Home noninvasive ventilation in severe COPD: in whom does it work and how?

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In patients with end-stage COPD, home noninvasive ventilation achieves its beneficial effect on health-related quality of life only partially through a reduction in arterial carbon dioxide https://bit.ly/3QFUKSF

Cite this article as: Raveling T, Vonk JM, Hill NS, *et al*. Home noninvasive ventilation in severe COPD: in whom does it work and how? *ERJ Open Res* 2024; 10: 00600-2023 [DOI: 10.1183/23120541.00600-2023].

Received: 18 Aug 2023
Accepted: 26 Oct 2023

Abstract

Background Not all hypercapnic COPD patients benefit from home noninvasive ventilation (NIV), and mechanisms through which NIV improves clinical outcomes remain uncertain. We aimed to identify "responders" to home NIV, denoted by a beneficial effect of NIV on arterial partial pressure of carbon dioxide (P_{aCO_2}), health-related quality of life (HRQoL) and survival, and investigated whether NIV achieves its beneficial effect through an improved P_{aCO_2}.

Methods We used individual patient data from previous published trials collated for a systematic review. Linear mixed-effect models were conducted to compare the effect of NIV on P_{aCO_2}, HRQoL and survival, within subgroups defined by patient and treatment characteristics. Secondly, we conducted a causal mediation analysis to investigate whether the effect of NIV is mediated by a change in P_{aCO_2}.

Findings Data of 1142 participants from 16 studies were used. Participants treated with lower pressure support (<14 *versus* ⩾14 cmH_2O) and with lower adherence (<5 *versus* ⩾5 $h \cdot day^{-1}$) had less improvement in P_{aCO_2} (mean difference (MD) −0.30 kPa, p<0.001 and −0.29 kPa, p<0.001, respectively) and HRQoL (standardised MD 0.10, p=0.002 and 0.11, p=0.02, respectively), but this effect did not persist to survival. P_{aCO_2} improved more in patients with severe dyspnoea (MD −0.30, p=0.02), and HRQoL improved only in participants with fewer than three exacerbations (standardised MD 0.52, p=0.03). The results of the mediation analysis showed that the effect on HRQoL is mediated partially (23%) by a change in P_{aCO_2}.

Interpretation With greater pressure support and better daily NIV usage, a larger improvement in P_{aCO_2} and HRQoL is achieved. Importantly, we demonstrated that the beneficial effect of home NIV on HRQoL is only partially mediated through a reduction in diurnal P_{aCO_2}.

Introduction

Patients with end-stage COPD are at risk of developing chronic hypercapnic respiratory failure (CHRF), which is characterised by severely disabling symptoms, poor health-related quality of life (HRQoL), and reduced survival [1]. During the past decade, home noninvasive ventilation (NIV) has gained acceptance as a treatment for CHRF due to COPD [2, 3]. Recently, we published a Cochrane systematic review on this

topic using pooled individual patient data [4]. We found that NIV improves ventilation, irrespective of being initiated in a stable disease state or following a hospitalisation for acute respiratory failure. In patients initiated on NIV in a stable phase, HRQoL and all-cause mortality is improved by home NIV, while in patients initiated after a severe exacerbation, NIV prolongs admission-free survival [4]. Nevertheless, notwithstanding these benefits, important issues still need to be addressed.

First, patient selection is currently not optimal. As recommended by guidelines, the presence of persistent hypercapnia is the only criterion to start home NIV [2, 3]. However, ∼20–30% of the patients do not experience a meaningful benefit or are unable to tolerate the NIV. Additionally, the individual response in terms of improved ventilation, HRQoL and survival varies between patients [5, 6]. Therefore, it might be insufficient to initiate such a demanding therapy on a single gas-exchange criterion. To optimise patient selection, it is key to identify patient and treatment characteristics of a favourable response to home NIV in terms of improvement in (daytime) ventilation, HRQoL and all-cause mortality.

Secondly, several theories have been proposed regarding the pathophysiological mechanisms by which home NIV achieves its beneficial effects, and the debate is still ongoing. In general, NIV is targeted to reach normocapnia during the night and preferably also during daytime [2, 3]. However, from a patient perspective, the primary goal of home NIV is to achieve a better HRQoL or survival. Unfortunately, to what extent the beneficial effect of NIV on patient-centred outcomes is achieved by the correction of hypercapnia, is uncertain. There are studies suggesting that this is not the sole contributor to its beneficial effect [5, 7]. More knowledge about what mechanisms improve patient-centred outcomes would be helpful to improve care.

