W. Windisch

Department of Pneumology, Clinic of Cologne, University of Witten/Herdecke

Clinic of Cologne, University of Witten/Herdecke, Department of Pneumology, Ostmerheimer Strasse 200, D-51109 Köln

windischw@kliniken-koeln.de

Noninvasive positive pressure ventilation in COPD

Educational aims

- To take up the ongoing debate on whether long-term noninvasive positive pressure ventilation (NPPV) should be applied in chronic obstructive pulmonary disease (COPD) patients with chronic hypercapnic respiratory failure.
- To elucidate the impact of NPPV techniques on NPPV success in COPD.
- To describe the technique and scientific evidence for the new concept of high-intensity NPPV.
- To provide practical considerations on how to commence high-intensity NPPV.
- To outline important unknowns regarding long-term NPPV in COPD patients.

Summary

Home mechanical ventilation, as provided by long-term NPPV, is a widely accepted treatment option for many patient groups with chronic hypercapnic respiratory failure, including also those with COPD, even though the rationale for long-term NPPV in COPD patients is still disputed. This is based on clinical observations that conventional NPPV using assisted ventilation and low mean inspiratory pressures of <18 cmH_2O reportedly failed to effectively improve respiratory function, most importantly gas exchange, while outcomes are also not convincingly improved by the addition of long-term NPPV to long-term oxygen treatment.

Recently, however, a promising technique of NPPV has been described, which aims at maximally improving gas exchange by the use of controlled ventilation and considerably higher inspiratory pressures, typically ranging 20–40 cmH_2O. This is known as high-intensity NPPV. This approach clearly contrasts with the conventional, low-intensity approach.

High-intensity NPPV has been shown to improve physiological parameters such as breathing pattern, gas exchange and lung function. In addition, it also provides clinical benefits, with improvements in dyspnoea, walking distance and specific aspects of health-related quality of life. The superiority of high- over low-intensity NPPV has been clearly established by randomised crossover trials.

HERMES syllabus link: modules B.1.4, D.1.6

Increasing evidence now exists to support the contention that long-term high-intensity NPPV offers a new therapeutic option in the treatment of hypercapnic COPD. However, the questions of whether high-intensity NPPV is also capable of improving survival and how to best select candidates to undergo long-term high-intensity NPPV remain pressing. This article also provides detailed practical descriptions of how to initiate high-intensity NPPV.

Chronic respiratory failure in COPD

The respiratory system

The respiratory system consists of two independent parts [1, 2]: the lungs, which are responsible for gas exchange; and the respiratory pump, which regulates mechanical movements to ventilate the lungs.

Any pathology of the lungs causes pulmonary failure leading to hypoxaemic respiratory failure. This indicates that gas exchange is impaired, with oxygen being primarily affected because of its poorer diffusion capacities compared with carbon dioxide. In this scenario, hypoxaemia, but not hypercapnia, is present on blood gas analysis. Pulmonary failure may even be accompanied by hypocapnia resulting from an increased demand of ventilation aimed at compensating for hypoxaemia.

This contrasts with ventilatory failure that primarily leads to hypercapnia in addition to hypoxaemia as a result of reduced alveolar ventilation. Ventilatory failure indicates failing of the respiratory pump and is most often the result of either an increased load being imposed on the respiratory muscles, or a decreased capacity of the respiratory muscles, or both, but it can also result from disturbances in respiratory drive [1, 2]. Acute development of ventilatory failure results in respiratory acidosis following increasing arterial carbon dioxide tension (P_{a,CO_2}). In contrast, when hypercapnia, and therefore, ventilatory failure occurs chronically, respiratory acidosis is typically compensated by metabolic (renal) retention of bicarbonate. This scenario is called chronic hypercapnic respiratory failure (chronic HRF).

