LONG-TERM NON-INVASIVE VENTILATION (NIV) FOR COPD PATIENTS WITH CHRONIC RESPIRATORY FAILURE

Stefano Nava,[1] Begüm Ergan[2]

1. Respiratory and Critical Care, Sant'Orsola Malpighi Hospital, Alma Mater Studiorum University of Bologna, Department of Specialist, Diagnostic and Experimental Medicine (DIMES), Bologna, Italy
2. Medical Intensive Care Unit, Department of Pulmonary and Critical Care, Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey

Disclosure: SN has received travel grants from Weinman, speaking fees from Respironics and ResMed, a research grant from Starmed, and free loans of equipment from Respironics, ResMed and Siare. BE has no conflicts of interest to declare.
Received: 20.08.13 **Accepted:** 16.10.13
Citation: EMJ Respir. 2013;1:54-62.

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a major health issue worldwide, with disease burden, healthcare costs, and mortality rates all significant and increasing. Non-invasive ventilation (NIV) is used to manage acute exacerbations of COPD associated with mild-to-moderate acidosis. Continuing NIV after discharge can reduce the risk of re-exacerbation, and decrease hospitalisation rates and healthcare resource use. A number of positive effects have been documented during NIV treatment in patients with stable hypercapnic COPD. These include reductions in hypercapnia and hypoxaemia, improvements in quality of life (QoL) and neuropsychological function, reduced hospital admissions and costs, and improved benefit from pulmonary rehabilitation. The effect of NIV targeting carbon dioxide reduction on long-term survival remains to be clearly determined, but is the subject of ongoing research. Overall, accumulating evidence suggests that NIV also has a role in the long-term management of stable hypercapnic COPD. It is expected that long-term NIV will be most useful for the subgroup of patients with frequent exacerbations of disease. Co-morbidities such as obesity, heart failure, or sleep-disordered breathing could further support the use of long-term NIV in the setting of stable hypercapnic COPD.

Keywords: Non-invasive ventilation, chronic obstructive pulmonary disease, randomised controlled trials, survival rate, hypercapnia.

INTRODUCTION

The term chronic obstructive pulmonary disease (COPD) encompasses the diagnoses of chronic bronchitis and emphysema. COPD is characterised by persistent, non-reversible airflow limitation. The main underlying feature is loss of elastic recoil of the lungs as a result of parenchymal destruction, along with airway inflammation.[1] The World Health Organization (WHO) estimates that 65 million people have moderate to severe COPD worldwide,[2] and COPD is a significant cause of mortality, ranking as the fifth leading cause of death in 2002.[2] The prevalence of COPD is rising; mortality from COPD is expected to increase to the third leading cause of death worldwide by 2030.[2]

Death from COPD is an important issue, however, the chronic nature of the disease and its significant impact on quality of life (QoL) (for patients and their caregivers) means that the burden of disease extends well beyond mortality. The European COPD Coalition estimates that the life experience of one in ten adults is limited by COPD.[3] Severe COPD has a symptom burden that is comparable to that of cancer,[4] and has a greater negative impact on health status than self-reported cardiovascular disease or diabetes.[5]

COPD also places a significant demand on healthcare resources. The annual direct cost of COPD in the US has been estimated to be more than $32 billion (USD),[6] and the mean in-hospital treatment cost for one patient with an acute exacerbation of COPD has been reported as $9,545 (USD).[7] In the European Union, total direct costs for respiratory disease account for around 6% of the total healthcare budget; in turn, COPD consumes 56% of the spend on respiratory disease (€38.6 billion).[8]

COPD is a chronic, progressive disease, and many patients will eventually develop chronic respiratory failure. This can be either hypoxic or hypercapnic in nature. Type 1 respiratory failure is characterised by hypoxaemia secondary to impaired gas exchange in the lungs, and can be treated by with long-term oxygen therapy. Hypercapnia is the main feature of type 2 respiratory failure and occurs as a result of impaired ventilation.[9] Type 2 respiratory failure is often associated with severe exacerbations of COPD,[10] and effective management strategies are essential.[11] Maintenance of appropriate gas exchange and sufficient ventilation has been highlighted as one of the key therapy objectives.[11] Clinical trial data show that mortality is much higher in COPD patients admitted to an intensive care unit (ICU) because of acute respiratory failure and who were discharged with non-reversible hypercapnia (defined as $PaCO_2$ ≥50 mmHg), than in those who were normocapnic at admission or discharge (reversible hypercapnia).[12] Higher mortality rates have also been documented in a subgroup of COPD patients who had a rise in $PaCO_2$ of ≥5 mmHg/year compared with those who had stable $PaCO_2$ values.[13]