For the Cochrane systematic review, we were able to pool the individual patient data of a vast majority of the randomised controlled trials (RCT) conducted in this field. A thorough analysis of these unique pooled data provides a first opportunity to identify patient and treatment characteristics that are associated with a favourable treatment outcome and to investigate whether the effect of NIV on patient-centred outcomes is mediated by a correction of hypercapnia. Therefore, the aim of this study was to investigate in patients with severe COPD whether 1) the effect of home NIV on diurnal ventilation, HRQoL and survival is dependent on specific patient and treatment characteristics, and 2) the extent to which the effect of home NIV on HRQoL and survival is mediated by an improved diurnal ventilation.

Methods

Data used in this study were collected for a Cochrane systematic review. The full protocol for this review was published elsewhere [8]. In short, we included RCTs comparing NIV at home plus standard therapy with standard therapy alone in participants with COPD, according to the most recent guideline of the Global Initiative for Chronic Obstructive Lung Disease [9]. Home NIV was applied through a facial mask (nasal and/or oronasal) and prescribed for ⩾5 h, for at least three consecutive weeks. In addition, participants received their usual standard COPD therapy. The intervention in the control group was standard therapy alone without home NIV, but sham treatment in the form of continuous positive airway pressure was permitted. More details on the search strategy and collection of the individual patient data are presented in the online supplementary material.

Investigation of subgroups

We investigated the following subgroups which were determined based on *a priori* postulated hypotheses.

1) Patients with greater clinical stability, defined by number of exacerbations in the year prior to initiation of NIV, benefit more; the cut-off was made based on the median value of the entire cohort.
2) Patients with a higher body mass index (BMI) benefit more; the cut-off was made based on observations that patients with BMI >25 $kg \cdot m^{-2}$ have a favourable outcome [5, 10–12].
3) The benefit might depend on the degree of airflow limitation (forced expiratory volume in 1 s (FEV_1)) [5, 11, 12]; as there is no guidance to a cut-off in literature, the cut-off was made based on the median value of the entire cohort.
4) Patients with higher arterial partial pressure of carbon dioxide (P_{aCO_2}) (>7.3 kPa) benefit more; the cut-off was made based on guidelines from a consensus report [13].
5) Patients with worse HRQoL impairment benefit more; as these data were standardised, the cut-off was the mean (zero; a negative value indicates worse HRQoL, a positive value indicates better HRQoL).
6) Patients with severe symptoms of dyspnoea benefit more; the cut-off was a modified Medical Research Council (mMRC) dyspnoea grade 4) [14].
7) Patients receiving higher ventilatory support benefit more, a pressure support (the difference between the inspiratory and expiratory positive airway pressure) >14 cmH_2O was used as cut-off [15].
8) Patients with better NIV adherence (>5 h per night) benefit more; the cut-off was made based on the inclusion criteria for the review that the NIV should be prescribed for ⩾5 h per night [8].

Data synthesis and analysis

We first dichotomised the subgroups based on the pre-specified cut-offs. As a measure of treatment effect, we calculated the absolute difference between the baseline and the 3-month end-point on the continuous outcome variables (P_{aCO_2}, Severe Respiratory Insufficiency questionnaire (SRI) and St George's Respiratory Questionnaire (SGRQ)) [16, 17]. The individual patient data of the SRI and SGRQ data were standardised, after which the SGRQ data were inverted and combined with the SRI data as a pooled measure of HRQoL. All time-to-event (death of any cause) data were used.

The individual patient data were analysed using a one-stage approach. Continuous individual patient data were analysed using linear mixed-effect models, with the 3-month change in P_{aCO_2} and HRQoL (z-scores) as outcome measure. Normality of the outcome distributions was required and was assessed by visual inspection of normal probability plots and histograms. Time-to-event data were analysed using a mixed-effects Cox regression analysis. To test if the effect of treatment was significantly different between the subgroups, we added the treatment, the indicator for the subgroup and the treatment by subgroup interaction to the model. All statistical models were conducted with a random effect on study level to account for the clustering of participants within the studies, and were adjusted for the confounders age, sex and timing of NIV initiation (stable disease *versus* after an episode of acute respiratory failure). An interaction p-value of 0.05 was considered statistically significant. In addition, we conducted sensitivity analysis to investigate whether the results would change if we did not categorise the predictors, by testing the interaction between the treatment and the continuous predictor variables.

To determine whether the effect of home NIV on HRQoL and survival was mediated by a change in P_{aCO_2}, a causal mediation analysis was conducted according to the causal inference analysis approach of Imai *et al*. [18]. For this analysis, the exposure variable was the treatment allocation, the mediator variable was the 3-month change in diurnal P_{aCO_2} and the outcome variable the 3-month change in HRQoL (total score and the subscales of the SRI) and all-cause mortality (time-to-event). The models estimate the mean difference (MD) between the treated and control group associated with the total effect (*i.e.* combined estimated effect of treatment and change in P_{aCO_2}), average causal mediation effect (*i.e.* estimated indirect effect of change in P_{aCO_2} on HRQoL) and the average direct effect (*i.e.* estimated direct effect of treatment on HRQoL). The mediator model was a linear mixed-effect model that included treatment and pre-treatment covariates (age, sex and timing of NIV initiation), to account for potential pre-exposure confounding. The outcome model was a linear mixed-effect model that included the mediator and treatment, as well as the aforementioned pre-treatment covariates. Both models were conducted with a random effect on study level.

