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ORIGINAL RESEARCH

Nasal high-flow versus noninvasive ventilation in patients with chronic hypercapnic COPD

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Background: Despite the encouraging results of noninvasive ventilation (NIV) in chronic hypercapnic COPD patients, it is also evident that some patients do not tolerate NIV or do not benefit from it. We conducted a study in which COPD patients with stable, chronic hypercapnia were treated with NIV and nasal high-flow (NHF) to compare effectiveness.

Methods: In a multi-centered, randomized, controlled, cross-over design, patients received 6 weeks of NHF ventilation followed by 6 weeks of NIV ventilation or vice-versa (TIBICO) between 2011 and 2016. COPD patients with stable daytime hypercapnia ($pCO_2 \geq 50$ mmHg) were recruited from 13 German centers. The primary endpoint was pCO_2 changes from baseline blood gas, lung function, quality of life (QoL), the 6 min walking test, and duration of device use were secondary endpoints.

Results: A total of 102 patients (mean±SD) age 65.3±9.3 years, 61% females, body mass index 23.1±4.8 kg/m^2, 90% GOLD D, pCO_2 56.5±5.4 mmHg were randomized. PCO_2 levels decreased by 4.7% (n=94; full analysis set; 95% CI 1.8–7.5, P=0.002) using NHF and 7.1% (95% CI 4.1–10.1, P<0.001) from baseline using NIV (indistinguishable to intention-to-treat analysis). The difference of pCO_2 changes between the two devices was −1.4 mmHg (95% CI −3.1–0.4, P=0.12). Both devices had positive impact on blood gases and respiratory scores (St. George's Respiratory Questionnaire, Severe Respiratory Insufficiency Questionnaire).

Conclusions: NHF may constitute an alternative to NIV in COPD patients with stable chronic hypercapnia, eg, those not tolerating or rejecting NIV with respect to pCO_2 reduction and improvement in QoL.

Keywords: noninvasive ventilation, nasal high-flow, COPD, hypercapnia

Introduction

Noninvasive ventilation (NIV) is the standard therapy for ventilatory failure in acute exacerbation of COPD. Increasing evidence of its effectiveness has been generated for more than two decades.[1] Studies have demonstrated a rapid improvement in blood gases as well as the reduction of respiratory rate, frequency of intubation, length of hospital stay, and mortality.[2]

Recent trials have shown that NIV also benefits COPD patients with chronic hypercapnia.[3–5] A multi-center study with 195 stable hypercapnic COPD patients revealed that NIV decreases 1-year mortality.[3] A further study confirmed reduced mortality and additionally showed reduced rates of exacerbation and hospital readmission.[4] Other parameters improved by NIV include hypercapnia, oxygen saturation, respiratory rate, dyspnea, 6-min walking test (6MWT)-distance, and quality of life (QoL).[3,5–10] Despite these encouraging results, it is also evident that some patients do not tolerate NIV or do not benefit from it.[9,11–13]

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Nasal high-flow (NHF) provides warmed and humidified gas administered through slightly enlarged nasal prongs. Oxygen fraction can be adjusted according to clinical requirements. Near-saturated humidity and gas warmed to body temperature allow tolerance of high flow rates. NHF results in only small increases of airway pressure, further reduced by opening the mouth.[14] NHF reduces minute volume, lowers respiratory rate, and decreases work of breathing.[15–18] The exhaled gas in the upper airways is rapidly washed out, and thus physiological dead-space is reduced.[19,20] The high flow rates delivered by NHF are sufficient to cover even high peak inspiratory flows, thereby avoiding the admixture of ambient air.[21]

In a recent study, NHF was found to be superior to standard nasal prongs (SNP) and NIV in patients with severe hypoxemic respiratory failure with regard to intubation rate and mortality.[22] Reintubation rates with NHF were lower than[23,24] or non-inferior[25] compared to either venturi mask, SNP or NIV, respectively.

In addition, there is mounting evidence that NHF leads to a reduction in partial pressure of CO_2 (pCO_2) reduction in hypercapnic patients over short periods.[15,26–29] NHF was also successful in reducing pCO_2 in a small pilot trial for 6 weeks.[27] Together with CO_2 wash-out studies[19,27] these results led us to hypothesize that NHF might benefit chronic hypercapnic COPD patients.

To test this hypothesis, we conducted a study in which COPD patients with stable, chronic hypercapnia were treated in a cross-over design with NIV and NHF for 6 weeks each. The primary endpoint was pCO_2 reduction compared to baseline.

