The role of NIV in chronic hypercapnic COPD following an acute exacerbation: the importance of patient selection?

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***Abstract*:** Recently, clear benefits have been shown from long-term noninvasive ventilation (NIV) in stable chronic obstructive pulmonary disease (COPD) patients with chronic hypercapnic respiratory failure. In our opinion, these benefits are confirmed and nocturnal NIV using sufficiently high inspiratory pressures should be considered in COPD patients with chronic hypercapnic respiratory failure in stable disease, preferably combined with pulmonary rehabilitation. In contrast, clear benefits from (continuing) NIV at home after an exacerbation in patients who remain hypercapnic have not been shown. In this review we will discuss the results of five trials investigating the use of home nocturnal NIV in patients with prolonged hypercapnia after a COPD exacerbation with acute hypercapnic respiratory failure. Although some uncontrolled trials might have shown some benefits of this therapy, the largest randomized controlled trial did not show benefits in terms of hospital readmission or death. However, further studies are necessary to select the patients that optimally benefit, select the right moment to initiate home NIV, select the optimal ventilatory settings, and to choose optimal follow up programmes. Furthermore, there is insufficient knowledge about the optimal ventilatory settings in the post-exacerbation period. Finally, we are not well informed about exact reasons for readmission in patients on NIV, the course of the exacerbation and the treatment instituted. A careful follow up might probably be necessary to prevent deterioration on NIV early.

Keywords: chronic obstructive, pulmonary disease, noninvasive ventilation, exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic disease with a high mortality and morbidity worldwide. According to the World Health Organization, it is the only chronic disease with increasing mortality (see http://www.who.int/respiratory/copd/burden). Patients with end-stage COPD frequently develop chronic respiratory failure (CRF) which is associated with end of life. In that stage of disease, treatment options are limited as until now, only long-term oxygen therapy has been proven to prolong life in these patients [Nocturnal Oxygen Therapy Trial Group, 1980]. However, once patients develop advanced hypercapnic respiratory failure, giving oxygen may not be sufficient, and support of ventilation might be necessary.

While there is no doubt that applying long-term nocturnal noninvasive ventilation (NIV) improves outcomes in patients with restrictive chest wall diseases and neuromuscular diseases [Simonds and Elliott, 1995; Leger *et al.* 1994], evidence for long-term application in COPD patients has been lacking for a long time. However, in the past 7 years, with a change in ventilatory strategy, clear benefits have been achieved also in COPD patients with CRF, though in stable disease [Windisch *et al.* 2002, 2005; Dreher *et al.* 2010, 2011]. Interestingly, until now, it has not been proven that nocturnal NIV would also improve the, for many patients, rather miserable situation after an exacerbation. In this review we will first briefly summarize the results of studies in stable hypercapnic COPD patients, while thereafter we will discuss the results of post-exacerbation studies more extensively.

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Nocturnal NIV in COPD patients with stable chronic hypercapnic respiratory failure

For 20 years now, studies have been investigating NIV in stable COPD patients with CRF [Casanova *et al.* 2000; Clini *et al.* 2002; Strumpf *et al.* 1991; Gay *et al.* 1996; Lin, 1996; McEvoy *et al.* 2009; Meecham Jones *et al.* 1995]. Most initial randomized controlled trials (RCTs) did not show clear benefits [Casanova *et al.* 2000; Clini *et al.* 2002; Strumpf *et al.* 1991; Gay *et al.* 1996; Lin, 1996; McEvoy *et al.* 2009]. Last year, an updated meta-analysis of individual patient data was published comparing NIV with conventional management in patients with COPD and stable CRF, showing that NIV in patients with stable COPD does not improve lung function, gas exchange, sleep efficiency or 6-minute walking distance [Struik *et al.* 2014a]. However, inspiratory pressures above 18 cm H_2O, a better compliance to the therapy, and a higher baseline arterial carbon dioxide levels ($PaCO_2$), were associated with significantly more reduction in $PaCO_2$ with therapy [Struik *et al.* 2014a].