Results are presented as mean±SD, median (interquartile range (IQR)) and as MD or hazard ratio with associated 95% confidence intervals. All analyses were conducted in RStudio Team (2016) (RStudio, Boston, MA, USA) using the "LMER" and "mediation" packages.

Results

Study selection and population

We included 21 studies and pooled the individual patient data of 16 studies [7, 15, 19–32]. The other five studies did not reply to our request for the individual patient data [33–37]. All studies were RCTs, of which two studies used a crossover design and the remaining studies used a parallel design. Three studies attempted to blind the study by using a sham device [20, 23, 32]. The full characteristics of the included studies are presented in supplementary table E1. The individual patient data 1142 participants were available of (table 1).

Improvement in P_{aCO_2} by subgroup

When all participants were considered, NIV reduced diurnal P_{aCO_2} by 0.54 kPa (95% CI −0.69 to −0.39 kPa) (figure 1). There was a statistically significant treatment-by-subgroup interaction observed for the pressure support subgroup, with a larger reduction in P_{aCO_2} in participants who were treated with a pressure support ⩾14 cmH_2O compared to participants treated with a pressure support <14 cmH_2O (MD 0.30 kPa, p=0.01). In addition, the sensitivity analysis revealed that more dyspnoeic participants (mMRC grade 4) had a larger reduction in P_{aCO_2} (p=0.02). Lastly, participants who used NIV for more hours per day showed a larger reduction in P_{aCO_2} (p<0.001). For the remaining subgroups, neither the treatment by subgroup interaction nor the sensitivity analysis was statistically significant.

Improvement in HRQoL by subgroup

In the total group, NIV improved HRQoL by a standardised mean difference (SMD) of 0.32 SD (95% CI 0.14 to 0.49 SD), which is equivalent to an improvement of 3.7 and 3.2 units on the SRI (SD=11.6 units)

TABLE 1 Baseline demographic profile of the participants allocated to noninvasive ventilation (NIV) and the control group

	NIV	Control	p-value
Participants	569	573	
Age years	64.9±8.6	66.3±8.0	0.006
Female	199 (35)	206 (36)	0.746
BMI kg·m^{-2}	24.2±5.6	24.3±6.0	0.859
FEV_1 L	0.69±0.27	0.68±0.25	0.614
FVC L	1.98±0.70	1.92±0.69	0.143
6MWD m	243±130	262±126	0.098
P_{aO_2} kPa	7.70±1.90	7.66±2.03	0.777
P_{aCO_2} kPa	7.54±1.14	7.39±1.10	0.029
SRI total score[#]	47.2±14.0	48.8±15.4	0.195
SGRQ total score[¶]	67.1±16.1	64.3±15.2	0.071
IPAP cmH_2O	17.8±4.9[§]		
EPAP cmH_2O	4.7±1.2[§]		
NIV adherence[+] h·day^{-1}	6.0±2.8[§]		

Data are presented as n, mean±SD or n (%), unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; 6MWD: 6-min walk distance; P_{aO_2}: arterial partial pressure of oxygen; P_{aCO_2}: arterial partial pressure of carbon dioxide; SRI: Severe Respiratory Insufficiency questionnaire; SGRQ: St George's Respiratory Questionnaire; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure. [#]: scaled 0–100 (higher scores indicate better health-related quality of life); [¶]: scaled 0–100 (higher scores indicate worse health-related quality of life); [+]: adherence to NIV after 3 months of NIV (data were read from the built-in counter); [§]: IPAP/EPAP and adherence data are missing from one study [29].