NON-INVASIVE VENTILATION

Acute non-invasive ventilation (NIV) has been shown to be a very effective treatment approach in patients with an acute exacerbation of COPD with mild-to-moderate respiratory acidosis, reducing mortality, need for endotracheal intubation, and length of hospital stay.[14-21] For patients who are treated acutely, continuation of NIV at home after discharge from hospital may be associated with a lower risk of recurrent severe COPD exacerbation.[22] In patients with chronic, stable COPD, the use of NIV in the home appears to decrease the need for physician care and hospitalisation.[23-27] In COPD patients at risk of recurrent admission, the use of home-based NIV has the potential to reduce hospital admissions and healthcare resource use.[28]

Long-Term NIV in Chronic Hypercapnic COPD: The Rationale

Physiologic studies have shown that mechanical ventilation can improve alveolar ventilation while reducing inspiratory effort in patients with stable chronic hypercapnic respiratory failure.[29] The possibility that reductions in CO_2 could be maintained underlies the rationale for using NIV in patients with chronic hypercapnic respiratory failure. The concept that hypercapnia in stable COPD patients, and thus hypoventilation, may be caused by chronic muscle fatigue, is why it was suggested to rest the respiratory muscles. Diaphragmatic contractile dysfunction has also been documented, even in the early stages of COPD.[30] However, this has not been confirmed in autopsy studies looking at the remodelling of the diaphragm, although fatigue-resistant fibres were seen more frequently in COPD patients compared with controls.[31]

Patients with COPD are likely to develop nocturnal hypoventilation, especially during rapid eye movement (REM) sleep when upper airway tone and accessory muscle activity is impaired. Nearly half (42%) of the COPD patients in one study had a >10 mmHg increase in $PaCO_2$ at night, resulting in progressive resetting of respiratory control to higher $PaCO_2$ values.[32,33] A low central respiratory drive may also contribute to the development of hypercapnia in COPD.

A number of potential mechanisms have been proposed to explain the beneficial effects of NIV in hypercapnic patients with COPD. One study reported an increase in the central responsiveness to CO_2, which was associated with improved day time blood gases, however, no change in inspiratory muscle pressure was found.[34] Other possibilities include changes in lung mechanics, improvement in ventilation/perfusion (V/Q) matching, recruitment of non-ventilated or poorly-ventilated alveolar units, and decreased pulmonary hypertension. However, this remains a controversial area of research and has been for more than 20 years, with all the mechanisms proposed not being mutually exclusive and having the potential to contribute to beneficial effects to differing extents.[35]

*See page 58 for abbreviations

Table 1. NIV in chronic hypercapnic COPD: RCTs with duration ≥3months.

