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

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. 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.

Recent trials have shown that NIV also benefits COPD patients with chronic hypercapnia. A multi-center study with 195 stable hypercapnic COPD patients revealed that NIV decreases 1-year mortality. A further study confirmed reduced mortality and additionally showed reduced rates of exacerbation and hospital readmission. Other parameters improved by NIV include hypercapnia, oxygen saturation, respiratory rate, dyspnea, 6-min walking test (6MWT)-distance, and quality of life (QoL). Despite these encouraging results, it is also evident that some patients do not tolerate NIV or do not benefit from it.
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. NHF reduces minute volume, lowers respiratory rate, and decreases work of breathing. The exhaled gas in the upper airways is rapidly washed out, and thus physiological dead-space is reduced. The high flow rates delivered by NHF are sufficient to cover even high peak inspiratory flows, thereby avoiding the admixture of ambient air.

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. Reintubation rates with NHF were lower than or non-inferior 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 CO2 (pCO2) reduction in hypercapnic patients over short periods. NHF was also successful in reducing pCO2 in a small pilot trial for 6 weeks. Together with CO2 wash-out studies 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 pCO2 reduction compared to baseline.

**Materials and methods**

**Study subjects**

COPD patients with chronic respiratory insufficiency and stable daytime hypercapnia (pCO2 ≥ 50 mmHg) were recruited from 13 hospitals in Germany. Patients were excluded if they had a type I or II exacerbation 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/m². 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-f). 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 pCO2 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 pCO2 reduction. 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 pCO2 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.\textsuperscript{3,32}

The full analysis set (intention to treat) included all patients who started treatment and had \(\text{pCO}_2\) values \(\geq 50\) 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 \(\text{pCO}_2\) levels of five randomized patients (\(\text{pCO}_2 \geq 50\) 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 \(\text{pCO}_2\) 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\(\pm 0.6\) L/min and \(\text{O}_2\) insufflation of 2.2\(\pm 0.9\) 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\(\pm 3.6\) cm H\(_2\)O and 4.6\(\pm 1.2\) cm H\(_2\)O respectively, \(\text{O}_2\) rate was 2.0\(\pm 0.7\) L/min and 13.3\(\pm 3.9\) 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\(\pm 3.3\) hrs/day compared to 3.9\(\pm 2.5\) 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

\(\text{pCO}_2\) 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 \(\text{pCO}_2\) 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, \(\text{pCO}_2\) levels decreased by 2.9 mmHg and 4.3 mmHg using NHF and NIV, respectively, and the difference of \(\text{pCO}_2\) 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 \(\text{pCO}_2\) (>5 mm Hg) was reached in 37% of patients during NHF use and 52% during NIV use. However, increases in \(\text{pCO}_2\) 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.

\(\text{PO}_2\), spirometry, 6MWT, and QoL are listed in Table 2. Changes from baseline tended to be small for \(\text{PO}_2\), spirometry, and 6MWT, but were significant and clinically meaningful for QoL. While using NHF, 61%
of patients improved their St. George’s Respiratory Questionnaire total 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.

Figure 1 Flowchart of enrolment, device usage and patients analyzed.

Abbreviations: NHF, nasal high-flow; NIV, noninvasive ventilation; PCO₂, the partial pressure of carbon dioxide in capillary blood.
**Table 1 Baseline demographic and clinical characteristics**

|                                      | N=94                  |
|--------------------------------------|-----------------------|
| Females                              | 57 (61%)              |
| Age (years)                          | 65.3±9.3              |
| BMI (kg/m²)                          |                       |
| BMI <18.5                            | 23.1±4.8              |
| 18.5 ≤ BMI <25                       | 20 (21%)              |
| 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<sup>a</sup> | 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%)                |
| O₂ insufflation (L/min)              | 2.0±0.9               |
| Capillary pCO₂ (mmHg)                | 56.5±5.4              |
| Capillary pO₂ (mmHg)                 | 68.9±16.0             |
| pH                                   | 7.399±0.036           |
| Base excess (BE, mmol/L)             | 8.4±3.8               |
| HCO₃⁻ (mmol/L)                       | 32.1±3.2              |
| FEV₁ (% predicted)                   | 28.5±10.2             |
| FVC (% predicted)                    | 48.0±15.0             |
| FEV₁/FVC (%)                         | 49.4±13.4             |
| Respiratory rate (breaths/min)       | 20.7±5.5              |

**Notes:** Values are numbers (%), mean SD or median (interquartile range). <sup>a</sup>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 pCO₂ 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 pCO₂ 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,<sup>3</sup> who found that capillary pCO₂ 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<sup>4</sup> observed similar reductions in pCO₂ 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 pCO₂.<sup>23–25,33</sup> Studies exploring the effect of NHF on pCO₂ in purely hypercapnic patients<sup>15,16,26–28,34</sup> suggest a dependence on the baseline pCO₂ value, as might be expected.<sup>16,34</sup>