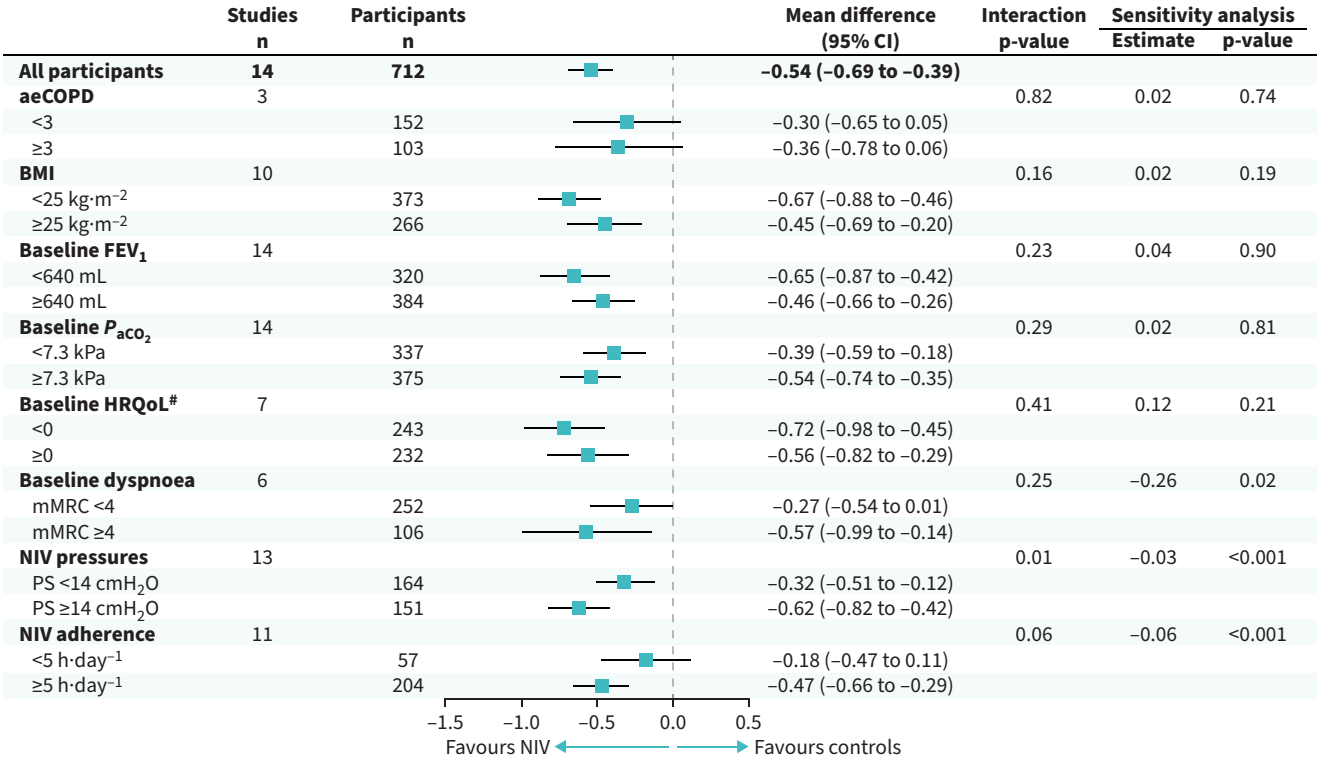

FIGURE 1 Subgroup analysis on the 3-month change in diurnal arterial partial pressure of carbon dioxide (P_{aCO_2}). Results are adjusted for age, sex and timing of initiation of noninvasive ventilation (NIV) (stable disease *versus* after an episode of acute respiratory failure), and are presented as the mean difference (95% CI); the vertical dashed line indicates no effect. aeCOPD: acute exacerbation of COPD; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; HRQoL: health-related quality of life; mMRC: modified Medical Research Council dyspnoea scale; PS: pressure support (the difference between the inspiratory and expiratory positive airway pressure). [#]: z-scores (a value of 0 indicates the mean of all participants, and a negative value indicates worse HRQoL).

and the SGRQ (SD=10.2 units), respectively (figure 2). Participants with fewer than three exacerbations in the year prior to inclusion showed an improvement in HRQoL, compared to participants with three or more exacerbations, in whom HRQoL did not change (SMD 0.52 SD, p=0.03). For the remaining subgroups, none of the treatment by subgroup interactions were statistically significant. However, sensitivity analysis revealed that with higher pressure support (p=0.002) and daily usage of NIV (p=0.02), the improvement in HRQoL was larger.

Improvement in all-cause mortality by subgroup

Data on survival were available for 710 participants. The median follow-up was 27 (IQR 11 to 44) months. When all participants were considered, the hazard ratio in the NIV treated group compared to the control group was 0.85 (95% CI 0.70 to 1.04). We did not find statistically significant treatment by subgroup interactions, nor for the sensitivity analysis (figure 3). Although not statistically significant, the sensitivity analyses showed that the improvement in survival might be larger with an increasing BMI (p=0.05).