Author, Date Study type Pt numbers	Treatment arms (median/mean $PaCO_2$, mmHg)	Mean EPAP/IPAP (cmH_2O)	Mean NIV use	Effects of NIV
Strumpf, 1991[50] RCT, crossover, 7 pts completed	Nocturnal NIV+SC (49.0) SC (49.0)	2/15	6.7 h/night	•Improved neuropsychological function •No changes in gas exchange, lung function, respiratory muscle strength, exercise endurance, sleep quality, and dyspnea ratings
Meecham Jones, 1995[47] RCT, crossover 14 pts completed	Nocturnal NIV+LTOT (55.8) LTOT (55.8)	2/18	6.9 h/night	•Improved daytime and overnight hypoxaemia and hypercapnia, sleep time, sleep efficiency, and QoL •No effect on lung function or 6MWD
Gay, 1996[44] RCT, parallel 4 pts completed NIV 6 pts control	Nocturnal NIV (54.7) Sham control with lowest expiratory pressure (48.5)	2/10	5.1 h/night	•No effect on gas exchange, lung function, exercise capacity, and sleep, but proportion of REM sleep decreased
Garrod, 2000[43] RCT, parallel 17 pts (NIV) 20 pts (exercise)	NIV+exercise training (44.2) Exercise training (46.1)	4/16	2.1 h/day >4 h in 29% of pts	•Improved oxygenation, exercise capacity and QoL (CRDQ total and fatigue scores)
Casanova, 2000[23] RCT, parallel 20 pts (NIV +SC) 24 pts (SC)	Nocturnal NIV+SC (50.7) SC (53.2)	4/12	6.2 h/day (1st half of study) 5.9 h/day (2nd half of study) <3 h/day in 11% of pts	•Improved dyspnoea (Borg scale) and psychomotor coordination •No effect on gas exchange, pulmonary function, cardiac function, exacerbations (number and severity), hospitalisations, intubations, and survival •Hospitalisation rate decreased in the first 3 m but was similar in the treatment groups at 6 m
Clini, 2002[24] RCT, parallel 43 pts (NIV + LTOT) 47 pts (LTOT)	NIV+LTOT (54.0) LTOT (55.5)	2/14	9.2 h/day (study protocol criteria was use for ≥5 h/night)	•Improved hypercapnia, resting dyspnoea and HRQoL (MRF-28) •No effect on lung function, inspiratory muscle strength, exercise tolerance, sleep quality, hospital/ICU admissions and length of stay, or mortality
Duiverman, 2008[40] RCT, parallel 24 pts (NIV + rehab) 32 pts (rehab)	Nocturnal NIV+rehabilitation (51.7) Rehabilitation (51.1)	6/20	7.7 h/day	•Improved hypercapnia, minute ventilation in quiet breathing, HRQoL (CRDQ fatique domain, MRF-28 total score and cognition domain) and daily step count •No effect on hypoxaemia, lung function, exercise tolerance

McEvoy, 2009[46] RCT-parallel 72 pts (NIV + LTOT) 72 pts (LTOT)	Nocturnal NIV+LTOT (52.6) LTOT (54.4)	5/13	4.5 h/day >4 h/day in 60% of pts	•Improved survival, sleep-related hypercapnia and sleep architecture •No effect on gas exchange and pulmonary function (assessed in first 12 m in a subgroup of pts with available data) •Worsening QoL (assessed in first 12 m; SF-36 general health and mental health) and mood state (vigour and confusion-bewilderment variables)
Cheung, 2010[22] RCT, parallel 23 pts (NIV) 24 pts (CPAP)	NIV (76.5) CPAP with 5 cmH_2O (80.3)	5/15	7-9 h/night (average)	•Reduced risk of recurrent severe COPD exacerbation •No effect on gas exchange, time to first readmission, adverse events, and survival
Funk, 2011[42] RCT, parallel (after 6 m of NIV treatment) 13 pts continuation 13 pts withdrawal	NIV continuation (57.0) NIV withdrawal (56.0)	5/20	NR	•Higher probability of clinical worsening in the NIV withdrawal group •Improved daytime pH and exercise capacity •No effect on gas exchange, pulmonary function, HRQoL, and the incidences of antibiotic or oral steroid therapy due to COPD exacerbation
De Backer, 2011[36] RCT, parallel 10 pts (NIV) 5 pts (medical therapy)	NIV (55.4) Medical therapy (52.4)	NR	Study protocol criteria was use for >5 h/day	•Improved gas exchange (change in oxygenation correlated with improved ventilation-perfusion match in functional imaging) and exercise tolerance •No effect on lung function
Duiverman, 2011[41] RCT, parallel 24 pts (NIV + rehab) 32 pts (rehab)	Nocturnal NIV +rehabilitation (NR) Rehabilitation (NR)	6/23	6.9 h/day	•Significant improvements in gas exchange, exercise tolerance, dyspnoea, FEV_1 (annual decline was 17 mL in NIV+rehab group versus 83 mL in rehab group), mood and HRQoL (MRF-28, SRI physical function domain). •No change in exacerbation rate
Murphy, 2012[48] RCT, crossover 7 pts completed	High-pressure NIV (64.5) High-intensity NIV (64.5)	5/29	6 h 37 min/night (high pressure) 6 h 33 min/night (high intensity)	•Similar gas exchange, sleep quality and quantity, and patient adherence in both NIV treatment arms •Respiratory component of SRI was lower in the high-intensity NIV group