The hypothesis that probably higher pressures are needed to improve gas exchange and thus to expect also clinically meaningful outcomes has been investigated by Windisch and coworkers [Windisch *et al.* 2002, 2005; Dreher *et al.* 2010, 2011]. Although the studies did not contain a control group getting standard care, they indeed showed that with higher pressures and a more controlled form of NIV aimed at a maximal reduction in $PaCO_2$ (so called high-intensity NIV), gas exchange but also lung function and health-related quality of life (HRQoL) improved more, and that this high-intensity NIV was well tolerated [Windisch *et al.* 2002, 2005; Dreher *et al.* 2010, 2011]. These promising results have now been confirmed in long-term RCTs [Duiverman *et al.* 2008, 2011; Köhnlein *et al.* 2014]. In addition, it has been shown that high-intensity NIV improves the outcomes of pulmonary rehabilitation in severe stable hypercapnic COPD, in terms of improvement in gas exchange, pulmonary function, exercise tolerance and HRQoL [Duiverman *et al.* 2008, 2011]. In 2014, the study of Köhnlein and colleagues showed, next to benefits in gas exchange, HRQoL and lung function, also a substantial survival benefit [Köhnlein *et al.* 2014].

With regards to the prevention of exacerbations, the only RCT showing any benefit of NIV in stable COPD patients was the Italian multicentre study of Clini and colleagues [Clini *et al.* 2002]. The total hospital admission rate decreased by 45% in the NIV group, and increased by 27% in the control group compared with the period before the start of the study. Furthermore, intensive care unit admissions decreased more in the NIV group (by 75%) than in the control group (by 20%). However, as this was not their primary outcome, these results were only hypothesis generating. Other studies in stable COPD patients could not reproduce these results, also because hospital admission did occur very infrequently [Duiverman *et al.* 2011; Köhnlein *et al.* 2014].

To conclude, although former studies and the most recent meta-analysis have shown that nocturnal NIV in stable hypercapnic COPD patients does not improve outcomes, the more recent trials using high-intensity NIV have shown important and relevant outcomes. In our opinion, these benefits are confirmed and nocturnal NIV should be considered in COPD patients with chronic hypercapnic respiratory failure in stable disease, preferably combined with pulmonary rehabilitation.

Nocturnal NIV in COPD patients with prolonged hypercapnia after acute respiratory failure due to a COPD exacerbation

During the natural history of COPD, exacerbations are an important contributor to morbidity and mortality [Global Initiative for Chronic Obstructive Lung Disease, 2015; Vestbo, 2004]. Unfortunately, patients often do not recover to baseline levels of lung function and symptoms and therefore COPD exacerbations are an important contributor to lung function decline, resulting in reduced physical activity, poorer quality of life and increased risk of death [Donaldson *et al.* 2002, 2005; Seemingal *et al.* 1998; Soler-Catalu *et al.* 2005].

The best predictor of getting an exacerbation is the occurrence of prior exacerbations, indicating that there is a group of patients susceptible to exacerbations, irrespective of lung function [Hurst *et al.* 2010]. Despite this, in patients with severe airflow obstruction, there are more 'frequent exacerbators' and exacerbations are often more severe, as indicated by more hospital admissions [Hurst *et al.* 2010].

NIV has become an established treatment in acute hypercapnic respiratory failure (AHRF) in

patients with a COPD exacerbation [Ram *et al.* 2004]. However, next to a high in-hospital mortality [Ram *et al.* 2004; Stefan *et al.* 2015], after discharge 60–80% of the patients are re-admitted within 1 year and 30–49% die within this first year after their hospital admission for AHRF [Chu *et al.* 2004; Echave-Sustaeta *et al.* 2010]. These disappointing outcomes raised the question of whether providing long-term NIV to patients who recover from their exacerbation but remain hypercapnic might improve outcomes.

Despite the fact that evidence has been lacking, in several countries patients suffering from frequent exacerbations with AHRF receive domiciliary NIV. This different attitude towards the initiation of domiciliary ventilation after an exacerbation might also explain the huge differences in prevalence of domiciliary ventilation in COPD which has been found between the different countries [Lloyd-Owen *et al.* 2005]. The initiation of domiciliary long-term NIV has consequently also been investigated in studies.

In 2003, Tuggey and colleagues performed a retrospective economic analysis of domiciliary NIV in a highly selected group of 13 patients having frequent exacerbations, treated in their clinic [Tuggey *et al.* 2003]. They showed that there was a significant reduction in the rate of admission (from a mean of five admissions in the year before NIV to a mean of two admissions in the year after NIV was initiated), and the total length of hospital stay per patient (17 days *versus* 8 days), leading to a net saving of £107.298 to the acute hospital providing a home NIV service for this highly selected group of patients. Of note, this study contained a highly preselected group of patients who were included at the moment that NIV was initiated successfully, representing a selection of patients that are probably most likely to benefit from this therapy.