Causal mediation analysis

Data on the change in P_{aCO_2} and HRQoL were available from 435 participants. There was a weak correlation between change in P_{aCO_2} and change in HRQoL after 3 months (Pearson's r −0.179, p<0.001; supplementary figure E1). In figure 4, the results of the causal mediation analysis are shown. There was a larger improvement in HRQoL in the NIV group compared to the control group (SMD 0.34, 95% CI 0.15 to 0.53). The causal mediation analysis differentiates this total effect into an average direct effect of NIV, and an average causal mediated effect of the change in P_{aCO_2}, and quantifies both pathways. The average direct effect of NIV on HRQoL contributes to 77% of the total effect of NIV (SMD 0.26, 95% CI 0.08 to 0.46). This direct effect is unexplained by a change in P_{aCO_2} and might either be a true effect of NIV, or may be explained by other mediators. The average causal mediated effect is a SMD 0.08 (95% CI 0.02 to

	Studies n	Participants n	SMD (95% CI)	Interaction p-value	Sensitivity analysis Estimate	Sensitivity analysis p-value
All participants	**7**	**474**	**0.32 (0.15 to 0.50)**			
aeCOPD	3			0.03	−0.061	0.16
<3		157	0.43 (0.14 to 0.72)			
≥3		103	−0.09 (−0.45 to 0.27)			
BMI	7			0.82	−0.001	0.99
<25 kg·m^{-2}		290	0.34 (0.12 to 0.56)			
≥25 kg·m^{-2}		184	0.31 (0.03 to 0.59)			
Baseline FEV_1	7			0.85	0.607	0.07
<640 mL		239	0.34 (0.09 to 0.59)			
≥640 mL		227	0.31 (0.05 to 0.56)			
Baseline P_{aCO_2}	7			0.34	0.090	0.34
<7.3 kPa		205	0.22 (−0.05 to 0.49)			
≥7.3 kPa		263	0.40 (0.16 to 0.63)			
Baseline HRQoL#	7			0.93	−0.044	0.60
<0		237	0.28 (0.04 to 0.51)			
≥0		237	0.26 (0.03 to 0.51)			
Baseline dyspnoea	3			0.61	0.053	0.64
mMRC <4		176	0.20 (−0.07 to 0.48)			
mMRC ≥4		97	0.32 (−0.05 to 0.70)			
NIV pressures	7			0.52	0.018	0.002
PS <14 cmH_2O		66	0.35 (0.09 to 0.61)			
PS ≥14 cmH_2O		132	0.25 (0.05 to 0.46)			
NIV adherence	6			0.53	0.030	0.02
<5 h·day^{-1}		34	0.36 (0.02 to 0.69)			
≥5 h·day^{-1}		126	0.25 (0.04 to 0.45)			

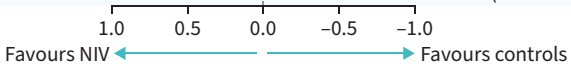

FIGURE 2 Subgroup analysis on the 3-month change in health-related quality of life (HRQoL) (z-scores of the Severe Respiratory Insufficiency and St George's Respiratory Questionnaire combined). Results are adjusted for age, sex and timing of initiation of noninvasive ventilation (NIV) (stable disease *versus* after an episode of acute respiratory failure), and are presented as the standardised mean difference (SMD) (95% CI); the vertical dashed line indicates no effect. aeCOPD: acute exacerbation of COPD; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; P_{aCO_2}: arterial partial pressure of carbon dioxide; mMRC: modified Medical Research Council dyspnoea scale; PS: pressure support (the difference between the inspiratory and expiratory postive airway pressure). #: z-scores (a value of 0 indicates the mean of all participants, and a negative value indicates worse HRQoL).