Materials and methods

Study subjects

COPD patients with chronic respiratory insufficiency and stable daytime hypercapnia ($pCO_2 \geq 50$ mmHg) were recruited from 13 hospitals in Germany. Patients were excluded if they had a type I or II exacerbation[30] within the last 4 weeks, had been treated with NIV during the last 14 days, or if their body mass index was higher than 30 kg/m^2. The full list of inclusion and exclusion criteria can be found in the Supplementary materials (section 2). All patients were at least 18 years of age and provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki. Local institutional review boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients (Ethical Committee at the Medical Faculty, Leipzig University 123/09-ff). The trial registered with clinicaltrials.gov (NCT02007772).

Study design

NHF and NIV were compared in a multi-centered, randomized, controlled, 12-week cross-over trial (randomized controlled trial; RCT) (6 weeks with each device, see Supplementary materials [section 1]). The primary goal was to provide an estimate of the difference between the devices regarding pCO_2 change.

Methods

Patients were randomly assigned to receive either NHF or NIV first. Randomization was performed centrally by the Clinical Trial Center Leipzig using block randomization with variable block length, stratified by trial site.

For NHF, we used the TNI 20 oxy and nasal prongs with medium bore outlets (TNI Medical AG, Wuerzburg, Germany). A flow rate of 20 L/min was stipulated by the study protocol and oxygen supplementation was not changed compared to baseline (spontaneous breathing with oxygen by nasal cannula). At the time of study inception, NHF devices did not delivered >20 L/min.

All centers were instructed to follow the German guidelines for humidification and NIV pressure settings. It was the general aim to adjust pressures to achieve optimal tolerability and pCO_2 reduction.[31] The preferred interface was an oronasal mask, but a nasal mask could be used in case of intolerance. Trial sites were free to choose their preferred NIV (listed in Table S1).

Patients were advised to use NIV and NHF for at least 6 hrs per day, preferably during sleep, but usage in the daytime was also accepted. Duration of ventilation was based on the devices' usage data.

Analysis

The primary endpoint was the change in pCO_2 between baseline and the end of the NIV or NHF treatment. The secondary endpoints were changes in capillary blood gases, lung function, 6MWT, QoL and compliance (see Supplementary materials [section 4]).

The rationale that motivated this trial was intrinsically the non-inferiority of NHF. Because of the paucity of data and lack of consensus regarding margins of equivalence in this context, we chose descriptive estimates for the primary analysis and a non-inferiority test as a secondary analysis. The sample size determination followed accordingly. Based on an

expected SD of 11% in paired differences taken from pilot data, a sample size of 70 patients was required to have a 95% CI spanning a width of 6% of the baseline value (difference in paired means, coverage corrected, nQuery 6.02). Taking drop-out into account, a recruitment of 100 patients was planned for this study. A test of non-inferiority of NHF with a margin of 5 mm Hg was specified in the statistical plan as a secondary analysis, based on mean treatment effects from two trials available at the time.[3,32]

The full analysis set (intention to treat) included all patients who started treatment and had pCO_2 values ≥50 mm Hg at screening and no <45 mm Hg at baseline. The per protocol set includes essentially those patients that received both devices and used them sufficiently (see Supplementary materials [section 3] for a precise definition).

Missing data were accounted for using multiple imputation (see Supplementary materials [section 4]). Outcomes were analyzed with a mixed model for repeated measures with the patient as a random variable. The difference between NHF and NIV devices was estimated along with a 95% CI. In one sensitivity analysis, the same mixed model was applied to non-imputed data. In a second sensitivity analysis, the trial center was included as a random term. A paired *t*-test was used to compare the duration of device usage. For data analysis and graphic presentation, we used the software package R (version 3.4.1).

Results

Patients

From May 2011 until November 2016, 102 patients were randomized, 94 of whom were included in the intention to treat analysis (Figure 1). Since the pCO_2 levels of five randomized patients (pCO_2≥50 mmHg at screening) decreased to below 45 mmHg at baseline, the indication for treatment was no longer given. Three further patients withdrew from the trial before receiving the first treatment.

The per protocol set contained 53 patients with similar demographic characteristics and baseline pCO_2 values to the full analysis set. Baseline characteristics are presented in Table 1, and list of concomitant diseases and medications can be found in Tables S2 and S3. All patients had no history of any lasting NIV treatment, but all were on long-term oxygen therapy.

Treatments

A total of 91 patients began NHF treatment with a flow rate of 19.8±0.6 L/min and O_2 insufflation of 2.2±0.9 L/min and 82 patients began NIV treatment with an oronasal mask (57), with a nasal mask (21), or with both (1). Three patients did not tolerate NIV very early on and terminated use within the first 24 hrs. An additional 11 patients terminated use of NIV early, six for device related, four for disease-related and one for study-related reasons. Sixteen patients terminated use of NHF early, six for device related, five for disease-related and five for study-related reasons. Mean inspiratory and expiratory positive airway pressures (IPAP and EPAP) were 20.5±3.6 cm H_2O and 4.6±1.2 cm H_2O respectively, O_2 rate was 2.0±0.7 L/min and 13.3±3.9 breaths/min for those in S/T mode (n=73).