*6MWD: 6 minute walking distance; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; CRDQ: Chronic Respiratory Disease Questionnaire; EPAP: expiratory positive airway pressure; FEV_1: forced expiratory volume in one second; h: hour; HRQoL: health-related QoL; IPAP: inspiratory positive airway pressure; LTOT: long-term oxygen therapy; m: month; MRF-28: Maugeri Foundation Respiratory Failure questionnaire; NIV: non-invasive ventilation; NR: not reported; $PaCO_2$: partial arterial carbon dioxide tension; pt: patient; QoL,: quality of life; RCT: randomised controlled trial; REM: rapid eye movement; SC: standard care; SRI: Severe Respiratory Insufficiency questionnaire.

Long-Term NIV in Hypercapnic COPD: Clinical Studies

The effects of adding chronic NIV to long-term oxygen therapy have been assessed in a number of studies (Table 1).[22-24,28,36-50] The most commonly studied outcomes can be classified as: physiological (gas exchange, lung function, and respiratory mechanics), health-related (dyspnoea relief, exercise tolerance, and health-related QoL), and disease-related morbidity (exacerbation frequency and characteristics, hospitalisations, intensive care unit admissions, and intubations). To date, no clear effect of NIV on major outcomes such as survival has been documented.[22-24,28,36-43,45-50]

A number of positive effects have been reported with use of NIV in patients with stable hypercapnic COPD. These include: reductions in hypercapnia and hypoxaemia,[22-25,28,35-41,43-46] improvements in QoL[24,47,51] and neuropsychological function,[50] reduced hospital admissions and costs,[28] improved benefit from pulmonary rehabilitation,[40,41,43] and a higher survival rate.[46] Details of the results from randomised, controlled clinical trials with duration of ≥3 months are shown in Table 1, and the findings of non-randomised trials are shown in Table 2.

Critical analysis of the available data is appropriate before any definitive decisions are made about the use of NIV in stable hypercapnic COPD. The difference in results between studies could be due to a number of factors, including heterogeneous patient populations (resulting from differing inclusion/selection criteria), differences in ventilator, ventilator settings and interfaces, and choice of study endpoints (e.g. CO_2 reduction). Another factor to consider is the relatively small number of patients included in each of these studies (Table 1). The conclusions of a recent meta-analysis of data from seven randomised, controlled clinical trials stated that no definitive conclusions can be drawn regarding the effects of NIV because the quality of evidence is only moderate as a result of the small sample sizes.[52] Therefore, there is a need for studies in this area to enrol a larger number of patients to provide more robust data.

One of the most significant unresolved issues in the field of NIV for stable COPD is defining the optimum ventilation strategy. Before concluding that NIV has no beneficial effects, it is important to confirm that effective ventilation has in fact been delivered. Finding an appropriate physiological target to guide the choice of ventilator mode and settings has proven difficult; to date, this has usually been defined as a specified decrease in $PaCO_2$. Studies that have utilised lower inspiratory pressures (10–12 cmH_2O) have not reported any beneficial effects of NIV on gas exchange or pulmonary function.[23,44] Conversely, use of higher inspiratory pressures (16–22 cmH_2O) in one randomised, controlled trial was associated with positive results for NIV,[47] suggesting that higher ventilating pressures might be more effective. Data from a retrospective study using inspiratory pressures of 17–40 cmH_2O showed improvements in hypercapnia and FEV_1 after 2 months, and a 2 year survival rate of 86%. However, there was no control group and patients also received daytime ventilation.[53]

Adherence to NIV is also a factor which could influence the outcome of therapy. The majority of studies encourage patients to use NIV for at least 5 hours per night, and only randomised studies advocating this level of therapy for at least 3 weeks were included in one meta-analysis. However, the overall finding was for a lack of significant effect of NIV on lung function, gas exchange and sleep efficiency, although improved walk distance was noted in some patients.[54] It is interesting to note that studies, which included in their protocol sufficient time for familiarisation with NIV treatment, tended to show greater benefits.[24,53,55]

Although some beneficial effects of NIV on health-related outcomes have been reported, the variety of assessment tools used makes determination of the overall effect of NIV on these parameters very difficult. For example, dyspnoea has been

Table 2. NIV in chronic hypercapnic COPD: non-randomised trials.