A similar situation was investigated in the USA, where chart reviews were conducted and compared in patients who were discharged with NIV *versus* patients who were discharged without NIV after an acute COPD exacerbation with AHRF requiring NIV.[33] In this cohort of patients, quite high inspiratory pressures were used (mean inspiratory positive airway pressure of 22 cm H_2O). Up to 180 days, in the NIV post discharge group compared to the group discharged without NIV, a significant reduction in hospital readmissions was observed, while no significant difference in mortality was found. However, also in this study a selection of patients was discharged with NIV, namely patients who were younger and compliant with the therapy. Furthermore, in both groups, but even more in the NIV discharge group, very frequently a history of obstructive sleep apnoea or obesity hypoventilation syndrome was noted (47.4% in the NIV discharge group *versus* 26.1% in the without NIV discharge group). This makes it questionable whether pure COPD patients were included in this study, or rather patients with overlap syndromes who could benefit from NIV because of their other underlying condition.

The third study to be discussed is from Funk and colleagues. They had to deal with the same situation, as patients were in their centre routinely evaluated for long-term NIV if they remained hypercapnic after an episode of AHRF requiring mechanical ventilation. For study purposes, these patients were randomised to continue or withdraw NIV after 6 months standard home NIV implemented after their exacerbation [Funk *et al.* 2011]. The main problem interpreting the results of this study is that the main part of primary end point, that is, the probability of clinical worsening defined as resumption of NIV due to severe dyspnoea or progressive hypercapnia, could by definition only be fulfilled in the withdrawal group. Looking more precisely into their results, it becomes clear that the part of the primary end point that could be fulfilled in both groups, ICU admission, was not different, occurring in two patients in the ventilation group *versus* three in the withdrawal group. Furthermore, daytime resting gas exchange did not deteriorate by withdrawing NIV, neither did HRQoL nor overall exacerbation rate. Finally, also this study included a selected group of patients as for example noncompliant patients were already filtered out during the run-in phase.

Two RCTs have been conducted including a control group not receiving home NIV after an acute exacerbation with AHRF [Cheung *et al.* 2010; Struik *et al.* 2014b]. A RCT with 'sham ventilation' as control [continuous positive airway pressure (CPAP) 5 cm H_2O] was published by Cheung and colleagues [Cheung *et al.* 2010]. They showed that when home NIV was provided after an exacerbation with AHRF, the proportion of patients developing recurrent AHRF was 38.5% *versus* 60.2% at 1 year, while this also seemed to occur earlier in the CPAP group. However, as patient numbers were small, and drop out was significant,

Table 1. Studies investigating NIV in COPD patients after an acute exacerbation with AHRF.

Study	Design	Ventilator settings	Primary outcome	Primary outcome	Survival	Important other outcomes
Tuggey *et al.* [2003] $N = 13$	Retrospective audit 1 year	Not shown	Cost analysis	Cost saving of £8254 per patient	Year after NIV: median 29 months	Admissions year before: 5 year after NIV: 2
Galli *et al.* [2014] $N = 166$	Retrospective: *NIV post-discharge versus no NIV* 6 months	IPAP 22 EPAP 6 BF unknown	Event-free survival (time without rehospitalization or death)	Adjusted HR# 3.29 (95% CI 2.05-5.27) Event at 6 months: *NIV*: 40% *No NIV*: 75%	6 months: ***NIV***: 10% ***No NIV***: 19%	–
Cheung *et al.* [2010] $N = 49$	RCT *BiPAP versus CPAP* 5 cm H_2O 1 year	IPAP 15 EPAP 5 BF 14/min	Recurrent exacerbation with AHRF (pH <7.35 and $PaCO_2$ >6 kPa) resulting in repeat NIV, intubation or death)	*NIV*: 38.5% *CPAP*: 60.2% (all AHRF)	Unclear Not significant	High drop out *NIV*: 8 *CPAP*: 4
Funk *et al.* [2011] $N = 26$	RCT *Continuation versus withdrawal* of NIV after 6 months 1 year	IPAP 10–20 EPAP 5 Patient-triggered	Time to clinical worsening: (1) ICU admission (2) NIV with severe dyspnoea (2a) or ↑$PaCO_2$ ⩾ 10% (2b)	*NIV*: 391 days ($n = 2$, 15%, 2 ICU) *Withdrawal*: 162 days ($n = 10$, 77%, 3 ICU)	No deaths	6MWD after 3 months *NIV*: 56 m *Withdrawal*: –17 m SGRQ, blood gases, FEV_1, steroid and antibiotic use not different
Struik *et al.* [2014b] $N = 201$	RCT *NIV versus Standard care* 1 year	IPAP 19 EPAP 5 BF 15/min	Time to event (readmission for respiratory cause or death)	*NIV*: 192 days (65% had an event) *Standard*: 198 days (64% had an event)	NIV: 30% Standard: 30%	Daytime $PaCO_2$ *NIV*: 7.7>6.4 kPa *Standard*: 7.4>6.6 kPa (Treatment effect: –0.5 kPa)