Treatment of chronic respiratory failure in COPD patients

The choice of treatment of chronic respiratory failure in COPD patients depends primarily on which part of the respiratory system is impaired. Chronic pulmonary failure with the hallmark of hypoxaemia is a well-justified basis for long-term oxygen treatment (LTOT), with well-documented improvements in long-term survival in COPD patients [3, 4]. In contrast, chronic HRF coupled with reduced alveolar ventilation requires artificial augmentation of alveolar ventilation, which can only be achieved by long-term mechanical ventilation, *i.e.* home mechanical ventilation (HMV). Typically, these patients also require LTOT in addition to HMV in order to manage chronic pulmonary and ventilatory failure simultaneously. HMV is typically performed intermittently with periods of mechanical ventilation followed by periods of spontaneous breathing; here, nocturnal ventilation is most often preferred allowing the patient to breathe spontaneously during daily activity, but a broad variety exists regarding daily use with extension of the duration as chronic HRF progresses [5–7].

In general, there are two different forms of delivery of long-term HMV [5–7]:

- Long-term invasive mechanical ventilation, which requires mechanical ventilation *via* stable tracheostoma.
- NPPV, which is typically delivered by connecting the natural airways of a patient and the artificial airways of the ventilator system by the use of face masks covering either the nose alone (nasal masks) or both the mouth and the nose (oronasal masks) [8].

For elective establishment of HMV, long-term NPPV is most often preferred over long-term invasive mechanical ventilation as long-term handling of the tracheostoma requires regular suctioning of airway secretions and higher amounts of nursing, impairs speaking and swallowing and impairs social life, particularly during periods of spontaneous breathing. Nevertheless, patients with unsuccessful weaning following intubation and mechanical ventilation to manage acute respiratory failure form an

increasingly important group of COPD patients with invasive long-term mechanical ventilation following tracheostomy [9].

Long-term NPPV in COPD

Introduction

Over the past three decades, NPPV as used for HMV has become a widely accepted treatment option for patients with chronic HRF that arises from various aetiologies such as COPD, restrictive thoracic disorders, neuromuscular disorders and obesity hypoventilation syndrome [5–7]. There is increasing evidence that HMV is capable of improving symptoms and health-related quality of life (HRQoL) in these patients [5–7, 9–12]. Thus, HMV should generally be considered in every patient presenting with symptomatic chronic HRF. Notably, robust data from uncontrolled studies are now available to support the notion that survival is increased when long-term NPPV is used to treat chronic HRF resulting from a range of restrictive and neuromuscular diseases [5–7, 12, 13], most importantly Duchenne muscular dystrophy [14]. While no randomised controlled trials have been performed to compare directly the outcome of patients who receive long-term NPPV with those who do not, such trials will, presumably, never be conducted because of ethical concerns. However, this further emphasises the rationale of long-term NPPV as used for HMV in restrictive and neuromuscular patients.

In clear contrast, the impact of HMV on survival in patients with COPD is still a matter of debate, and the rationale for long-term NPPV in COPD patients has been continually challenged [15, 16]. The aim of this article is, therefore, to take up the ongoing debate on whether long-term NPPV should be applied in COPD patients with chronic HRF. Importantly, the impact of NPPV techniques on NPPV success will be discussed, with the new concept of high-intensity NPPV being described and evaluated according to the most recent literature. Practical considerations regarding high-intensity NPPV will be provided in detail.

The classic randomised controlled trials

In 2003, a meta-analysis including the four most important randomised controlled trials (RCTs) at that time concluded that 3 months of NPPV in COPD patients did not improve lung function, gas exchange or sleep efficiency [15]. Importantly, P_{a,CO_2} did not improve: it only decreased nonsignificantly, by 1.5 mmHg. Thus, NPPV did not measurably augment alveolar ventilation. This is in clear contrast to studies on patients with restrictive diseases, in whom NPPV has been shown to result in considerable improvements in blood gases, both while on NPPV and during subsequent spontaneous breathing [5–7, 12, 17].

It should be noted that assisted but not controlled ventilation was used in all studies included in this meta-analysis, and inspiratory positive airway pressures (IPAP) were low (table 1).

The subsequent study by CLINI et al. [18] used pressure support ventilation set in the spontaneous/timed mode and with a back-up respiratory rate of 8 breaths·min^{-1}, indicating that assisted ventilation was primarily used [18]. Again, pressure levels were low, although IPAP was set to the individually tolerated maximum (table 1). As a consequence, the effect of NPPV on P_{a,CO_2} was negligible and survival was not improved by the addition of long-term NPPV to LTOT compared with LTOT alone. Very similarly, in a study by CASANOVA et al. [19], NPPV using comparably low pressure settings improved neither alveolar ventilation as estimated from P_{a,CO_2} nor survival.