Author, Date Study type Pt numbers	Study arms	Mean NIV use	Effects of NIV
Tuggey, 2003[28] 13 pts	Cost analysis in patients with recurrent exacerbations before and after domiciliary NIV	-	•Use of NIV decreased costs by €11,720 per patient per year •Number of hospital admissions decreased from 5 to 2 •Length of hospital stay decreased from 78 to 25 days
Nava, 2001[49] 13 pts (NIV) 8 pts (rehab)	Nocturnal NIV Rehabilitation	6.6 h/night	•Reduced resting $PaCO_2$ (associated with decreased diaphragmatic effort) •Acute reduction in $PaCO_2$ in the first trial of NIV was a strong predictor of the final outcome

COPD: chronic obstructive pulmonary disease; h: hours; NIV: noninvasive ventilation; $PaCO_2$: partial arterial carbon dioxide tension.

assessed using four different scales in different studies. Similar differences have been documented with respect to health-related QoL: studies that have used instruments that are validated and specific for chronic respiratory failure (such as the Maugeri Respiratory Failure-28 (MRF28) and Severe Respiratory Insufficiency questionnaires) have found NIV to have a positive effect on QoL, whereas trials utilising more general tools (Short Form-36 and St George's Respiratory Questionnaire) reported no change or even worsened QoL during NIV.[24,40,46,47,56] It is being increasingly recognised that disease-specific tools are more appropriate and useful in COPD patients with chronic respiratory failure.[55,57,58]

Long-Term NIV in Hypercapnic COPD: the Practicalities

Despite a lack of consensus and large-scale controlled clinical trial data, accumulating evidence for the beneficial effects of long-term NIV in hypercapnic COPD patients is starting to be incorporated into clinical practice guidelines. The UK NICE guidelines[59] state: "Adequately treated patients with chronic hypercapnic respiratory failure who have required assisted ventilation (whether invasive or non-invasive) during an exacerbation or who are hypercapnic or acidotic on LTOT should be referred to a specialist centre for consideration of long-term NIV." This recommendation refers to a very specific subgroup of patients with very severe disease who are at the highest risk for mortality and are likely to benefit from NIV therapy as a last resort.[22,34,42,60] In these patients, NIV might induce relative clinical stability by reducing the likelihood of recurrent exacerbations and hospitalisations. German invasive and non-invasive ventilation guidelines[61] recommend long-term NIV when $PaCO_2$ is >50 mmHg during the day, or >55 mmHg at night.

The Eurovent study showed that decisions about when and how to start NIV in patients with COPD are highly dependent on local guidelines and each physician's current clinical practice.[62] In addition, optimal ventilator settings for NIV in patients with chronic hypercapnic COPD are the subject of debate. It has been shown that the empirical titration of NIV (i.e. based on the clinician's experience and judgment) may result in worse patient/ventilator interaction and sleep compared with physiologic titration (i.e. based on recording of respiratory mechanics, with the goal of reducing inspiratory effort by ≥50% and the load imposed by the presence of intrinsic positive end-expiratory pressure (PEEP) by 80%).[63-65] Recently, high inspiratory pressures (≈30 cmH_2O) and respiratory rates (20 breaths/minute) were used to ventilate chronic hypercapnic COPD patients in order to achieve maximal $PaCO_2$ reduction.[39] This approach, called high-intensity NIV (HI-NIV), has been shown to improve spontaneous diurnal blood gases to a greater extent than the traditional approach using lower pressures.[39] In a physiological study, HI-NIV was

able to significantly improve $PaCO_2$ and work of breathing compared with low intensity NIV.[66] However, marked reductions in cardiac output and stroke volume might limit the application of HI-NIV in patients with pre-existing cardiac disease.[66] A long-term randomised study is ongoing in Germany to determine the effect of NIV targeting CO_2 reduction on long-term survival.[67] There is a practical consensus that patients with COPD who have substantial daytime hypercapnia and superimposed nocturnal hypoventilation are most likely to benefit from NIV.