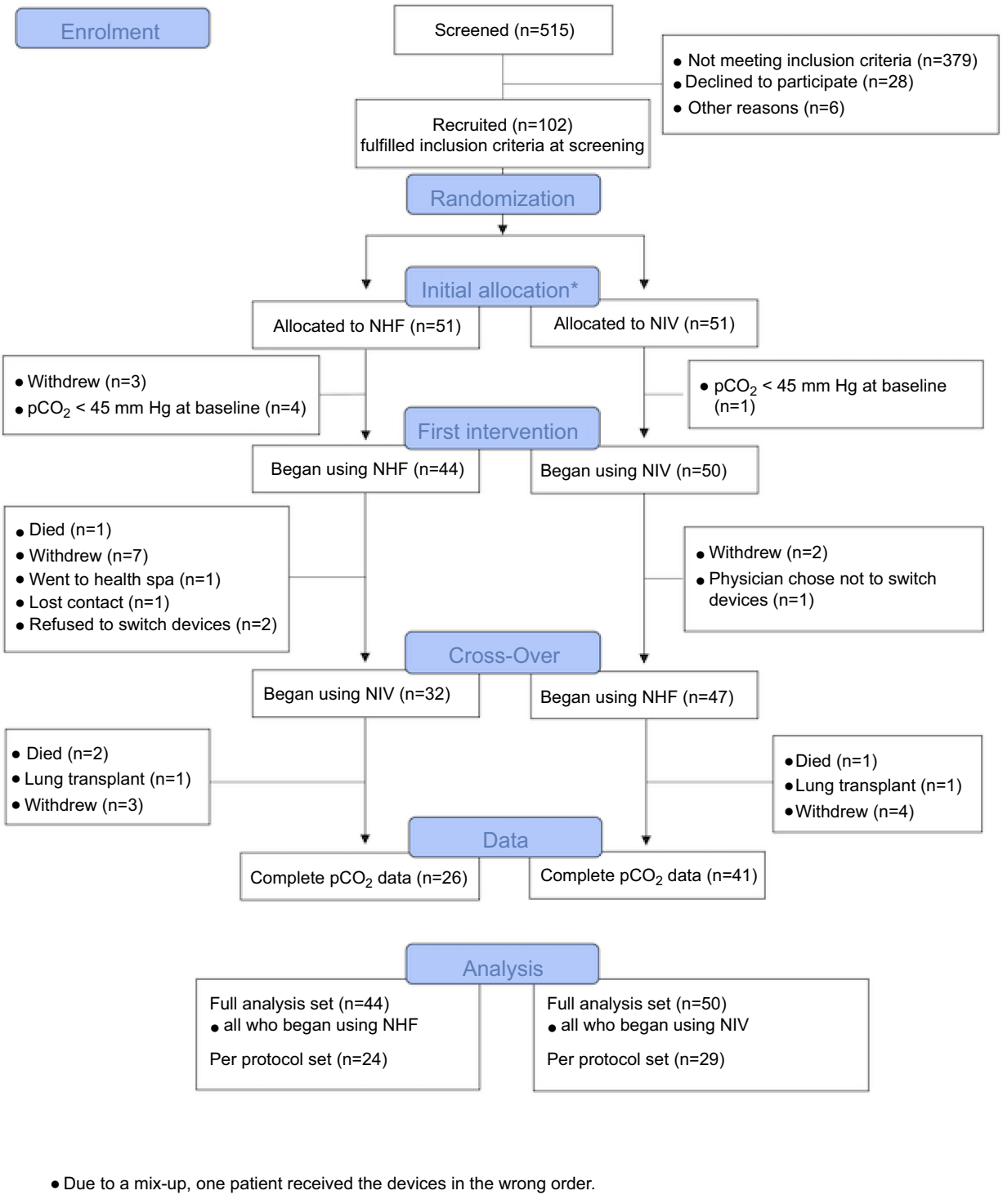
Data on time used were available for 70 NHF devices (77%), 54 NIV devices (66%), and for 47 patients who used both. Mean duration of NHF usage was 5.2±3.3 hrs/day compared to 3.9±2.5 hrs/day for NIV. The mean difference for those who used both was 1.6 hrs/day (95% CI, 0.9–2.4; P<0.001) for NHF versus NIV (Figure S1).