Interestingly, low pressure settings were again used in the most recent long-term RCT, from Australia [20] (table 1), although the physiological ineffectiveness of this approach had been well documented in all preceding RCTs. Predictably, after 12 months, there was again no clear reduction in P_{a,CO_2} during

Table 1 Mean inspiratory positive airway pressures (IPAP) and mean expiratory positive airway pressures (EPAP) in the six randomised controlled trials on noninvasive positive pressure ventilation in chronic obstructive pulmonary disease patients. The first four trials were included in the meta-analysis published in 2003 [15]

First author	Date of publication	Reference	IPAP cmH$_2$O	EPAP cmH$_2$O
STRUMPF	1991	21	15	2
MEECHAM JONES	1995	22	18	2
GAY	1996	23	10	2
CASANOVA	2000	19	12	4
CLINI	2002	20	14	2
MCEVOY	2009	20	13	5

spontaneous breathing in the NPPV group compared with the patients receiving LTOT alone, although transcutaneously measured carbon dioxide tension improved while on nocturnal NPPV. With 144 patients, this is the largest study to date, and although it did show a slight survival benefit for patients receiving NPPV, it was at the cost of reduced HRQoL.

In summary, between 1991 and 2009, several RCTs assessed the effects of long-term NPPV when added to LTOT compared with LTOT alone. All these studies used considerably low IPAP settings. As a consequence, improvements in alveolar ventilation as estimated from P_a,CO_2 were minor and no clear improvement in outcome has been shown in those trials that have assessed outcome. The conventional approach of long-term NPPV using low pressure settings that fails to improve gas exchange can therefore not be regularly recommended for COPD patients with chronic HRF.

The level of IPAP is important

It is important to note that the RCT that used the highest IPAP level (mean IPAP 18 cmH$_2$O) also produced the strongest reduction in P_a,CO_2 [22]. Very similarly, a recent systematic review again concluded that RCTs did not show improved gas exchange when NPPV was used, but a subset of non-RCTs were mentioned, in which gas exchange, dyspnoea and HRQoL were reportedly improved while lung hyperinflation and diaphragmatic work of breathing

were reduced by NPPV [16]. These trials used considerably higher pressure settings than the RCTs included in the systematic review. This clearly underlines the importance of sufficient pressure levels for successful long-term NPPV in COPD patients. This has led to the development of high-intensity NPPV.

High-intensity NPPV

Definition

High-intensity NPPV refers to a new approach to NPPV that aims at maximally improving gas exchange in COPD patients with chronic HRF by increasing ventilator settings to the individually tolerated maximum if necessary or to the level necessary to achieve normocapnia (table 2). Several trials have now established this concept for COPD patients [11, 17, 24–33]. For the purpose of maximally decreasing elevated P_a,CO_2 values, controlled ventilation with high IPAP levels typically ranging 20–40 cmH$_2$O is implemented in the hospital setting and subsequently used for HMV. This technique clearly contrasts with the conventional approach to using assisted ventilation with low inspiratory positive pressures (table 1).

Physiological and clinical effects of high-intensity NPPV

High-intensity NPPV is very effective. Several physiological variables and parameters are reportedly improved by high-intensity NPPV (table 3). Most importantly, from a physiological point of view, high-intensity NPPV results in an improved breathing pattern and gas exchange. It also improves lung function. At first glance, this may be incomprehensible. However, it has been suggested that NPPV has an effect on the airways. Possible mechanisms that have been put forward include a reduction in airway oedema or even stretching open of chronically fibrosed airways [34]. In particular, reduction of airway oedema, which may be caused by hypercapnia [35], seems to be important and underlines why maximal reduction of P_a,CO_2 is physiologically important.

The physiological effectiveness of high-intensity NPPV also transfers to clinical benefits (table 3). Most importantly, high-intensity NPPV has been shown to improve dyspnoea, walking distance and specific aspects of HRQoL.

