1.2±1.5	0.5±0.7	–0.7 (–1.7 to 0.2)	0.107
Breaks, s	159±194	35±54	–124 (–243 to –3)*	0.045
$TcPCO_2$†, mm Hg				
Pre	52.3±5.9	46.9±5.6	–5.4 (–10.1 to –0.6)*	0.022
Post	56.1±7.0	49.8±5.5	–6.3 (–11.5 to –1.0)*	0.026
Max	58.0±6.9	52.3±4.9	–5.7 (–10.7 to –0.7)*	0.022
Average	56.1±6.4	50.4±4.8	–5.7 (–10.4 to –0.9)*	0.022
SpO_2†, %				
Average	92.7±3.0	96.0±3.2	3.3 (0.7 to 5.9)*	0.01
Min	89.6±3.9	93.5±5.2	3.9 (0.1 to 7.8)*	0.01
HR†, bpm				
Average	101.0±10.5	104.6±14.1	3.6 (–6.6 to 13.8)	0.475
Max	111.7±12.6	113.2±15.9	1.5 (–10.3 to 13.3)	0.8
Dyspnoea‡, pts	5.9±1.7	2.7±1.6	–3.2 (–4.6 to –1.9)*	<0.001
Respiratory effort‡, pts	5.8±1.7	3.0±1.5	–2.8 (–4.1 to –1.5)*	<0.001
Leg fatigue‡, pts	3.9±1.8	4.5±1.2	0.6 (–0.7 to 1.8)	0.511

*Significant between-group difference.
†Data are the average weekly measures of $TcPCO_2$, SpO_2 and HR which was continuously measured during the session.
‡Data are the mean±SD of each training session for all participants in the control-group or HI-NIV group.
CG, control-group; HI-NIV, high-intensity nocturnal non-invasive ventilation; HR, heart rate; SpO_2, oxygen saturation; $TcPCO_2$, transcutaneous carbon dioxide.

of 1-point.[25] The differences in breathlessness during the post-PR CET suggest changes in the sensation of dyspnoea during exercise beyond the reduction seen by using NIV. Furthermore, significant and clinically relevant improvements in QoL[23] and anxiety[24] were achieved only in the $HI\text{-}NIV_{group}$ with significant between-group differences for the CRQ-total score and CRQ-emotional function domain.

This is the first RCT investigating the effects of HI-NIV during ET versus ET without, as part of PR in people with very severe COPD and CHRF, who are already using and familiar with nocturnal NIV. To the best of our knowledge, this is the first study to report patient-related outcomes during ET-sessions along with participant perceptions of HI-NIV. Our results add to previous studies that have compared ET with NIV to without in normocapnic people with COPD who were NIV-naïve and did not have a clinical need for nocturnal NIV.[11] Previous trials have used different modes of ventilatory support, such as bilevel, proportional assist ventilation and inspiratory pressure support, while also using comparatively low to moderate levels of support compared with HI-NIV used in the present study.[15 26–30]

To the best of our knowledge, the study by Vitacca *et al*[14] is the only study to have investigated the use of NIV during ET in people with CHRF using nocturnal NIV. However, their population was less severe than the current study (Vitacca *et al*[14] vs current study): FEV_1 %pred.: NIV-group: 40.3±23.1 vs 22±6; control-group: 42.8±20.2 vs 22±8 and consisted of a mixed participant-group with CHRF from restrictive thoracic disease or COPD. Additionally, the ventilatory support provided during exercise was lower compared with the current study, even though the NIV settings were based on the nocturnal settings (IPAP, cm H_2O: 17.4±3.5 vs 26±3.5; EPAP, cm H_2O: 6.5±1.2 vs 5.7±0.8). Despite these differences, the study reported a significant improvement in CET post-training in favour of the NIV-group, attributed primarily to large changes in the COPD-subgroup. Unlike the findings of this study, where both groups showed clinically significant improvements in CET, only the NIV-group showed significant and clinically relevant CET-increases while changes in 6MWD, were similar, with no significant between-group differences.[14] A post-hoc analysis of the current study found that age (r=–0.493, p=0.012) and resting ph (r=0.488, p=0.013) were the only significant predictors for absolute change in cycle endurance time (ΔCET_{time}).