Primary and secondary endpoints

PCO_2 levels decreased by 2.8 mm Hg (95% CI 1.1–4.6) or 4.7% (95% CI 1.8–7.5) using NHF and 4.2 mm Hg (95% CI 2.4–6.0) or 7.1% (95% CI 4.1–10.1) from baseline using NIV. The difference of pCO_2 changes between the two devices was −1.4 mmHg (95% CI −3.1–0.4), where the minus sign indicates that NIV had a stronger effect (Table 2). This difference lies within the non-inferiority margin of 5 mm Hg, P<0.001. Sensitivity analyses demonstrated that neither a completer case analysis nor the introduction of a random effect from the centers alters this result meaningfully. In the per protocol set, pCO_2 levels decreased by 2.9 mmHg and 4.3 mmHg using NHF and NIV, respectively, and the difference of pCO_2 changes between the devices was −1.3 (95% CI −3.0–0.4) mmHg and thus indistinguishable from that of the full analysis set. There was no indication that the order of devices was relevant (P=0.59). Blood samples were taken a median of 7.0 hrs (IQR: 4.6–8.7) after stopping use of the device.

A considerable reduction in pCO_2 (>5 mm Hg) was reached in 37% of patients during NHF use and 52% during NIV use. However, increases in pCO_2 were observed in 26% with NHF and 22% with NIV (Figure 2). An exploratory analysis of reasons for good/poor response can be found in section 5 of the Supplementary materials.

PO_2, spirometry, 6MWT, and QoL are listed in Table 2. Changes from baseline tended to be small for pO_2, spirometry, and 6MWT, but were significant and clinically meaningful for QoL. While using NHF, 61%



• Due to a mix-up, one patient received the devices in the wrong order.

Figure 1 Flowchart of enrolment, device usage and patients analyzed.
Abbreviations: NHF, nasal high-flow; NIV, noninvasive ventilation; PCO_2, the partial pressure of carbon dioxide in capillary blood.

of patients improved their St. George's Respiratory Questionnairetotal scores by at least 4 points and a similar 54% while using NIV. Differences in the endpoints listed in Table 2 were not generally significant between NHF and NIV.

Safety

Four patients died during the trial, two while using NHF and two while using NIV (see Supplementary materials [section 7]). Other adverse events are listed according to the device used upon onset of the event in Table 3.

Table 1 Baseline demographic and clinical characteristics

	N=94
Females	57 (61%)
Age (years)	65.3±9.3
BMI (kg/m^2)	23.1±4.8
BMI <18.5	20 (21%)
18.5 ≤ BMI <25	37 (39%)
BMI ≥25	37 (39%)
Heart rate (bpm)	82.3±12.9
Six-minute walking test (m)	236±135
Time since COPD diagnosis (years)	7.1 (3.3 to 11.7)
Smoking	
Current smoker	19 (21%)
Ex-smoker	69 (77%)
Never smoked	2 (2%)
Number of pack years	40 (28 to 51)
Number of exacerbations in last 12 months[a]	1.8±2.2
0 exacerbations	24 (26%)
1–2 exacerbations	46 (51%)
≥3 exacerbations	21 (23%)
Number with hospital stay	1.2±1.6
CAT score	24.7±7.6
GOLD classification 2011	
D	79 (90%)
C	6 (7%)
B or A	3 (3%)
O_2 insufflation (L/min)	2.0±0.9
Capillary pCO_2 (mmHg)	56.5±5.4
Capillary pO_2 (mmHg)	68.9±16.0
pH	7.399±0.036
Base excess (BE, mmol/L)	8.4±3.8
HCO_3^- (mmol/L)	32.1±3.2
FEV_1 (% predicted)	28.5±10.2
FVC (% predicted)	48.0±15.0
FEV_1/FVC (%)	49.4±13.4
Respiratory rate (breaths/min)	20.7±5.5

Notes: Values are numbers (%), mean SD or median (interquartile range). [a]Data were unavailable for 3 patients.
Abbreviation: BMI, body mass index.

Discussion

In this randomized, controlled, multi-centered cross-over trial, NHF was similarly effective to NIV with modest improvements in capillary pCO_2 in both groups and a slight tendency in favor of NIV. This is the first RCT providing evidence that NHF is effective in COPD patients with stable chronic hypercapnia.

NHF and NIV reduced capillary pCO_2 by 2.8 mmHg (4.7%) and 4.2 mmHg (7.1%), respectively. These results for NIV correspond well to those of Köhnlein et al,[3] who found that capillary pCO_2 was lowered by 7.4% after 1 year of treatment and differed by 5.1% from the control group. A recent trial by Murphy et al[4] observed similar reductions in pCO_2 by 6.2 mmHg after 6 weeks.