Ventilator settings are often determined based on gas-exchange parameters recorded during the daytime and on patient-reported tolerance, but NIV is usually applied in order to correct nocturnal hypoventilation. Therefore, nocturnal monitoring and/or alternative monitoring with the ventilator software would be preferable to allow better titration of NIV pressures, taking into account sleep abnormalities.[68]

CONCLUSION

NIV is currently used primarily for the management of acute exacerbations of COPD. However, accumulating evidence suggests that NIV also has a role in the long-term management of patients with stable hypercapnic COPD. Early nocturnal NIV therapy in these patients may reduce hospitalisation rates, improve QoL, and reduce healthcare costs, but further research is needed. It is expected that long-term NIV will be most useful for hypercapnic COPD patients with frequent exacerbations of disease. Co-morbidities such as obesity or obstructive sleep apnoea (OSA) might be further factors that support the use of long-term NIV.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2013; http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf.

2. World Health Organization. Chronic Respiratory Diseases. COPD Burden. 2013; http://www.who.int/respiratory/copd/burden/en/. Accessed 6 August, 2013.

3. European COPD Coalition. Prevalence in EU. http://www.copdcoalition.eu/about-copd/prevalence. Accessed 6 August, 2013.

4. Joshi M, Joshi A, Bartter T. Symptom burden in chronic obstructive pulmonary disease and cancer. Curr Opin Pulm Med. 2012;18(2):97-103.

5. Janson C, Marks G, Buist S, et al. The impact of COPD on health status: findings from the BOLD study. Eur Respir J. 2013. [Epub ahead of print]

6. Owens RL, Malhotra A. Sleep-disordered breathing and COPD: the overlap syndrome. Respir Care. 2010;55(10):1333-46.

7. Perera PN, Armstrong EP, Sherrill DL, Skrepnek GH. Acute exacerbations of COPD in the United States: inpatient burden and predictors of costs and mortality. Copd. 2012;9(2):131-41.

8. European Respiratory Society, European Lung Federation. European Lung White Book. Sheffield: European Respiratory Society; 2003.

9. Roussos C, Macklem PT. The respiratory muscles. N Engl J Med. 1982;307(13):786-97.

10. Derenne JP, Fleury B, Pariente R. Acute respiratory failure of chronic obstructive pulmonary disease. Am Rev Respir Dis. 1988;138(4):1006-33.

11. Calverley PM. Respiratory failure in chronic obstructive pulmonary disease. Eur Respir J Suppl. 2003;47:26s-30s.

12. Costello R, Deegan P, Fitzpatrick M, McNicholas WT. Reversible hypercapnia in chronic obstructive pulmonary disease: a distinct pattern of respiratory failure with a favorable prognosis. Am J Med. 1997;102(3):239-44.

13. Aida A, Miyamoto K, Nishimura M, Aiba M, Kira S, Kawakami Y. Prognostic value of hypercapnia in patients with chronic respiratory failure during long-term oxygen therapy. Am J Respir Crit Care Med. 1998;158(1):188-93.

14. Angus RM, Ahmed AA, Fenwick LJ, Peacock AJ. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. Thorax. 1996;51(10):1048-50.

15. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet. 1993;341(8860):1555-7.

16. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333(13):817-22.

17. Celikel T, Sungur M, Ceyhan B, Karakurt S. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest. 1998;114(6):1636-42.

18. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med. 1995;151(6):1799-806.

19. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ. 2003;326(7382):185.

20. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet. 2000;355(9219):1931-5.

21. Thys F, Roeseler J, Reynaert M, Liistro G, Rodenstein DO. Noninvasive ventilation for acute respiratory failure: a prospective randomised placebo-controlled trial. Eur Respir J. 2002;20(3):545-55.

