LONG-TERM NIV IN COPD – WHO AND WHEN?

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Chairpersons and moderators

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Speakers

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Round-table discussion panel

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MEETING SUMMARY

Dr Wijkstra opened this symposium on long-term non-invasive ventilation (NIV) in the treatment of chronic obstructive pulmonary disease (COPD). Dr Köhnlein presented data from a recent randomised controlled trial (RCT) of NIV for the treatment of severe stable COPD.[1] Dr Cheval discussed the use of telemonitoring in French patients with COPD. The meeting concluded with a round-table discussion on the international practice of home mechanical ventilation (HMV) for COPD, moderated by Dr Wijkstra and Prof Windisch with contributions from Dr Köhnlein, Dr Nava, Dr Hart, and Prof Pépin.

Introduction

Doctor Peter Wijkstra

Dr Wijkstra welcomed the audience to the ResMed-sponsored satellite symposium on NIV for COPD. The audience were invited to engage in discussion with the speakers at the end of each presentation.

NIV for Chronic COPD – When and How?

Doctor Thomas Köhnlein

There are currently no universal guidelines for the use of NIV in patients with COPD, but a number of national guidelines exist. For example, the German

Society for Pneumology (DGP) published guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure (CRF) in 2010.[2] These guidelines are expected to be updated in 2016 and an English translation may be downloaded from www.pneumologie.de. The DGP guidelines list five criteria that could lead to chronic NIV in COPD patients with CRF:[2] 1) hypercapnia, respiratory acidosis, and acute exacerbation; 2) hypercapnia and post-acute ventilator therapy; 3) repeated (at least two per year) severe exacerbations needing hospitalisation with respiratory acidosis; 4) chronic elevated daytime arterial carbon dioxide pressure ($PaCO_2$) ≥50 mmHg; 5) nocturnal $PaCO_2$ ≥55 mmHg or partial pressure of transcutaneous carbon dioxide ($PtcCO_2$) increase ≥10 mmHg overnight.

A number of studies have attempted to address the question of whether the provision of NIV to a hypercapnic but stable COPD patient receiving medication and long-term ventilation would provide additional benefit (Table 1).[3-7] Following on from these studies, a recent RCT published in *The Lancet Respiratory Medicine*[1] hypothesised that long-term NIV targeted to reduce hypercapnia would improve survival in patients with advanced, stable, hypercapnic COPD. The trial's primary outcome was overall mortality, and secondary outcomes included changes from baseline in blood gases, exercise capacity, quality of life (QoL), and lung function.[1] Patients were eligible for inclusion if they had been stable for at least 4 weeks with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV COPD,[8] were moderately or severely hypercapnic with $PaCO_2$ ≥7 kPa (51.9 mmHg) and had not been acidotic, or had an exacerbation. The 1-year trial used a parallel-group design with the comparator group receiving guideline-based medical treatment and long-term oxygen therapy if indicated, and with the intervention group also receiving NIV for a minimum of 6 hours per day. Power calculations determined that 150 patients were required in each group. Somewhat differently from previous trials, the target of ventilation was reduction of baseline $PaCO_2$ by ≥20%, assessed during spontaneous breathing 1 hour after NIV. Patient disposition and demographics are shown in Figure 1 and Table 2, respectively.

Table 1: Clinical studies of domiciliary NIV for stable chronic obstructive pulmonary disease.