Most studies on NHF have either excluded hypercapnic patients or studied a population containing both normo- and hypercapnic patients and have thus found little or no reduction in pCO_2.[23–25,33] Studies exploring the effect of NHF on pCO_2 in purely hypercapnic patients[15,16,26–28,34] suggest a dependence on the baseline pCO_2 value, as might be expected.[16,34]

A recent study compared long-term oxygen therapy (LTOT) with and without NHF in 29 stable hypercapnic COPD patients. NHF inhibited the LTOT-induced increase in pCO_2 and improved QoL.[35] Another recent study demonstrated unaltered lung function in COPD patients during brief NHF use.[29]

In most studies with hypercapnic patients, blood gas samples were taken during NHF treatment or immediately thereafter.[15,16,26,27] In this trial, blood gases were taken after a minimum of 3 hrs following respiratory support to a) reflect the situation in an outpatient clinic and b) provide data on lasting effects. However, this lag period might result in smaller treatment effects compared to studies with shorter intervals.[16,27] In a previous, similarly designed pilot study, but without similar delay, we observed a more pronounced pCO_2 reduction both with NHF and NIV.[27] It is plausible that pCO_2 rises during the day after night-time use of respiratory support. The mentioned NIV trials on chronic hypercapnic COPD patients were designed with a 1-hr delay between NIV use and blood gas analysis.[3,4]

Changes in secondary endpoints were very similar between the two devices and suggest effective respiratory support for COPD patients. In particular, improvements in QoL, a well-established benefit of NIV,[9] were comparable with those of NHF treatment. The respiratory rate was reduced in NHF only. The 6MWT-distance increased with both devices although this was not significant for NHF. Changes in exacerbation rates and re-hospitalizations could not be assessed within the 6-week time frame. We present individual patient data on capillary pCO_2 as a waterfall plot, demonstrating the large variance in individual response and providing data on the numbers

Table 2 Primary and secondary outcomes

	Baseline	Change using NHF	*P*-value (NHF)	Change using NIV	*P*-value (NIV)	Difference in change between NHF and NIV	*P*-value (NHF vs NIV)
Basic physiological parameters							
Respiratory rate (breaths/min)	20.3	−1.4 (−2.9 to −0.0)	**0.046**	−0.1 (−1.6 to 1.3)	0.84	1.3 (−0.1 to 2.7)	0.076
Heart rate (beats/min)	82.0	2.0 (−2.0 to 6.0)	0.33	5.0 (1.0 to 9.0)	**0.015**	3.0 (−1.1 to 7.1)	0.15
Blood gas analysis							
pCO_2 (mm Hg)	56.5	−2.8 (−4.6 to −1.1)	**0.0020**	−4.2 (−6.0 to −2.4)	**<0.001**	−1.4 (−3.1 to 0.4)	0.12
pO_2 (mm Hg)	68.9	1.4 (−3.1 to 6.0)	0.53	0.8 (−3.8 to 5.3)	0.74	−0.7 (−5.3 to 3.9)	0.77
SaO_2 (%)	93.7	0.3 (−0.7 to 1.4)	0.53	0.0 (−1.1 to 1.1)	0.98	−0.3 (−1.4 to 0.8)	0.55
Base excess (mmol/L)	8.4	−1.5 (−2.2 to −0.7)	**<0.001**	−2.0 (−2.7 to −1.3)	**<0.001**	−0.5 (−1.2 to 0.2)	0.14
HCO_3^- (mmol/L)	32.1	−1.5 (−2.2 to −0.8)	**<0.001**	−2.2 (−2.9 to −1.5)	**<0.001**	−0.7 (−1.4 to 0.0)	0.056
pH	7.40	−0.00 (−0.01 to 0.01)	0.99	0.01 (−0.01 to 0.01)	0.59	0.00 (−0.01 to 0.01)	0.86
Spirometry							
FVC (% predicted)	47.9	0.8 (−2.1 to 3.7)	0.58	2.3 (−0.6 to 5.2)	0.12	1.5 (−1.2 to 4.2)	0.28
FEV1 (% predicted)	28.4	1.1 (−0.6 to 2.8)	0.21	2.0 (0.2 to 3.7)	**0.027**	0.9 (−0.8 to 2.5)	0.30
FEV1/FVC (%)	50.1	0.9 (−2.2 to 3.9)	0.57	1.2 (−1.8 to 4.2)	0.43	0.3 (−2.6 to 3.3)	0.42
R_{tot} (% predicted)[a]	301.7	1.10 (0.99 to 1.22)	0.064	0.98 (0.89 to 1.09)	0.72	0.89 (0.80 to 0.99)	**0.033**
RV (% predicted)	244.2	−2.3 (−19.0 to 14.4)	0.79	1.8 (−14.9 to 18.5)	0.83	4.1 (−12.7 to 20.9)	0.63
RV/TLC (% predicted)	181.2	−0.6 (−7.3 to 6.2)	0.86	2.9 (−3.9 to 9.6)	0.40	3.5 (−3.4 to 10.3)	0.32
Respiratory muscle assessment							
$P_{0.1}$ (% predicted)[a]	279.6	1.06 (0.95 to 1.19)	0.31	1.03 (0.91 to 1.15)	0.65	0.97 (0.87 to 1.08)	0.53
PI_{max} (% predicted)	37.1	0.0 (−3.2 to 3.2)	0.98	2.3 (−0.9 to 5.5)	0.16	2.2 (−0.8 to 5.2)	0.14
Six-minute walking test (m)	233.0	15.2 (−4.8 to 35.2)	0.14	25.5 (5.5 to 45.5)	**0.013**	10.3 (−10.0 to 30.6)	0.31
SRI							
Respiratory Complaints	43.8	3.9 (0.7 to 7.2)	**0.018**	2.8 (−0.4 to 6.1)	0.085	−1.1 (−4.3 to 2.1)	0.50
Physical Functioning	32.1	5.0 (1.0 to 9.0)	**0.015**	4.8 (0.8 to 8.8)	**0.020**	−0.2 (−4.2 to 3.8)	0.92
Attendant Symptoms and Sleep	54.6	7.5 (3.1 to 11.9)	**0.0010**	5.1 (0.7 to 9.5)	**0.024**	−2.4 (−6.8 to 2.0)	0.28
Social Relationships	67.9	1.5 (−2.8 to 5.9)	0.48	−0.4 (−4.8 to 3.9)	0.85	−1.9 (−6.3 to 2.4)	0.37
Anxiety	54.4	2.7 (−2.0 to 7.4)	0.26	4.0 (−0.7 to 8.7)	0.092	1.3 (−3.3 to 6.0)	0.57
Psychological Well-Being	53.1	3.0 (−0.3 to 6.3)	0.078	3.7 (0.4 to 7.1)	**0.027**	0.8 (−2.5 to 4.1)	0.65
Social Functioning	47.6	1.3 (−2.2 to 4.9)	0.46	1.5 (−2.1 to 5.0)	0.41	0.2 (−3.4 to 3.7)	0.93
Summary Scale	50.6	3.5 (1.1 to 5.8)	**0.0039**	2.7 (0.3 to 5.0)	**0.025**	−0.8 (−3.1 to 1.5)	0.50