NIV, noninvasive ventilation; IPAP, inspiratory positive airway pressure (cmH_2O); EPAP, expiratory airway pressure (cmH_2O); BF, backup breathing frequency set by the ventilator; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; AHRF, acute hypercapnic respiratory failure; $PaCO_2$, arterial carbon dioxide tension; ICU, intensive care unit; 6MWD, 6-minute walking distance; SGRQ, St. George Respiratory Questionnaire; FEV_1, forced expiratory volume in 1 second.
#HR: hazard ratio, subjects who did not use NIV post-discharge had inferior event-free survival through 180 days compared with patients who used NIV post-discharge after matching the groups for age, FEV_1, the existence of obstructive sleep apnoea/obesity hypoventilation (OSA/OHS), home oxygen therapy, and admission date, and additionally adjusting for OSA/OHS and $PaCO_2$ at discharge.

Table 2. Timing of initiation of NIV after an exacerbation in completed and ongoing randomized controlled trials.

Study	Status	Inclusion criteria regarding timing of initiation of chronic NIV
Cheung *et al.* [2010]	Completed and published	>48 h independence from NIV for AHRF Hypercapnia not an inclusion criterion
Struik *et al.* [2014b]	Completed and published	>48 h independence from ventilatory support for AHRF After 48 hours $PaCO_2 > 6$ kPa
Murphy *et al.*, Guy's and St Thomas' NHS Foundation Trust, London, UK. [ClinicalTrials.gov identifier: NCT00990132]	Recruitment is finished, waiting for follow-up results	Acute COPD exacerbation with AHRF ⩾2 weeks previously (at least 2 weeks following resolution of the respiratory acidosis) At enrollment in the study, $PaCO_2 >$ 7 kPa
NIVOLD study, University Hospital Rouen, France [ClinicalTrials.gov identifier: NCT01526642]	Terminated, not published yet	Patients weaned from ventilation for acute COPD exacerbation ⩾7 days with stable arterial blood gas for at least 2 days: $PaCO_2 > 7.3$ kPa and pH > 7.35
Ankjærgaard *et al.*, Gentofte Hospital Copenhagen, Denmark [ClinicalTrials.gov identifier: NCT01513655]	Running, still recruiting	The home NIV treatment is a direct continuation of the acute treatment, patients are not weaned. So, persistent hypercapnia is not an inclusion criterion

NIV, noninvasive ventilation; AHRF, acute hypercapnic respiratory failure; $PaCO_2$, arterial carbon dioxide tension.
Status of the trials not published yet retrieved from ClinicalTrials.gov, and through contact with study coordinators.

the study was probably underpowered to find significant differences in time to first admission. Furthermore, survival rates were not different, but it remains also unclear from the study exactly how many patients died and for what reasons. Drop out rates were also high because of discomfort with the treatment. It must be noted, however, that inspiratory pressures were rather low [mean inspiratory positive airway pressure (IPAP) 14.8, mean expiratory airway pressure (EPAP) 5 cm H_2O]. Also, the use of a sham control group with CPAP should be discussed as this could also have been harmful.

A recently published large multicentre RCT by Struik and colleagues could not demonstrate an improvement in time to readmission or death by adding NIV for 1 year in patients with prolonged hypercapnia after an episode of NIV for AHRF despite the use of higher inspiratory pressures indeed leading to more improvement in gas exchange, and the frequent addition of pulmonary rehabilitation post-exacerbation [Struik *et al.* 2014b]. One year after discharge, 56% *versus* 57% of patients (NIV *versus* standard treatment) were readmitted to hospital and, in both groups, 30% of the patients had died.