	Casanova et al.[3] 2000	Clini et al.[4] 2002	McEvoy et al.[5] 2009	Díaz et al.[6] 2002	Windisch et al.[7] 2005
Design and size	RCT (n=24 vs 20)	RCT (n=47 vs 39)	RCT (n=72 vs 72)	RCT (n=18 vs 18)	Uncontrolled (n=34)
Age, years	68 vs 64	66 vs 64	69 vs 67	67 vs 67	63
BMI, kg/m^2	25.0 vs 25.0	25.0 vs 26.0	25.4 vs 25.5	25.0 vs 24.9	28.3
FEV_1, L	0.87 vs 0.82	-	0.55 vs 0.63	0.81 vs 0.72	1.03
$PaCO_2$, mmHg	53.0 vs 50.0	55.5 vs 54.0	54.4 vs 52.6	56.0 vs 57.0	53.3
Compliance	5.9 h/day, 11% <3 h/day	9.2 h/night in compliant group (>5 h/night)	4.5 h/day, 60% >5 h/night	3.0 h/day for 5 days/week for 3 weeks	–
IPAP/EPAP, cm H_2O	12.0/4.0	14.0/2.0	12.9/5.1	18.0/2.0	27.7
Mode	Bilevel, spontaneous	Bilevel, timed, back up rate 8	Bilevel, spontaneous	Bilevel, spontaneous	Pressure controlled
Therapeutic target for NIV	Reduced respiratory muscle activity	Reduced CO_2 by day, SaO_2 >90% overnight	Reduced sleep-disordered breathing	Maximum tolerated IPAP during day	Normalisation of $PaCO_2$
12-month survival	78% vs 78%	–	80% vs 72%	–	–
24-month survival	–	83% vs 82%	68% vs 53%	–	86%

BMI: body mass index; EPAP: expiratory positive airway pressure; FEV_1: forced expiratory volume in 1 second; IPAP: inspiratory positive airway pressure; NIV: non-invasive ventilation; $PaCO_2$: arterial carbon dioxide pressure; RCT: randomised controlled trial; SaO_2: arterial oxygen saturation.