(*Continued*)

Table 2 (Continued).

	Baseline	Change using NHF	*P*-value (NHF)	Change using NIV	*P*-value (NIV)	Difference in change between NHF and NIV	*P*-value (NHF vs NIV)
SGRQ							
Symptoms	72.7	−11.9 (−17.2 to −6.6)	**<0.001**	−11.6 (−16.9 to −6.3)	**<0.001**	0.3 (−5.0 to 5.6)	0.92
Activity	84.5	−4.4 (−7.8 to −1.0)	**0.011**	−4.2 (−7.6 to −0.9)	**0.014**	0.2 (−3.2 to 3.5)	0.92
Impacts	57.3	−5.8 (−9.7 to −2.0)	**0.0035**	−6.5 (−10.3 to −2.6)	**0.0011**	−0.7 (−4.5 to 3.1)	0.72
Total	68.1	−6.2 (−8.9 to −3.5)	**<0.001**	−6.9 (−9.6 to −4.2)	**<0.001**	−0.7 (−3.4 to 2.0)	0.62
Modified Borg Scale							
Before 6 min walk	4.4	−0.2 (−0.8 to 0.4)	0.45	−0.2 (−0.8 to 0.4)	0.47	0.0 (−0.6 to 0.6)	0.96
After 6 min walk	5.9	−0.3 (−0.9 to 0.4)	0.39	−0.4 (−1.0 to 0.2)	0.19	−0.1 (−0.8 to 0.5)	0.65
VAS regarding state of health	3.7	1.0 (0.2 to 1.8)	0.015	0.9 (0.1 to 1.7)	0.027	−0.1 (−0.9 to 0.7)	0.81
Assessment of Devices	–	–		–		−0.2 (−0.4 to 0.2)	0.29

Notes: Numbers in brackets are 95% CI. [a]These "changes" columns refer to an n-fold change with respect to baseline, ie, the baseline value of R_{tot} is 301.7% of the predicted value, and using NHF it changed 1.10-fold. The final column is a ratio of the two changes. The analyses in this table are based on imputation meaning the full-analysis set (n=94) was used. For SRI and SGRQ, one of the trial centers did not distribute the questionnaires so that n=80. Bold values are representative of $p<0.05$.

Abbreviations: SGRQ, St. George's Respiratory Questionnaire; SRI, Severe Respiratory Insufficiency Questionnaire; NHF, nasal high-flow; NIV, noninvasive ventilation.

who respond well and poorly. A similar spectrum of responses has not yet been described in a comparably clear fashion, although it has been mentioned in the literature.[3,4,11,12,35] The SD we observed for pCO_2 changes is roughly comparable to that reported in other studies, suggesting that they observed a similar spectrum of responses.