Summarizing these publications there are several important items to be discussed. An important issue when comparing results of these different trials is that different end points were used. In the study of Struik and colleagues the primary end point (readmission or death) was reached quite often also in the NIV group (65% in the NIV group *versus* 64% in the control group) [Struik *et al.* 2014b]. However, no detailed information was provided on the reason for admission, whether or not AHRF was present and what kind of treatment was necessary. Of note, the NIV patients more often used oral corticosteroids which might have negatively affected outcomes. In the study of Cheung and colleagues, although the occurrence of AHRF was reduced with NIV, in a significant proportion of patients a concurrent illness occurred, and although these illnesses required ICU admission, they were not included

in their primary outcome (four patients in the NIV group *versus* one patient in the control group) [Cheung *et al.* 2010]. In the study of Funk and colleagues only two patients in the NIV group worsened so much that they had to be admitted to the ICU [Funk *et al.* 2011]. However, it is unknown how many patients deteriorated without an obligatory ICU admission, as this was not defined in their primary outcome. Furthermore, patients were monitored very closely with in-hospital visits including an overnight stay every 3 months. Thus before drawing definite conclusions it is necessary to have more detailed information about why patients on NIV are admitted to hospital, how often AHRF occurs and how severe the case was despite NIV and what kind of treatment is instituted.

Second, it seems that the studies, although they have all included COPD patients after an exacerbation, included patients in different disease stages, with or without comorbidity or pre-existent CRF. This might have influenced outcomes. In the retrospective analysis of Galli and colleagues, the standard treatment group performed worse (75% re-admitted or death in 6 months) compared with the other studies [Galli *et al.* 2014]. In this study comorbidities, also cardiac comorbidities, were very frequent while in the other studies these patients were excluded [Struik *et al.* 2014b] or rarely there [Funk *et al.* 2011; Cheung *et al.* 2010]. Although this might have influenced outcomes negatively in the control group in the study of Galli and colleagues, it probably represents real life best. On the other hand, patients who exacerbate with AHRF but do not suffer from CRF, probably do not need chronic nocturnal NIV as we know that some of these patients return to normocapnia after recovery [Costello *et al.* 1997]. The more stable patients from Funk and colleagues, with proven CRF, had a better prognosis when NIV was initiated [Funk *et al.* 2011]. On the other hand, in the study of Struik and colleagues, 26% of the patients in the standard treatment group became spontaneously eucapnic after 3 months, thus probably representing a part of the patients that do not need long-term NIV at all [Struik *et al.* 2014b]. However, one should consider that if the authors would have been able to preselect the chronic hypercapnic patients, as was done in the study of Funk and colleagues, this might have resulted in a higher event rate in especially the standard treatment arm. Moreover, the NIV group might have performed better as the CRF would be counterbalanced by the NIV. What was shown in the study of Struik and colleagues [Struik *et al.* 2014b], however, was a comparable deterioration rate in the control group compared with the studies of Funk and colleagues and Cheung and coworkers [Funk *et al.* 2011; Cheung *et al.* 2010], but a higher event rate in the NIV group. The latter cannot be explained by this patient selection issue. Overall, it has been hypothesized that the indication for NIV post-exacerbation should be set later as this brings the opportunity to select the patients who suffer from acute CRF. However, this issue of timing remains challenging, as we should select the patients that are suffering from CRF, have deteriorated this time and will deteriorate in the future because of acute CRF, while we do not want to wait too long as event rates are high and events usually also occur during the first 100 days after the exacerbation [Galli *et al.* 2014; Funk *et al.* 2011; Cheung *et al.* 2010]. Future studies should try to incorporate these points by (a) selecting patient with more severe remaining hypercapnia and (b) lengthening the time frame (an overview of the previous RCTs regarding these aspects is given in Table 2).

Finally, differences in outcomes and reported benefits of NIV could theoretically be a matter of differences in ventilator settings providing insufficient ventilatory support. From the studies performed in CRF we have learnt that higher inspiratory pressures are necessary to improve gas exchange. However, we are insufficiently informed about probable disadvantages of this high-intensity NIV [Lukácsovits *et al.* 2012]. In the study of Struik and colleagues the highest pressures were used indeed leading to improved gas exchange while clear benefits in terms of survival or readmission rates did not result [Struik *et al.* 2014b]. However, it should also be noted that in the NIV group, there were patients that remained severely hypercapnic, which might indicate that the improvement in ventilation with these settings was still suboptimal [Struik *et al.* 2014b].