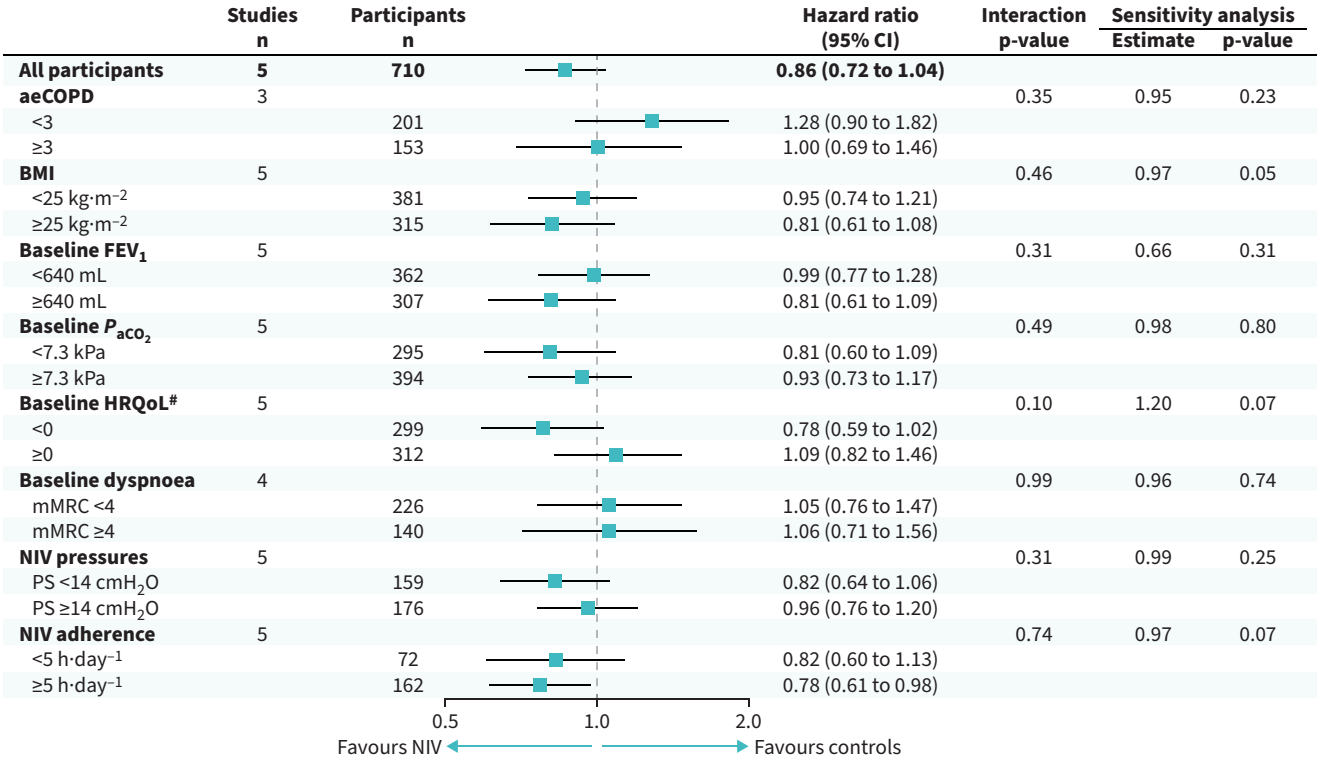

FIGURE 3 Subgroup analysis on all-cause mortality. Results are adjusted for age, sex and timing of initiation of noninvasive ventilation (NIV) (stable disease *versus* after an episode of acute respiratory failure), and are presented as the hazard ratio (95% CI); the vertical dashed line indicates a hazard ratio of zero (no effect). aeCOPD: acute exacerbation of COPD; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; P_{aCO_2}: arterial partial pressure of carbon dioxide; HRQoL: health-related quality of life; mMRC: modified Medical Research Council dyspnoea scale; PS: pressure support (the difference between the inspiratory and expiratory postive airway pressure). #: z-scores (a value of 0 indicates the mean of all participants, and a negative value indicates worse HRQoL).

0.14) which means that 23% of the effect of NIV is caused by a change in diurnal P_{aCO_2}. Additionally, looking at the SRI subscales, mediation analyses showed that 8–20% of the effect of NIV on the subscales of the SRI is explained by a change in P_{aCO_2} (supplementary table E2).

The hazard ratio of all-cause mortality of patients treated with NIV compared to control patients was 0.86 (95% CI 0.72–1.04) when all patients were considered (n=710). 225 patients dropped out of the analysis when the mediator (3-month change in P_{aCO_2}) was added to the model. When the remaining patients were considered, the hazard ratio of NIV was 0.93 (95% CI 0.74–1.18). A critical assumption of the causal mediation analysis is an effect of treatment on the outcome variable. As this assumption could not be fulfilled, we did not conduct this analysis further. Additionally, when looking only at NIV treated participants, there was no difference in the 3-month change in P_{aCO_2} between participants who died during follow-up, compared to participants who survived (supplementary table E3).

Discussion

The present study investigated whether the effect of home NIV is dependent on specific patient and treatment characteristics, and to what extent the effect of home NIV is mediated by improved diurnal ventilation. Using a large set of pooled individual patient data obtained from 16 studies, we showed that with higher inspiratory pressures and with better adherence to the NIV, a larger reduction in P_{aCO_2} is achieved, but the effect of these parameters on HRQoL is only minor. Interestingly, the severity of the airflow obstruction and ventilatory impairment does not seem to be associated with the effect of NIV on patient-centred outcomes, but frequent exacerbations were associated with less HRQoL benefit. More importantly, our study is the first that quantifies the contribution of P_{aCO_2} reduction achieved by NIV to the total effect of NIV on HRQoL. We found that the beneficial effect on HRQoL is achieved only partially through a reduction in diurnal P_{aCO_2}, strengthening the evidence for a multifactorial origin of the beneficial effect of home NIV.