Many clinicians would agree that not every patient will benefit from NIV. However, there are only few dependable criteria for predicting success.[3,4,11–13,16,32] We found non-responders in roughly comparable numbers using both devices. Exploratory analyses showed that a variety of demographic and disease-specific markers were not associated with the extent of the pCO2 response. A non-negligible minority of patients had higher levels of pCO_2 with ventilatory support compared to the beginning of the study. Such responses might derive from the fact that we performed a "real life" study in which the health of chronically ill patients can deteriorate despite the use of noninvasive respiratory support.

It is important to note that in this study, NHF was administered with a relatively moderate flow of 20 L/min, which was state of the art at trial conception. This trial demonstrates that NHF with a flow of 20 L/min is a good treatment option in stable hypercapnic COPD patients. However, it is likely that treatment with higher flow rates will result in further improvements.[16,27]

An important prerequisite for an effective treatment of COPD patients by NIV is the choice of a sufficient pressure difference combined with respiratory rate control and adequate duration of treatment.[3–5,36] In this regard, the settings applied in our trial are slightly different from those applied in the studies of Murphy et al (median IPAP 24 cmH_2O, EPAP 4 cmH_2O, respiratory rate 14/min) and Köhnlein et al (mean IPAP 21.6 cmH_2O, EPAP 4.8 cmH_2O, respiratory rate 16/min).[3,4] In our trial, NHF and NIV were used on average for 5.2 hrs/day (data available from 77% of patients) and 3.9 hrs/day (66% of patients), respectively. In the study of Köhnlein et al, NIV was used for 5.9 hrs/day (47% of patients). Murphy et al reported a mean use of 4.7 hrs/day (84% of patients) after comparable 6 weeks. When compared to NIV, the longer use of NHF observed in our trial might indicate better tolerance. A number of studies have indeed demonstrated improved comfort of NHF over other devices.[16,23,37]

Earlier studies indicated that NIV is effective at reducing pCO_2 only in patients with stable hypercapnia.[3,4,32] In particular, hypercapnia can even be reversible after acute exacerbation[32,38] and it is uncertain whether or not NIV