As the future of PR includes an increase in the involvement of patients in their therapy with a greater personalisation,[31] we believe that this study provides

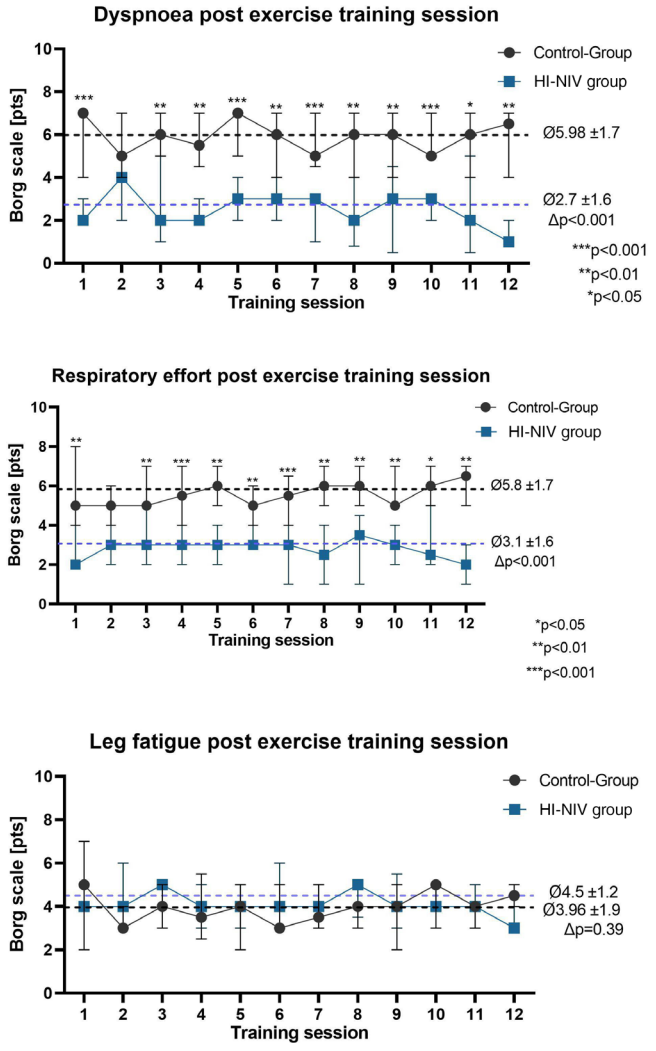

Figure 2 Postexercise training parameters (dyspnoea, respiratory effort and leg fatigue) collected via modified Borg scale. HI-NIV, high intensity nocturnal non-invasive ventilation.

important knowledge to strengthen the recommendation of existing PR-guidelines[32] to offer NIV during ET to those people who are already receiving nocturnal NIV. Based on the acute physiological responses to using HI-NIV during exercise,[8] it was theorised that ET with HI-NIV could allow higher training-intensities and that this would result in greater improvements in exercise capacity. While the increase in exercise capacity using HI-NIV was not significant and training workload/duration was not different between groups, those training with HI-NIV had significantly shorter exercise break durations than those training without, while reporting significantly less dyspnoea (table 3, figure 2). A possible explanation for reduced break durations and dyspnoea may be the significantly lower $TcPCO_2$ and higher SpO_2 when training with HI-NIV compared with without, indicating a lower drive to breathe or a reduction in dynamic hyperinflation, both factors of breathlessness in COPD.[33]

While the participants who trained with HI-NIV showed a significant reduction in $TcPCO_2$ and dyspnoea, this did not result in a significant improvement in exercise capacity above that seen in the control-group. This may be due to the intense physiological stimulus provided by the ET part of the PR-programme, which included daily ET-sessions and increasing ET-duration, overpowering the ability of NIV during exercise to accelerate physiological changes in this very severe and physically limited patient-group. Despite this, the significant effect of HI-NIV on dyspnoea is an important finding as breathlessness is a key symptom of COPD[34] and one of the three most important outcomes of PR.[35] The results indicate that using HI-NIV during exercise is a safe and feasible way to personalise PR and increase comfort for these patients who are already familiar with NIV. The control-group also showed that ET without NIV was feasible and effective, though with significantly higher $TcPCO_2$ and dyspnoea. While high, it is worth noting that the mean change in $TcPCO_2$ during training in the control-group was not significantly different to that seen in a similar but larger group of hypercapnic people with COPD after a single exercise test using oxygen alone suggesting it was not abnormal.[36]