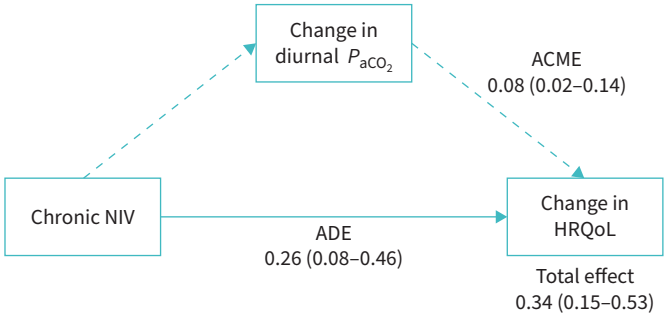

FIGURE 4 Results of the causal mediation analysis estimating the average direct effect (ADE) and the average causal mediation effect (ACME), with 95% confidence intervals, of treatment with home noninvasive ventilation (NIV) and change in arterial partial pressure of carbon dioxide (P_{aCO_2}) on the change in health-related quality of life (HRQoL) among COPD patients (five studies, 428 participants).

Since the introduction of high-intensity NIV, a ventilatory strategy targeting nocturnal correction of hypercapnia using high inspiratory pressures, it has been advocated that the improved ventilation is responsible for the benefits of home NIV. However, beneficial effects on patient-centred outcomes such as HRQoL and mortality might be mediated by more than just improved ventilation. Interestingly, our subgroup analyses show that greater pressure support indeed result in a larger reduction in diurnal P_{aCO_2}, but the added value of higher pressure support on the improvement in HRQoL is small. Also, higher pressure support does not seem to result in a better survival, and diseased patients seem to have a comparable response to NIV in terms of reduced P_{aCO_2}. The results of our causal mediation analysis support this as we found that the effect of NIV on HRQoL, both on the total score and specific subscales was only partially mediated by a change in P_{aCO_2}. This reinforces that correction of hypercapnia remains a reasonable target of home NIV as it contributes to a portion of the benefit on HRQoL, but also indicates that pursuit of high pressures at the detriment of patient comfort is likely to be deleterious.

What factors predict a favourable response to NIV is an open question, especially concerning when to start home NIV. Current guidelines mention only chronic hypercapnia as a criterion to start NIV [2, 3]. We aimed to identify parameters that may predict a more pronounced effect. Interestingly, in patients experiencing frequent exacerbations, HRQoL is not improved by home NIV, in contrast to patients with fewer exacerbations, despite a comparable reduction in P_{aCO_2}. It is known that frequent exacerbations of COPD negatively impact HRQoL [38]. Despite being able to prolong the time to readmission, home NIV does not seem to affect the number of exacerbations in the first year after NIV initiation [4]. Therefore, NIV seems unable to counteract the negative effects of these frequent exacerbations on HRQoL. These findings might suggest that caregivers should discuss and probably dampen expectations with their patients regarding the effect of home NIV on HRQoL in patients in whom frequent exacerbations persist, although we must acknowledge that only three studies contributed data to this subgroup. Future studies are needed investigating this differential response in stable and frequently exacerbating patients. In addition, we found that patients experiencing severe symptoms of dyspnoea have a greater reduction in P_{aCO_2}, but this difference in treatment response was not found on the HRQoL or survival outcome. Lastly, we conclude that patients with less severe disease (based on better FEV_1 and P_{aCO_2}) do not seem to experience less effect on HRQoL or survival, since none of these subgroups by treatment interactions showed statistical significance. So based on these results, there is no reason to withhold home NIV from patients with mild hypercapnia or relatively preserved FEV_1. Given the limited number of factors that we could investigate, we strongly advocate for more research to identify better criteria and emphasise that the target of NIV should be on patient-centred outcomes and not solely on improving ventilation.

In recent years, there has been increasing interest in the clinical phenotyping of COPD. Recently, Janssens *et al.* [11] identified two distinct phenotypes of patients with COPD using home NIV. A "respiratory" phenotype, characterised by severe airflow obstruction, low BMI and few systemic comorbidities, and a "systemic" phenotype, characterised by moderate airflow obstruction, high BMI and a high rate of comorbidity. Their data showed a survival difference between the phenotypes favouring the systemic phenotype. This confirms the findings of earlier trials that BMI and FEV_1 are related to prognosis in end-stage COPD [5, 10, 12]. It should be noted that despite this difference in prognosis, it remains unclear if there is a difference in the response to home NIV between both phenotypes. The study by Borel *et al.* [12] suggests that a survival benefit is only present in patients with COPD and a high BMI. However, this

study included a high number of patients with obstructive sleep apnoea (OSA). There is evidence that treatment of OSA with continuous positive airway pressure in patients with COPD (the overlap syndrome) greatly improves survival [39]. In many of the included studies in our analyses, patients with (severe) OSA and high BMI were excluded, and thus we analysed a population of patients with homogeneous COPD, without the confounding effect of OSA overlap or severe obesity. Our analysis of this homogeneous COPD population indicates that there is no difference in the benefit of NIV in terms of improved HRQoL and survival between the respiratory and systemic phenotypes.