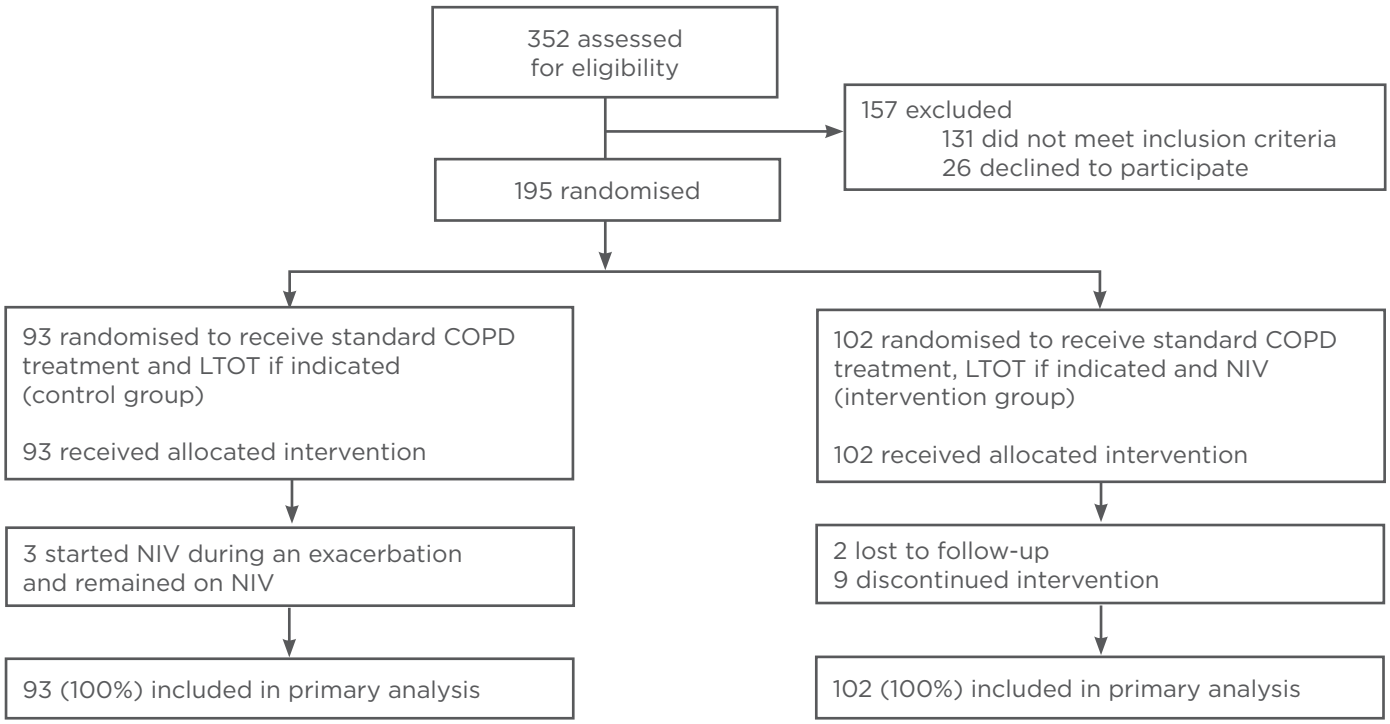

Figure 1: Patient disposition.[1]

COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; NIV: non-invasive ventilation.

Table 2: Patient demographics.[1]

	Control group (n=93)	NIV group (n=102)
Age, years	64.4 (8.0)	62.2 (8.6)
Male, n (%)	56 (60)	65 (64)
BMI, kg/m^2	24.5 (5.8)	24.8 (5.8)
FVC, % predicted	53.3 (13.8)	50.4 (13.3)
FEV_1, % predicted	27.5 (8.9)	26.0 (11.0)
FEV_1/FVC, %	41.2 (11.4)	40.4 (11.5)
Residual volume/total lung capacity, %	72.7 (8.9)	73.0 (8.5)
pH	7.39 (0.05)	7.39 (0.04)
$PaCO_2$, kPa	7.7 (0.7)	7.8 (0.8)
PaO_2, kPa*	8.7 (1.9)	8.6 (2.1)
SaO_2, %*	90.8 (5.9)	90.3 (6.2)
HCO_3^-, mmol/L	33.9 (4.1)	34.3 (4.0)
Base excess, mmol/L	8.0 (3.9)	7.8 (3.8)
6-minute walk distance, m	249.6 (145.3)	226.7 (121.2)
Long-term oxygen treatment, n (%)	60 (65)	67 (66)

Data are mean (standard deviation), unless otherwise stated.

*In patients with long-term oxygen treatment, oxygen was applied via nasal cannula at the previously prescribed flow rate.

BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; HCO_3^-: bicarbonate; NIV: non-invasive ventilation; $PaCO_2$: arterial carbon dioxide pressure; PaO_2: arterial oxygen pressure; SaO_2: arterial oxygen saturation.

In the NIV group, the mean inspiratory and expiratory pressures were 21.6±4.7 mmHg and 4.8±1.6 cm H_2O, respectively, and all patients had received pressure support (PS) ventilation with a backup frequency of 16.1±3.6 (range: 2–24) breaths per minute. Using a cut-off value of 14 breaths per minute, 70 (69%) patients were deemed to have had controlled or partially controlled ventilation and the mean daily NIV usage was 5.9±3.1 hours.

$PaCO_2$ was reduced with the use of NIV by approximately 17% within the first 5.3 days and remained stable throughout the observation period. There was a non-significant increase in the NIV group's 6-minute walk distance (approximately 35 m) that met the suggested minimum clinically important difference in almost half of the patients (44%), whereas a significant improvement in FEV_1 (2.8% [0.2–5.4%]; p=0.034) was reported. Improvements in health-related QoL were observed in the General Health Perception component of the SF-36 and were above the minimal clinically important difference of 4.0 in the St George's Respiratory Questionnaire (SGRQ) (5.8 points more for the NIV group than for the control group). Significant improvements were also observed in the NIV group's Severe Respiratory Insufficiency score (5.6 point increase, 95% confidence interval [CI]: 0.1–11.1; p=0.0445). All-cause mortality was statistically lower in the NIV group at 1 year (12% [12 of 102 patients] in the NIV group and 33% [31 of 93 patients] in the control group; hazard ratio: 0.24, 95% CI: 0.11–0.49; p=0.0004) and this advantage was maintained up to at least 2,000 days after randomisation in patients still under observation. The mechanism of this improvement is not clear but the results suggest that a survival advantage appears early and remains throughout the observation period.