22. Cheung AP, Chan VL, Liong JT, et al. A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. Int J Tuberc Lung Dis. 2010;14(5):642-9.

23. Casanova C, Celli BR, Tost L, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest.

2000;118(6):1582-90.

24. Clini E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J. 2002;20(3):529-38.

25. Jones SE, Packham S, Hebden M, Smith AP. Domiciliary nocturnal intermittent positive pressure ventilation in patients with respiratory failure due to severe COPD: long-term follow up and effect on survival. Thorax. 1998;53(6):495-8.

26. Leger P, Bedicam JM, Cornette A, et al. Nasal intermittent positive pressure ventilation. Long-term follow-up in patients with severe chronic respiratory insufficiency. Chest. 1994;105(1):100-5.

27. Perrin C, El Far Y, Vandenbos F, et al. Domiciliary nasal intermittent positive pressure ventilation in severe COPD: effects on lung function and QoL. Eur Respir J. 1997;10(12):2835-9.

28. Tuggey JM, Plant PK, Elliott MW. Domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD: an economic analysis. Thorax. 2003;58(10):867-71.

29. Brochard L, Isabey D, Piquet J, et al. Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. N Engl J Med. 1990;323(22):1523-30.

30. Ottenheijm CA, Heunks LM, Sieck GC, et al. Diaphragm dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;172(2):200-5.

31. Levine S, Kaiser L, Leferovich J, Tikunov B. Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease. N Engl J Med. 1997;337(25):1799-806.

32. Becker HF, Piper AJ, Flynn WE, et al. Breathing during sleep in patients with nocturnal desaturation. Am J Respir Crit Care Med. 1999;159(1):112-8.

33. O'Donoghue FJ, Catcheside PG, Ellis EE, et al. Sleep hypoventilation in hypercapnic chronic obstructive pulmonary disease: prevalence and associated factors. Eur Respir J. 2003;21(6):977-84.

34. Elliott MW, Mulvey DA, Moxham J, Green M, Branthwaite MA. Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions. Eur Respir J. 1991;4(9):1044-52.

35. Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. Ann Inter Med. 1994;120(9):760-70.

36. De Backer L, Vos W, Dieriks B, et al. The effects of long-term noninvasive ventilation in hypercapnic COPD patients: a randomized controlled pilot study. Intern J Chron Obstruct Pulmon Dis. 2011;6:615-24.

37. Diaz O, Begin P, Andresen M, et al. Physiological and clinical effects of diurnal noninvasive ventilation in hypercapnic COPD. Eur Resp J. 2005;26(6):1016-23.

38. Diaz O, Begin P, Torrealba B, Jover E, Lisboa C. Effects of noninvasive ventilation on lung hyperinflation in stable hypercapnic COPD. Eur Respir J. 2002;20(6):1490-8.

39. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax. 2010;65(4):303-8.

40. Duiverman ML, Wempe JB, Bladder G, et al. Nocturnal non-invasive ventilation in addition to rehabilitation in hypercapnic patients with COPD. Thorax. 2008;63(12):1052-7.

41. Duiverman ML, Wempe JB, Bladder G, et al. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. Respir Res. 2011;12:112.

42. Funk GC, Breyer MK, Burghuber OC, et al. Long-term non-invasive ventilation in COPD after acute-on-chronic respiratory failure. Respir Med. 2011;105(3):427-34.

43. Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;162(4 Pt 1):1335-41.

44. Gay PC, Hubmayr RD, Stroetz RW. Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. Mayo Clin Proc. 1996;71(6):533-42.

45. Lin CC. 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. 1996;154(2 Pt 1):353-8.

46. McEvoy RD, Pierce RJ, Hillman D, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax. 2009;64(7):561-6.

47. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. Am J Respir Crit Care Med. 1995;152(2):538-44.

48. Murphy PB, Brignall K, Moxham J, Polkey MI, Davidson AC, Hart N. High pressure versus high intensity noninvasive ventilation in stable hypercapnic chronic obstructive pulmonary disease: a randomized crossover trial. Int J Chron Obstruct Pulmon Dis. 2012;7:811-8.