Table 2 *High-intensity noninvasive positive pressure ventilation (NPPV)*

Definition and aims	• Originally described for patients with chronic hypercapnic respiratory failure due to COPD • Long-term NPPV aimed at achieving normocapnia or – if hypercapnia cannot be totally avoided – lowest possible P_a,CO_2 values using high ventilator settings, as maximally tolerated or necessary
Device and mode	• Home care devices are typically used • Pressure-limited NPPV is preferred (fewer gastrointestinal side effects due to less variation in peak inspiratory pressures), but using volume-limited NPPV is also possible • Mode: assist/control

Conventional (low-) *versus* high-intensity NPPV: RCTs

In a recent crossover trial, the new concept of high-intensity NPPV (mean IPAP 29 mbar and controlled ventilation) was compared directly to the conventional approach (assisted ventilation, mean IPAP 15 mbar), labelled as low-intensity NPPV [24]. Both strategies have been used for 6 weeks at home in random order, respectively. The mean treatment effect between low- and high-intensity NPPV was >9 mmHg for nocturnal Pa,CO$_2$ (primary outcome) in favour of high-intensity NPPV. High-intensity NPPV was thus shown to be superior to the conventional and widely used form of low-intensity NPPV in terms of controlling nocturnal hypoventilation. As a consequence, high-intensity NPPV, but not low-intensity NPPV, improved dyspnoea during physical activity, lung function and specific aspects of HRQoL [24].

It might be speculated that high-intensity NPPV would not be nearly as well tolerated as low-intensity NPPV. Interestingly, the opposite turns out to be true: patients spent on average 3.6 additional hours per day on NPPV when using high-intensity NPPV compared with the average time spent on low-intensity NPPV [24]. In addition, drop-outs occurred only while on low- but not on high-intensity NPPV [24]. Thus, more effective ventilation as achieved by more aggressive forms of NPPV results in better patient adherence, which is attributable to improved HRQoL and more effectively ameliorated symptoms as shown by this trial. However, more days (on average 2.5) spent in hospital were necessary to get patients acclimatised to high-intensity NPPV compared with low-intensity NPPV [24]. Given the clear advantages of high-intensity NPPV, however, this additional time would appear to be justified.

Another important issue is leakage during nocturnal NPPV [30]. Here, it might be suspected that higher ventilator settings, and, as a consequence, higher amounts of leakage, provided by high-intensity NPPV would disrupt sleep quality. High-intensity NPPV does indeed produce more leakage than low-intensity NPPV [24]. However, a very recent trial directly comparing high- and low-intensity NPPV in a crossover design demonstrated that sleep quality was comparable between both approaches [31]. In addition, sleep quality was reportedly good during high-intensity NPPV [31].

Another very recent physiological randomised crossover study confirmed that high-intensity

Table 3 Physiological and clinical effects of high-intensity noninvasive positive pressure ventilation (NPPV) [11, 17, 24–33]

Physiological effects

- Improvement in blood gases during NPPV
- Improvement in daytime blood gases during subsequent spontaneous breathing following periods of nocturnal NPPV
- Improvement in breathing pattern with increased tidal volume during spontaneous breathing following periods of nocturnal NPPV
- Improvement in lung function
- Improvement in global inspiratory muscle strength
- Increments in haematocrit in anaemic patients
- Reduction of haematocrit in patients with polyglobulia
- Superior to conventional (low-intensity) NPPV using assisted ventilation with low IPAP regarding the improvement of blood gases

Clinical effects

- Improvement in HRQoL assessed by questionnaires specific to CRF
- Improvement in dyspnoea during walking while breathing spontaneously
- Improvement in dyspnoea and walking distance during NPPV-aided walking compared with walking unaided by NPPV
- Acceptable sleep quality
- Superior adherence to therapy *versus* conventional (low-intensity) NPPV using assisted ventilation with low IPAP

NPPV is more effective than conventional (low-intensity) NPPV in improving gas exchange and in reducing inspiratory effort [33]. However, this study also revealed that high-intensity NPPV may induce a reduction in cardiac output. Although the clinical impact of this observation still needs to be verified, as this was a purely physiological study, care must be taken in patients with pre-existing cardiac disease when considering high-intensity NPPV. Despite this, robust data now exist to support the use of high-intensity NPPV as the first choice for HMV in patients with COPD.