In clinical practice, patients with COPD who are treated in intensive care or high-dependency units receiving acute NIV tend to improve and begin breathing spontaneously. However, the question of whether the patient should be placed on long-term HMV once discharged is unclear. A study of patients who had been discharged from intensive care or a high-dependency unit after an acute exacerbation and randomised to NIV or standard treatment showed that, after 1 year, the combined endpoint of readmission for a respiratory cause or death was approximately equal irrespective of home NIV.[9] This study also failed to demonstrate a difference in survival time.[9] The authors postulate that these findings are due to the fact that both patient groups were hypercapnic during their initial hospital stay, both groups saw an improvement in the 3 months following discharge, and then both groups remained normocapnic throughout the observational period.[9] Patients should be re-assessed 3 months after an acute exacerbation to determine whether long-term domiciliary NIV is appropriate.

In conclusion, long-term domiciliary use of NIV in patients with advanced, stable COPD targeted at markedly reducing hypercapnia improves mortality, health-related QoL, and exercise capacity.

Telemonitoring for COPD Patients

Doctor Christine Cheval

The ResMed AirView™ is a clinician-managed telemonitoring platform for patients using continuous positive airway pressure or NIV compatible with Air Solutions' AirSense 10™, AirCurve™, Lumis™, and S9™ series devices. The system's dashboard provides an at-a-glance overview of compliance, unintentional leaks, and other clinical parameters over 90 days. The system provides several different report formats, including compliance only (usage, settings, leaks, and apnoea/hypopnoea index), compliance with clinical parameters, and detailed reports for the last 7 days.

The current trend in France for COPD patients is a reduction in long-term oxygen therapy with an increase in NIV and NIV with oxygen[10] and, due to compliance issues, these patients are ideal candidates for telemonitoring. The Köhnlein study described above is changing the way patients with COPD are ventilated around the world, but is based on a mean hospital stay of 5.6 days.[1] However, the titration period for French patients is limited to a few days, with a follow-up visit 1–2 weeks later. This provides an opportunity for a new treatment pathway: an initial 1-day titration followed by telemonitoring with or without $PtcCO_2$.

When optimising titration, the first task is the control of unintentional leaks.[11,12] The second task is setting the expiratory positive airway pressure (EPAP) level,[12] as the hospital stay is not always representative of home variations, especially in overlap patients. Telemonitoring of NIV enables these parameters to be monitored and adjusted remotely or with the help of homecare providers.

Exacerbation is a major cause of death in COPD and is associated with increased costs. Liu et al.[13] developed a scoring system for predicting a 90-day re-exacerbation in hospitalised patients with acute exacerbations (Table 3). Patients are placed into one of three groups depending on their score (2–6, 7–8, or >9). The higher the score, the greater the risk of an exacerbation in the next 90 days.

A prospective observational study of COPD patients showed that telemonitoring may also provide the ability to predict the occurrence of exacerbations on a regular basis.[14] Data collected included the duration of NIV each day, respiratory rate, and the percentage of inspiratory cycles triggered by the patient. EXACT-PRO® (EXAcerbations of Chronic pulmonary disease Tool) diaries were collected at monthly visits, and if the diary indicated that there had been an exacerbation then this was confirmed by two pulmonologists. Following an exacerbation, the follow-up period was divided into two blocks of 5 days. This proof-of-concept study showed that daily variations in respiratory rate and the percentage of cycles triggered by the patient are predictors of an exacerbation.

In a study of COPD patients treated at home with long-term NIV, a nightly use of >5 hours per day was associated with a better prognosis in the subgroup of 'obese COPD' patients. In contrast, NIV efficacy was rather limited in 'non-obese COPD', and an NIV use of >9 hours per day could predict poor outcomes.[15]

In conclusion, controlling leaks is crucial for successful NIV and recent data suggest that compliance with NIV of at least 5–6 hours per day is necessary to achieve a survival benefit in COPD.[15] New algorithms offer the possibility of auto-adjustable EPAP or PS, allowing a period of home titration. AirView allows remote monitoring of these parameters, enabling physicians to react promptly and take appropriate action. Telemonitoring could potentially help to predict exacerbations and prevent hospitalisation by facilitating early intervention with appropriate treatment. However, more data are required to better define criteria and monitoring methods, and these need to be included in the software. For example, which respiratory rate thresholds should be used, and how often? Telemonitoring is time-consuming and requires a redefinition of the roles and tasks of different stakeholders, e.g. clinicians, nurses, physiotherapists, and homecare providers. This will require a new treatment pathway supported by regulations and reimbursement, combined with economic analyses of the impact of this new approach. Ultimately, there will be a need for patients to become more involved in their treatment.