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 pCO₂ and improved QoL.<sup>35</sup> Another recent study demonstrated unaltered lung function in COPD patients during brief NHF use.<sup>29</sup>

In most studies with hypercapnic patients, blood gas samples were taken during NHF treatment or immediately thereafter.<sup>15,16,26,27</sup> 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.<sup>16,27</sup>

In a previous, similarly designed pilot study, but without similar delay, we observed a more pronounced pCO₂ reduction both with NHF and NIV.<sup>27</sup> It is plausible that pCO₂ 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.<sup>3,4</sup>

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,<sup>9</sup> 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 pCO₂ 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**         |          |                  |              |                  |              |                                          |                     |
| pCO₂ (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                |
| pO₂ (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                |
| SaO₂ (%)                       | 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                |
| HCO₃⁻ (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                |
| R₅₋₁ (% predicted)             | 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** |        |                  |              |                  |              |                                          |                     |
| P₀₋₁ (% predicted)             | 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                |
| Plₐ₋₅₋₁ (% 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)  | 0.0015       | 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)
The SD we observed for pCO2 and it is uncertain whether or not NIV. In this regard, the settings applied only in patients with stable hypercapnia. Studies of Murphy et al (median IPAP 24 cmH2O, EPAP 4.8 cmH2O) in our trial are slightly different from those applied in their 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 (mean IPAP 20.2 cmH2O, EPAP 4 cmH2O, respiratory rate 14/min) and Köhnlein et al (mean IPAP 21.6 cmH2O, EPAP 4.8 cmH2O, respiratory rate 16/min). SGRQ, Severe Respiratory Insufficiency Questionnaire; NHF, nasal high-flow, NIV, noninvasive ventilation.

### Table 2 (Continued)

|                  | Baseline | Change using NHF (NHF) | Change using NIV (NIV) | P-value (NHF) | P-value (NIV) | Difference in change between NHF and NIV | P-value vs NIV |
|------------------|----------|------------------------|------------------------|---------------|---------------|----------------------------------------|----------------|
| **SGRQ**         |          |                        |                        |               |               |                                        |                |
| Symptoms         | 72.7     | –11.9 (–17.2 to –6.6)  | –11.6 (–16.9 to –6.3)  | <0.001        | <0.001        | 0.3 (–5.0 to 5.6)                      | 0.92           |
| Activity         | 84.5     | –4.4 (–7.8 to –1.0)    | –4.2 (–7.6 to –0.9)    | 0.011         | 0.014         | 0.2 (–3.2 to 3.5)                      | 0.92           |
| Impacts          | 57.3     | –5.8 (–9.7 to –2.0)    | –6.5 (–10.3 to –2.6)   | 0.0035        | 0.0011        | –0.7 (–4.5 to 3.1)                     | 0.72           |
| Total            | 68.1     | –6.2 (–8.9 to –3.5)    | –6.9 (–9.6 to –4.2)    | <0.001        | <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)     | –0.2 (–0.8 to 0.4)     | 0.45          | 0.47          | 0.0 (–0.6 to 0.6)                      | 0.96           |
| After 6 min walk | 5.9      | –0.3 (–0.9 to 0.4)     | –0.4 (–1.0 to 0.2)     | 0.39          | 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)       | 0.9 (0.1 to 1.7)       | 0.015         | 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. “These “changes” columns refer to an n-fold change with respect to baseline, i.e., the baseline value of R, 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.

### Table 2 (Continued)

|                  | Baseline | Change using NHF (NHF) | Change using NIV (NIV) | P-value (NHF) | P-value (NIV) | Difference in change between NHF and NIV | P-value vs NIV |
|------------------|----------|------------------------|------------------------|---------------|---------------|----------------------------------------|----------------|
| **Assessment of Devices** |          |                        |                        |               |               |                                        |                |
| VAS regarding state of health | 3.7      | 1.0 (0.2 to 1.8)       | 0.9 (0.1 to 1.7)       | 0.015         | 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. “These “changes” columns refer to an n-fold change with respect to baseline, i.e., the baseline value of R, 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.

### Table 2 (Continued)

|                  | Baseline | Change using NHF (NHF) | Change using NIV (NIV) | P-value (NHF) | P-value (NIV) | Difference in change between NHF and NIV | P-value vs NIV |
|------------------|----------|------------------------|------------------------|---------------|---------------|----------------------------------------|----------------|
| **Baseline Change using NHF** |          |                        |                        |               |               |                                        |                |
| Difference in change |          |                        |                        |               |               |                                        |                |
| P-value |          |                        |                        |               |               |                                        |                |
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, 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)CO2, (partial) pressure of carbon dioxide; (p)O2, (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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