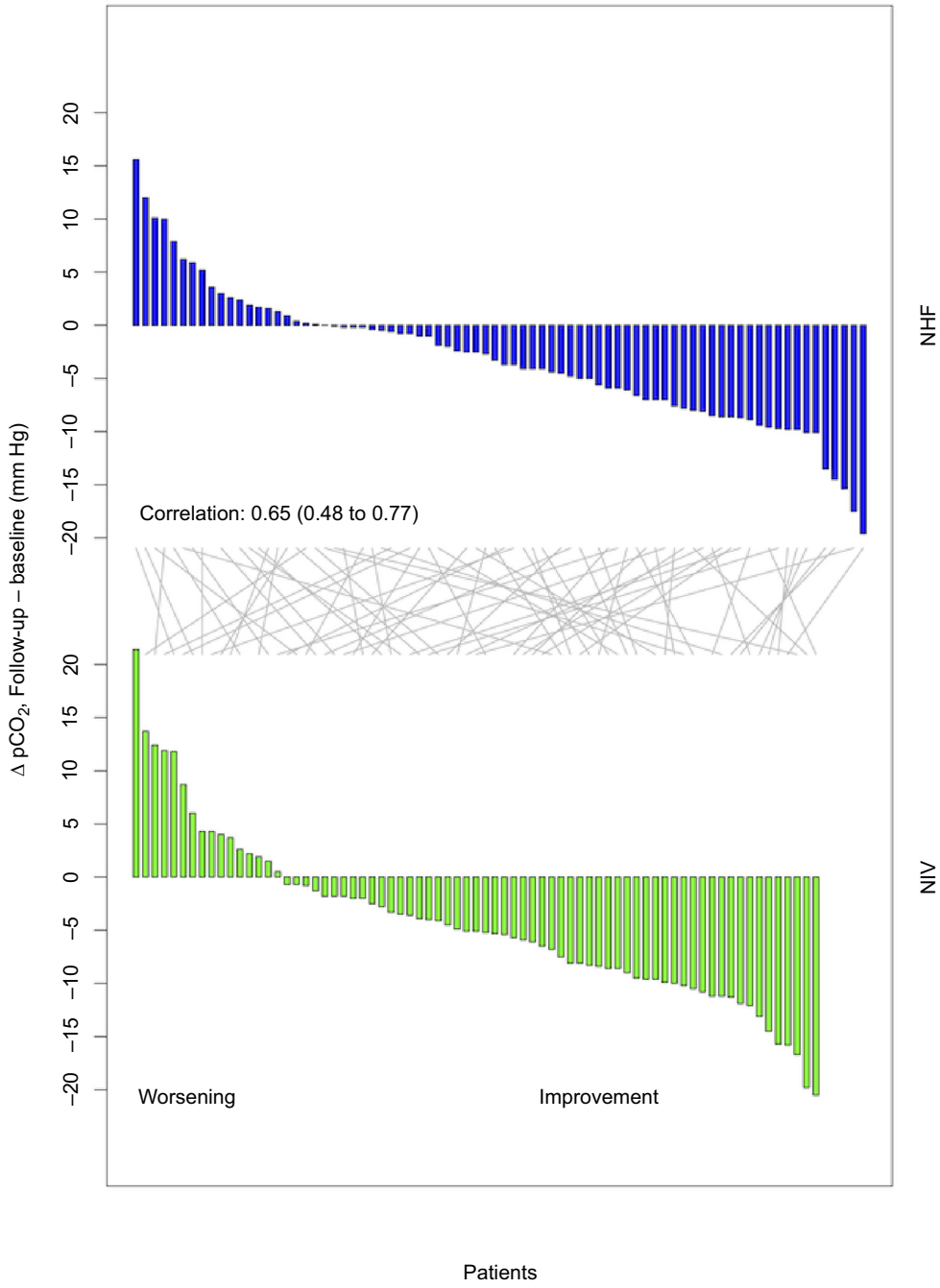


Figure 2 Waterfall plot depicting the individual change in carbon dioxide levels in capillary blood (pCO_2) before and after intervention.
Notes: NHF, nasal high-flow; NIV, noninvasive ventilation. ΔpCO_2 is the difference in partial pressures of carbon dioxide in capillary blood between baseline and follow-up. Each bar represents ΔpCO_2 for a single patient and the grey lines show how the patients in the upper and lower halves correspond, ie, the grey line connects a given patient before and after cross-over. The correlation coefficient between changes with NHF and NIV (95% CI) is shown for patients that used both devices.

then has any added benefit. Our minimum 4-week exacerbation-free interval was chosen to exclude transient hypercapnia at the time of inclusion in the study.

Limitations of our study include lower usage times of NIV, slightly lower pressure difference (IPAP-EPAP) compared to previous studies[3,4] and the use of an NHF device with a restriction of 20 L/min flow. This may have influenced the efficacy of the devices. Moreover, the trial was registered after about one-quarter of the patients had been recruited, the data for usage time were incomplete and blinding was not possible. Strengths of this study are the cross over design, the demonstration of a lasting effect and the exclusion of patients with transient hypercapnia following exacerbation.

Table 3 There were a total of 38 non-lethal SAEs among 21 patients (9 only NHF, 8 only NIV, 4 patients with both devices)

	NHF	NIV
Death	2	2
Number of SAEs (non-lethal)	17	21
Respiratory		
Dyspnoea	–	1
Exacerbation	11	7
Atelectasis	1	–
Hypercapnic respiratory failure	1	–
Mechanical ventilation	1	1
Pneumonia	–	1
Pneumothorax spontaneous	–	1
Pulmonary failure	–	1
Respiratory acidosis	1	–
Cardiac		
Myocardial infarction	1	–
Decompensation	1	1
Panic attack		2
Other	–	7
Number of AEs (not also SAEs)	33	55
Respiratory/possibly related to device		
Aerophagia	–	5
Bronchitis acute	1	–
Claustrophobia	–	1
Coldness local	–	1
Conjunctivitis	–	1
COPD exacerbation	13	13
Dyspnoea	–	3
Ear problem	–	1
Epistaxis/nasal dryness/nasal irritation	5	2
Hemoptysis	1	–
Insomnia	1	1
Middle ear disorder	1	–
Oral thrush	1	1
Panic attacks	1	1
Rib pain	1	–
Cardiac		
Decompensation	–	1
Tachycardia	–	1
Signs of right-heart failure	4	7
Other	4	16

Abbreviations: SAE, serious adverse event; NHF, nasal high-flow; NIV, noninvasive ventilation.

In summary, we have shown that NHF may well represent an alternative to NIV in chronic hypercapnic COPD patients with comparable effectiveness. Future studies will have to elucidate the question of how pCO2 reduction may translate into a benefit on survival or other clinical outcomes.

Abbreviations list

(p)CO_2, (partial) pressure of carbon dioxide; (p)O_2, (partial) pressure of oxygen; 6MWT, 6-min walking test; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; LTOT, long-term oxygen therapy; NHF, nasal high-flow; NIV, noninvasive ventilation; QoL, quality of life; RCT, randomized controlled trial; SNP, standard nasal prongs.

Data sharing statement

The authors will share the statistical analysis plan and study protocol upon request. An online supplement will be available. The data will be available for 5 years. Further data will be shared upon qualified request, in particular for meta-analyses or individual patient meta-analyses. In the latter case, those requesting data will be asked to provide a copy of an institutional review board approval and show that the meta-analysis has been registered in a public registry.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

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