Table 3: Prediction of short-term re-exacerbation in patients with acute exacerbation of chronic obstructive pulmonary disease.[13]

	–1	0	1	2	3
Age range, years		<65	65–70	71–77	>77
GOLD grade		1	2	3	4
Frequency of exacerbation in previous year		0	1–2	≥3	
Presence of pleural effusion		No		Yes	
Use of accessory respiratory muscles		No	Yes		
Use of NIV		No	Yes		
Use of oxygen		No		Yes	
Use of inhaled corticosteroids	Yes	No			
Use of long-acting β_2-agonists	Yes	No			
Length of hospital stay, days		≤10	11–20	21–30	>30

GOLD: Global Initiative for Chronic Obstructive Lung Disease; NIV: non-invasive ventilation.

International Practice of HMV for COPD

Round-table discussion moderated by Doctor Peter Wijkstra and Professor Wolfram Windisch with contributions from Doctor Thomas Köhnlein, Doctor Stefano Nava, Doctor Nick Hart, and Professor Jean-Louis Pépin.

The session concluded with a lively discussion initiated by questions from the audience. The first topic was the problem of initiation of NIV in the home. The panel concluded that although home initiation of NIV is not suitable for all patients, it may be particularly suitable for patients with neuromuscular disorders such as Duchenne's muscular dystrophy and those with obesity-related respiratory failure. The panel noted that the main goal of telemonitoring is to monitor patients, not to initiate ventilation, and that the information collected needs to be acted upon promptly.

Reduction of CO_2 is critical for the success of NIV, but the panel was divided as to whether this was a direct effect or a surrogate marker of something else, such as a decompensated ventilatory pump. A recent large study in Japan has suggested that hypercapnia may in fact have protective effects.[16] Reducing $PaCO_2$ is an important goal in NIV that drives improvement in exercise tolerance and, ultimately, QoL. These improvements in exercise tolerance may be responsible for the observed survival advantage conferred by NIV.

When questioned on whether the panel would initiate NIV in normocapnic COPD patients during normal clinical practice, the consensus was that NIV was not suitable in these patients and conventional ventilation strategies such as simple PS were more appropriate. Nevertheless, it is important to select a ventilation strategy on a case-by-case basis.

Following this, the subject of whether to stop NIV when a hypercapnic patient becomes normocapnic was raised. The panel noted that it is important to consider whether the patient is becoming normocapnic as a result of the NIV or due to the natural course of the disease. In appropriate cases, NIV time can be reduced gradually over several nights and eventually stopped completely.

The audience was asked to consider whether there was now enough evidence to place all COPD patients on either standard ventilation or NIV. A straw poll revealed that placing hypercapnic COPD patients on NIV as standard is not widespread. The panel agreed that patients with high CO_2 and frequent exacerbations were the right candidates to target since widespread ventilation of hypercapnic patients might be uneconomical.

There is evidence that NIV in patients with COPD improves physiology, QoL, and long-term survival; in the final discussion, the panel members were asked for their views on the future of research in the field. Important topics included the health economics of widespread NIV use, patients with comorbidities, and the correct selection of patients, especially those who do not tolerate NIV or who are not efficiently treated by NIV in terms of the goal of reducing CO_2. Crucially, more basic research is urgently required to understand why chronic NIV in COPD might improve survival in these severely impaired patients.

Meeting Close

Doctor Peter Wijkstra

Dr Wijkstra thanked the speakers for their presentations as well as the audience for their questions and discussion points. With a final thank you to ResMed for having organised the symposium, the meeting was brought to a close.

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