Additional parameters that could potentially affect the outcome of NIV should also be studied. First, static lung hyperinflation has been shown to be a strong predictor of respiratory symptoms, HRQoL and survival [10, 40]. In clinical practice, these hyperinflated patients often present with dyspnoea on exertion as a primary complaint and may experience difficulties adapting to the ventilator. Unfortunately, nocturnal use of NIV does not seem to have carryover ameliorative effects on resting dyspnoea [4]. Therefore, we hypothesise that patients with severe hyperinflation might experience less symptomatic benefit during the day from home NIV than those with less hyperinflation, but we did not have the data to test this. Second, psychological symptoms such as anxiety and depression might be of relevance. The prevalence of these symptoms is high in patients with end-stage COPD [41, 42] and they may influence the effectiveness of home NIV, as studies have shown that these symptoms relate to changes in P_{aCO_2} [5], and HRQoL [43, 44]. Lastly, given the results of the study on clinical phenotypes by JANSSENS *et al.* [11], we advocate for more research on systemic comorbidities and markers for systemic inflammation with regard to the response to home NIV.

We were able to obtain the individual patient data of a large majority of the RCTs conducted in this field, leading to a unique analysis of the data of >1000 participants, but we acknowledge that not all included studies provided the individual patient data, which could have introduced a selection bias. We chose a follow-up of 3 months for the P_{aCO_2} and HRQoL outcomes. Although this may be a short period, positive studies all showed that the majority of improvement was achieved in the first months, with only minor improvement thereafter [24, 26, 45]. A longer follow-up would introduce bias, as patients with the most severe disease might have died. Unfortunately, we were unable to investigate with these pooled data whether the effect of NIV on survival was mediated by a change in P_{aCO_2}. The first available data of the P_{aCO_2} was after 3 months. By using this as the mediator variable, survival data of participants who died prior to the 3-month follow-up (225 participants) could not be used. This is of relevance, as the survival benefit might primarily be achieved in the first few months after initiation of NIV, at least as suggested by the largest study (24) that contributed data and showed an impressive survival benefit. Ideally, an earlier end-point should be used as the mediation variable, for example using the change in P_{aCO_2} immediately following NIV initiation. Additionally, we have used daytime P_{aCO_2} as the mediator outcome. It has been shown that nocturnal NIV may reduce P_{aCO_2} during subsequent spontaneous breathing [46], but we recognise that due to a severely limited ventilatory capacity, P_{aCO_2} may rise during spontaneous daytime breathing even if the nocturnal carbon dioxide (CO_2) is adequately corrected by the NIV. Therefore, a nocturnal CO_2 measurement might be more relevant than a daytime assessment. Lastly, to increase statistical power to detect differences, we pooled participants that were initiated in a clinically stable condition with participants who were initiated following an acute exacerbation into one population. Although we corrected for the timing of NIV initiation, we realise that current guidelines do make a distinction between the timing of initiation. This is of particular relevance, as recent studies suggest that home NIV is most likely cost effective only for post-exacerbation patients [47], and earlier initiation after an exacerbation leading to hospitalisation may yield better outcomes [48].

Conclusion

Our data confirm that the effect of home NIV on diurnal hypercapnia is more pronounced with higher ventilatory pressures and improved NIV adherence. However, the influence of these parameters on changes in HRQoL is minor, and they do not impact survival. The data are also suggestive of a small causal relationship between improved diurnal ventilation and change in HRQoL. Although additional research is still needed, this finding may bring us one step closer to unravelling the black box of the pathophysiological mechanisms of home NIV in patients with severe COPD.

Provenance: Submitted article, peer reviewed.

Conflict of interest: T. Raveling reports a travel grant from Breas Medical. N.S. Hill reports consulting fees from Philips, consulting fees and payments from Fisher & Paykel, and participates in boards of Breas and Philips. C. Casanova reports consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline,

Menarini and Novartis, and participates in boards of AstraZeneca and GlaxoSmithKline. E. Clini reports consulting fees from Chiesi Italia and Novartis, payments from AstraZeneca, Boehringer Ingelheim and GaxoSmithKline, and meeting/travel support from Boehringer Ingelheim and Chiesi. T. Köhnlein reports support from Grifols Deutschland GmbH. P.B. Murphy reports grants and payments from Fisher & Paykel, Resmed, Breas Medical and Philips Respironics, and payments from Chiesi and Genzyme. M.L. Duiverman reports grants from Resmed, Philips, Lowenstein, Vivisol, Sencure and Fisher & Paykel, and payments from Chiesi and Breas Medical. P.J. Wijkstra reports grants from Resmed, and grants and consulting fees from Philips.

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