In this study, all participants who used HI-NIV during exercise reported that it made breathing easier. Most participants (n=12/13) stated that they would prefer to continue exercising with NIV rather than oxygen alone. In comparison to a previous study with participants naïve to NIV, a higher percentage of participants in this trial (91.7%) felt comfortable using the mask (online supplemental figure 3: Q8) to assist breathing while exercising, compared with 72.2% by Dennis *et al*.[17] Furthermore, no participant dropped out due to intolerance of HI-NIV, indicating a good compliance in this NIV-acclimatised group compared with previous trials.[15 29] At the end of the current trial, participants of the $HI\text{-}NIV_{group}$ were able to setup, operate and exercise with HI-NIV without the direct assistance of the respiratory therapist indicating a possibility that, HI-NIV may be used during exercise outside a formal clinical setting. Future research may also investigate the use of HI-NIV during ET outside the clinic in this severe but non-naïve patient group as a potential method to maintain PR effects.

This study had some limitations. The calculated sample size was based on limited data available from Vitacca *et al*[14] and in retrospect was not large enough to detect significant changes in CET-duration when training with HI-NIV in people with very severe COPD and CHRF additionally to the effects of ET during PR. However, this trial is the largest conducted so far in this very ill population and future trials can use the results for sample size calculations (a post-hoc power analysis is presented in online supplemental table 5). Even with the small sample size, changes in dyspnoea and QoL were significant as secondary endpoints, providing a starting point for future trials despite no adjustment of the secondary endpoints for multiple measures being conducted. Second, while

the 3 week inpatient PR-programme is shorter than other outpatient PR-programmes, this is standard care in Germany and is comparable since both groups improved their exercise capacity beyond the MID for change in CET for PR.[22] Finally, in retrospect, dyspnoea may have been the more appropriate outcome for this very severe group as training response can vary and the distress during exercise due to breathlessness is one of the most frequent problems experienced by patients with COPD and a major determinant of impaired QoL,[37] increased anxiety and symptoms of depression.[38] Therefore, further research should consider using dyspnoea as primary outcome.

CONCLUSION

HI-NIV could be a useful addition to ET during PR in people with very severe COPD, CHRF and nocturnal NIV as participants completed the programme with less dyspnoea and similar significant increases in exercise capacity. As no adverse events occurred and 12 of 13 participants elected to continue using HI-NIV during ET, people comfortable managing and using nocturnal NIV should be offered the chance to use it during exercise.

As modern PR offers greater individualisation of programmes, adjuncts which can increase comfort for patients with end-stage lung disease such as HI-NIV during exercise may help clinicians and therapists personalise treatment and get better tolerance and outcomes.

Author affiliations
[1]Department of Pulmonary Rehabilitation, Philipps-University of Marburg, Marburg, Germany
[2]Institute for Pulmonary Rehabilitation Research, Schoen Klinik Berchtesgadener Land, Schoenau am Koenigssee, Germany
[3]Zamanian Laboratory, Department of Pulmonary and Critical Care Medicine, Stanford University, Stanford, California, USA
[4]Faculty of Medicine and Health, Sydney University, Sydney, New South Wales, Australia
[5]Research and Innovation Management, Biostatistics, Paracelsus Medical University, Salzburg, Austria
[6]Department of Ophthalmology and Optometry, Paracelsus Medical University, Salzburg, Austria
[7]Research Program Experimental Ophthalmology and Glaucoma Research, Paracelsus Medical University, Salzburg, Austria
[8]Department of Sleep and Respiratory Medicine, Evangelical Hospital Goettingen-Weende, Bovenden, Germany
[9]Teaching Hospital, Paracelsus Medical University Salzburg, Salzburg, Austria

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ORCID iDs
Tessa Schneeberger http://orcid.org/0009-0003-3638-6478
Inga Jarosch http://orcid.org/0000-0002-7147-7418

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