49. Nava S, Fanfulla F, Frigerio P, Navalesi P. Physiologic evaluation of 4 weeks of nocturnal nasal positive pressure ventilation in stable hypercapnic patients with chronic obstructive pulmonary disease. Respiration. 2001;68(6):573-83.

50. Strumpf DA, Millman RP, Carlisle CC, et al. Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. Am Rev Respir Dis. 1991;144(6):1234-9.

51. Tsolaki V, Pastaka C, Karetsi E, et al. One-year non-invasive ventilation in chronic hypercapnic COPD: effect on QoL. Respir Med. 2008;102(6):904-11.

52. Struik FM, Lacasse Y, Goldstein R, Kerstjens HM, Wijkstra PJ. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013;6:CD002878.

53. Windisch W, Kostic S, Dreher M, Virchow JC, Jr., Sorichter S. Outcome of patients with stable COPD receiving controlled noninvasive positive pressure ventilation aimed at a maximal reduction of Pa(CO2). Chest. 2005;128(2):657-62.

54. Wijkstra PJ, Lacasse Y, Guyatt GH, et al. A meta-analysis of nocturnal noninvasive positive pressure ventilation in patients with stable COPD. Chest. 2003;124(1):337-43.

55. Budweiser S, Hitzl AP, Jorres RA, Schmidbauer K, Heinemann F, Pfeifer M. Health-related QoL and long-term prognosis in chronic hypercapnic respiratory failure: a prospective survival analysis. Respir Res. 2007;8:92.

56. Windisch W, Freidel K, Schucher B, et al. Evaluation of health-related QoL using the MOS 36-Item Short-Form Health Status Survey in patients receiving noninvasive positive pressure ventilation. Intensive care Med. 2003;29(4):615-21.

57. Struik FM, Kerstjens HA, Bladder G, et al. The Severe Respiratory Insufficiency Questionnaire scored best in the assessment of health-related QoL in chronic obstructive pulmonary disease. J Clin Epidemiol. 2013;66(10):1166-74.

58. Windisch W, Freidel K, Schucher B, et al. The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related QoL in patients receiving home mechanical ventilation. J Clin Epidemiol. 2003;56(8):752-9.

59. National Institute of Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2010; http://publications.nice.org.uk/chronic-obstructive-pulmonary-disease-cg101. Accessed 6 August, 2013.

60. Chu CM, Chan VL, Lin AW, Wong IW, Leung WS, Lai CK. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure.

Thorax. 2004;59(12):1020-5.

61. Windisch W, Walterspacher S, Siemon K, Geiseler J, Sitter H, German Society for P. Guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure. Published by the German Society for Pneumology (DGP). Pneumologie. 2010;64(10):640-52.

62. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J. 2005;25(6):1025-31.

63. Fanfulla F, Delmastro M, Berardinelli A, Lupo ND, Nava S. Effects of different ventilator settings on sleep and inspiratory effort in patients with neuromuscular disease. Am J Respir Crit Care Med. 2005;172(5):619-24.

64. Fanfulla F, Taurino AE, Lupo ND, Trentin R, D'Ambrosio C, Nava S. Effect of sleep on patient/ventilator asynchrony in patients undergoing chronic non-invasive mechanical ventilation. Respir Med. 2007;101(8):1702-7.

65. Vitacca M, Nava S, Confalonieri M, et al. The appropriate setting of noninvasive pressure support ventilation in stable COPD patients. Chest. 2000;118(5):1286-93.

66. Lukacsovits J, Carlucci A, Hill N, et al. Physiological changes during low- and high-intensity noninvasive ventilation. Eur Resp J. 2012;39(4):869-75.

67. Kohnlein T, Criee CP, Kohler D, Welte T, Laier-Groeneveld G. [Multicenter study on "non-invasive ventilation in patients with severe chronic obstructive pulmonary disease and emphysema(COPD)"]. Pneumologie. 2004;58(8):566-9.

68. Janssens JP, Borel JC, Pepin JL, SomnoNIV Group. Nocturnal monitoring of home non-invasive ventilation: the contribution of simple tools such as pulse oximetry, capnography, built-in ventilator software and autonomic markers of sleep fragmentation. Thorax. 2011;66(5):438-45.