Practical approach: how to establish high-intensity NPPV

High-intensity NPPV is typically established in a step-wise approach. Although complex treatment modalities often require an individually adapted procedure, the single steps necessary for initiating high-intensity NPPV have a typical

order as listed in table 4. This approach is successful in the majority of cases and can be used as guidance, particularly by beginners. Nevertheless, changing the order or using a modified approach may sometimes increase success and may be used by more experienced persons. Pitfalls and practical advice for solving problems while initiating high-intensity NPPV are listed in table 5.

Important unknowns, future considerations and final conclusion

Long-term survival

High-intensity NPPV offers a new and promising therapeutic option in the treatment of chronic HRF that arises from COPD, as it improves several physiological and clinical parameters. However, a pressing question remains: is long-term high-intensity NPPV also capable of prolonging life in these patients? This has yet not been investigated, and needs to be tested by future long-term RCTs.

HRQoL

It is a matter of debate whether improved long-term survival is the most important aim of long-term NPPV in advanced COPD patients. Improvements of sleep quality, dyspnoea, HRQoL and physical activity appear to be at least comparably important.

In particular, the evaluation of HRQoL is important for patients with chronic and non-curable disorders, such as end-stage COPD [36–38]. Furthermore, from a patient's point of view, the effect of HMV on HRQoL may be even more important than its effect on long-term survival.

It is important to note that the choice of tool used to assess HRQoL in clinical trials substantially impacts on the results, and that specific treatment interventions, such as HMV, can only be reliably evaluated in case of specific questionnaires being used to assess the effects of treatment on HRQoL. For example, in the previously mentioned Australian RCT, HRQoL deteriorated during HMV [20]. Here, instruments specific to chronic HRF were not used, NPPV was physiologically only sparsely effective and mean adherence to therapy was only 4.5 hours per night, which could explain the findings of deteriorating HRQoL.

Two questionnaires have been specifically designed to assess HRQoL in COPD patients with chronic respiratory failure: the Maugeri Foundation Respiratory Failure item set (MRF-28); [39] and the Severe Respiratory Insufficiency Questionnaire (SRI) [40, 41], the latter being specific for chronic HRF and patients receiving HMV. Several professional translations of the SRI have been or are being provided (table 6).

Table 4 *High-intensity noninvasive positive pressure ventilation (NPPV): practical approach*

- Use NPPV in the daytime first, with the primary aim of establishing tolerance, but also with control of blood gases and vital parameters including blood pressure.

- Start with assisted NPPV first. For this purpose, the lowest back-up respiratory rate and most sensitive trigger threshold are typically used in addition to low IPAP levels, normally ranging between 12–16 cmH$_2$O. EPAP levels are low at this time.

- Once assisted NPPV is tolerated, carefully increase IPAP in a step-wise approach until maximal tolerance is reached, usually up to 30 (range 20–40) cmH$_2$O. The individually tolerated maximum may differ greatly between individuals.

- Next, increase the respiratory rate just beyond the spontaneous rate (not more) to establish controlled ventilation, but avoid excessively high respiratory rate settings that cause dynamic hyperinflation.

- Then, set EPAP in order to avoid dynamic hyperinflation according to subjective comfort (usually 3 and 6 cmH$_2$O), and similarly, set the inspiratory:expiratory ratio to 1:2 or lower. EPAP settings may be higher when upper airway obstruction is simultaneously treated (COPD + obstructive sleep apnoea syndrome).

- Once daytime tolerance is acceptable, apply nocturnal NPPV. Do not apply nocturnal NPPV too early when the patient is not comfortable with daytime NPPV.

- Adjust ventilator settings according to subjective tolerance and nocturnal monitoring of blood gases. Sometimes settings can be modified considerably at the first control visit in hospital after the patients has been acclimatised to NPPV at home for some weeks.