In conclusion, there is at the moment insufficient evidence to support the use of home nocturnal NIV in patients with prolonged hypercapnia after a COPD exacerbation with AHRF. However, some uncontrolled trials might have shown some benefits in patients that remain hypercapnic (long enough) after an acute exacerbation with AHRF. The challenge will be to select, preferably beforehand, the patients that will benefit

most. As this is not always possible in clinical practice, studies mainly focus on adequate timing post-exacerbation. The data of a large British RCT, a French RCT and a Danish RCT are expected which include patients who remained hypercapnic after different time periods (Table 2). Furthermore, there is insufficient knowledge about the optimal ventilatory settings in the post-exacerbation period. Finally, we are not well informed about exact reasons for readmission in patients on NIV, the course of the exacerbation and the treatment instituted. A careful follow up might be necessary to prevent early deterioration on NIV [Funk *et al.* 2011].

Overall summary

Nocturnal NIV is an evidence-based therapy for the treatment of CRF in stable COPD patients improving survival and HRQoL (evidence level B). In patients who remain hypercapnic after an acute COPD exacerbation with ARF, there is at the moment insufficient evidence to support the continued use of home nocturnal NIV. However, further studies are necessary to select the patients that optimally benefit, select the right moment to initiate home NIV, select the optimal ventilatory settings and to choose optimal follow-up programmes.

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References

Casanova, C., Celli, B., Tost, L., Soriano, E., Abreu, J., Velasco, V. *et al.* (2000) Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. *Chest* 118: 1582–1590.

Cheung, A., Chan, V., Liong, J., Lam, J., Leung, W., Lin, A. *et al.* (2010) A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis* 14: 642–649.

Chu, C., Chan, V., Lin, A., Wong, I., Leung, W. and Lai, C. (2004) Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. *Thorax* 59: 1020–1025.

Clini, E., Sturani, C., Rossi, A., Viaggi, S., Corrado, A., Donner, C. F. *et al.* (2002) The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 20: 529–538.

Costello, R., Deegan, P., Fitzpatrick, M. and McNicholas, W. (1997) Reversible hypercapnia in chronic obstructive pulmonary disease: A distinct pattern of respiratory failure with a favorable prognosis. *Am J Med* 102: 239–244.

Donaldson, G., Seemungal, T., Bhowmik, A. and Wedzicha, J. (2002) Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 57: 847–852.

Donaldson, G., Wilkinson, T., Hurst, J., Perera, W. and Wedzicha, J. (2005) Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 171: 446–452.

Dreher, M., Ekkernkamp, E., Walterspacher, S., Walker, D., Schmoor, C., Storre, J. *et al.* (2011) Non-invasive ventilation in COPD: Impact of inspiratory pressure levels on sleep quality. *Chest* 140: 939–945.

Dreher, M., Storre, H., Schmoor, C. and Windisch, W. (2010) High-intensity *versus* low-intensity noninvasive ventilation in stable hypercapnic COPD patients: A randomized cross-over trial. *Thorax* 65: 303–308.

Duiverman, M., Wempe, J., Bladder, G., Jansen, D., Kerstjens, H., Zijlstra, J. *et al.* (2008) Nocturnal non-invasive ventilation in addition to rehabilitation in hypercapnic patients with COPD. *Thorax* 63: 1052–1057.

Duiverman, M., Wempe, J., Bladder, G., Vonk, J., Zijlstra, J., Kerstjens, H. *et al.* (2011) Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. *Respir Res* 12: 112.

Echave-Sustaeta, J., Comeche Casanova, L., García Luján, R., Sayas Catalan, J., Gómez de la Cámara, A. and López Encuentra, A. (2010) Prognosis following acute exacerbation of COPD treated with non-invasive mechanical ventilation. *Arch Bronconeumol* 46: 405–410.

Funk, G., Breyer, M., Burghuber, O., Kink, E., Kirchheiner, K., Kohansal, R. *et al.* Long-term non-invasive ventilation in COPD after acute-on-chronic respiratory failure. *Respir Med* 105: 427–434.

Galli, J., Krahnke, J., James Mamary, A., Shenoy, K., Zhao, H. and Criner, G. (2014) Home non-invasive ventilation use following acute hypercapnic respiratory failure in COPD. *Respir Med* 108: 722–728.