Table 5 *Pitfalls and practical advice for problems with setting up high-intensity noninvasive positive pressure ventilation (NPPV) in COPD patients*

- Tolerance of higher IPAP levels can last from minutes to several days or even weeks: individual adjustment is inevitable. Sometimes significant modification of settings is feasible at the first control in-hospital visit after having discharged patients for acclimatisation in the home environment.
- In cases of co-existing upper airway obstruction, higher EPAP levels are required. On the other hand, higher EPAP reduces the effective IPAP (which is IPAP minus EPAP); thus, avoid high EPAP levels if not required.
- For controlled NPPV (final aim), respiratory rates are typically set to 1 breath·min^{-1} higher than during spontaneous breathing; thus, avoid excessively high respiratory rates, even though controlled ventilation is the aim.
- Try out several masks. For nocturnal NPPV, use oronasal masks because of potentially substantial leakage; for daytime NPPV, a nasal mask is often better tolerated. Again: individual adjustment is mandatory.
- Several days in hospital are usually necessary to establish high-intensity NPPV.
- Use humidification in cases of dry mucous membrane.
- Leakage is unavoidable, but should be kept as low as possible.
- Gastrointestinal side-effects can be managed by medication, positioning and adjustment (reduction) of ventilator settings; here, pressure-limited NPPV is superior to volume-limited NPPV.
- Care must be taken in patients with pre-existing cardiac disease as high-intensity NPPV may induce a reduction in cardiac output.

Importantly, HRQoL has been shown to improve substantially following NPPV commencement when using both the MRF-28 [11] and the SRI [11, 17, 24, 32]. In particular, HRQoL benefits gained by long-term high-intensity NPPV are reportedly substantial in COPD patients and comparable to those in patients with restrictive and neuromuscular diseases [11]. Therefore, there is no doubt that HRQoL improves in COPD patients when NPPV is physiologically effective and when HRQoL is assessed by appropriate questionnaires.

NPPV during physical activity

NPPV has also been used during physical activity. High-intensity NPPV when applied during walking increased gas exchange, dyspnoea and walking distance [32]. A 3-month RCT demonstrated that NPPV also augmented the benefits of pulmonary rehabilitation in patients with chronic HRF due to COPD, particularly regarding gas exchange and HRQoL, again specifically assessed by the MRF-28 and the SRI [48]. This further demonstrates that the indication for NPPV is broader than just improved survival.

Patient selection

Scientifically established criteria for patient selection in high-intensity NPPV are missing

and need to be established in the future. It may be possible that patients with severe symptoms may benefit primarily in terms of HRQoL improvements. In addition, those patients with recurrent exacerbations producing respiratory acidosis may benefit in terms of survival. This is purely speculative, of course, but recent research has demonstrated that the institution of long-term NPPV following an acute exacerbation

Table 6 *Severe Respiratory Insufficiency Questionnaire (SRI): intercultural adaption*

Language	Status	References
German	Original version validated	[40, 41]
Spanish	Translated version validated	[42, 43]
English	Translated version validated	[44]
Norwegian	Translated version validated	[45]
Dutch	Translation finished	[46]
French	Translation finished	[47]
Swedish	Translation finished	
Greek	Translation finished	
Japanese	Translation finished	
Hebrew	Translation in progress	

complicated by respiratory acidosis and the need for acute mechanical ventilation was capable of preventing recurrent clinical deterioration [49, 50]. Whether this impacts on survival needs to be elucidated in the future.

Conclusion

There is an ongoing debate about whether long-term NPPV should be used to treat chronic hypercapnic respiratory failure arising from COPD. The conventional approach using assisted ventilation and low inspiratory pressures of <18 cmH_2O produces only minor physiological improvements and lacks clear evidence for improved quality of life and survival. In contrast, the new approach of high-intensity NPPV using controlled ventilation and inspiratory pressures of >20 (on average 30) cmH_2O is promising as it clearly improves breathing pattern, blood gases, lung function, dyspnoea, walking distance and aspects of quality of life, which are specific to chronic respiratory failure, but its impact on long-term survival still needs to be elucidated. Notably, the superiority of high- over low-intensity NPPV has been clearly established by randomised cross-over trials. However, it should be acknowledged that most of the evidence and experience favouring high-intensity NPPV as described in this article comes from the research of the author of this article and from his group, although other groups have recently documented the feasibility of this approach [33]. Nevertheless, more experience with high-intensity NPPV at different centres and in different countries is needed. For this purpose, the present article has provided detailed descriptions of how to practically initiate high-intensity NPPV in COPD patients with chronic HRF.

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