Gay, P., Hubmayr, R. and Stroetz, R. (1996) Effectiveness of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. *Mayo Clin Proc* 71: 533–542.

Global Initiative for Chronic Obstructive Lung Disease (2015) *Global Strategy for the Diagnosis, Management and Prevention of COPD*. Available from: http://www.goldcopd.org/.

Hurst, J., Vestbo, J., Anzueto, A., Locantore, N., Müllerova, H., Tal-Singer, R. *et al.* for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators (2010) Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 363: 1128–1138.

Köhnlein, T., Windisch, W., Köhler, D., Drabik, A., Geiseler, J., Hartl, S. *et al.* for the COPD study group (2014) Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease. A prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2: 698–705.

Leger, P., Bedicam, J., Cornette, A., Reybet-Degat, O., Langevin, B., Polu, J. *et al.* (1994) Nasal intermittent positive pressure ventilation. Long-term follow-up in patients with severe chronic respiratory insufficiency. *Chest* 100: 100–105.

Lin, C. (1996) Comparison between nocturnal nasal positive pressure ventilation combined with oxygen therapy and oxygen monotherapy in patients with severe COPD. *Am J Respir Crit Care Med* 154: 353–358.

Lloyd-Owen, S., Donaldson, G., Ambrosino, N., Escarabill, J., Farre, R., Fauroux, B. *et al.* (2005) Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *Eur Respir J* 25: 1025–1031.

Lukácsovits, J., Carlucci, A., Hill, N., Ceriana, P., Pisani, L., Schreiber, A. *et al.* (2012) Physiological changes during low- and high-intensity noninvasive ventilation. *Eur Respir J* 39: 869–875.

McEvoy, R., Pierce, R., Hillman, D., Esterman, A., Ellis, E., Catcheside, P. *et al.* (2009) Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax* 64: 561–566.

Meecham Jones, D., Paul, E., Jones, P. and Wedzicha, J. (1995) Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *Am J Respir Crit Care Med* 152: 538–544.

Nocturnal Oxygen Therapy Trial Group (1980) Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive lung disease. *Ann Intern Med* 93: 39–48.

Ram, F., Picot, J., Lightowler, J. and Wedzicha, J. (2004) Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 3: CD004104.

Seemungal, T., Donaldson, G., Paul, E., Bestall, J., Jeffries, D. and Wedzicha, J. (1998) Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 157: 1418–1422.

Simonds, A. and Elliott, M. (1995) Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. *Thorax* 50: 604–609.

Soler-Catalu, J., Martez-Garc, M., Rom Schez, P., Salcedo, E., Navarro, M. and Ochando, R. (2005) Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 60: 925–931.

Stefan, M., Nathanson, B., Higgins, T., Steingrub, J., Lagu, T., Rothberg, M. *et al.* (2015) Comparative effectiveness of noninvasive and invasive ventilation in critically ill patients with acute exacerbation of chronic obstructive pulmonary disease. *Crit Care Med.* [Epub ahead of print]

Struik, F., Lacasse, Y., Goldstein, R., Kerstjens, H., Wijkstra, P. *et al.* (2014a) Nocturnal noninvasive positive pressure ventilation in stable COPD. A systematic review and individual patient data meta-analysis. *Respir Med* 108: 329–337.

Struik, F., Sprooten, R., Kerstjens, H., Bladder, G., Zijnen, M., Asin, J. *et al.* (2014b) Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for

acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax* 69: 826–834.

Strumpf, D., Millman, R., Carlisle, C., Grattan, L., Ryan, S., Erickson, A. *et al.* (1991) Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 144: 1234–1239.

Tuggey, J., Plant, P. and Elliott, M. (2003) Domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD: an economic analysis. *Thorax* 58: 867–871.

Vestbo, J. (2004) What is an exacerbation of COPD? *Eur Respir Rev* 13: 6–13.

Windisch, W., Kostic, S., Dreher, M., Virchow, J. and Sorichter, S. (2005) Outcome of patients with stable COPD receiving controlled noninvasive positive pressure ventilation aimed at a maximal reduction of $PaCO_2$. *Chest* 128: 657–662.

Windisch, W., Vogel, M., Sorichter, S., Hennings, E., Bremer, H., Hamm, H. *et al.* (2002) Normocapnia during nIPPV in chronic hypercapnic COPD reduces subsequent spontaneous $PaCO_2$. *Respir Med* 96: 572–579.