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High-intensity non-invasive ventilation in stable hypercapnic COPD: Evidence of efficacy and practical advice

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ABSTRACT

Patients with end-stage chronic obstructive pulmonary disease (COPD) frequently develop chronic hypercapnic respiratory failure (CHRF), with disabling symptoms and poor survival. The use of long-term nocturnal non-invasive ventilation (NIV) to treat CHRF in COPD has long been subject of debate due to conflicting evidence. However, since the introduction of high-intensity NIV (HI-NIV) in COPD, physiological and clinical benefits have been shown. HI-NIV refers to specific ventilator settings used for NIV aimed at achieving normocapnia or the lowest partial arterial carbon dioxide pressure ($PaCO_2$) values as possible. This review will provide an overview of existing evidence of the efficacy of HI-NIV stable COPD patients with CHRF. Secondly, we will discuss hypotheses underlying NIV benefit in stable hypercapnic COPD, providing insight into better patient selection and hopefully more individually titrated HI-NIV. Finally, we will provide practical advice on how to initiate and follow-up patients on HI-NIV, with special emphasis on monitoring that should be available during the initiation and follow-up of HI-NIV, and will discuss more extended monitoring techniques that could improve HI-NIV treatment in the future.

Key words: chronic obstructive pulmonary disease, electromyography, non-invasive ventilation, monitoring.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease with high morbidity and mortality worldwide.[1] Patients with end-stage COPD frequently develop chronic hypercapnic respiratory failure (CHRF). CHRF results in fatigue, (morning) headache, loss of energy and dyspnoea leading to impaired health-related quality of life (HRQoL).[2] Moreover, chronic hypercapnia seems to be related to poorer survival[3–5] and repeated hospitalizations with acute-on-chronic respiratory failure, a condition that has also been associated with poor survival.[6]

The use of long-term nocturnal non-invasive ventilation (NIV) to treat CHRF in COPD has long been subject of debate due to conflicting evidence.[7–16] However, since the introduction of high-intensity NIV (HI-NIV), physiological and clinical benefits of long-term NIV have been shown in patients with COPD.[17–23] HI-NIV refers to specific ventilator settings aimed at achieving normocapnia or lowest $PaCO_2$ values as possible.[24] As the most important feature of HI-NIV is setting a clear gas exchange goal, titration of HI-NIV settings is a form of 'personalized medicine'. Nevertheless, for achieving HI-NIV goals in COPD, often both a high inspiratory positive airway pressure (IPAP) level and a high back-up respiratory rate (BURR) are required, although the additional effect of the latter is debated.[25]

This review gives an overview of existing evidence of efficacy of HI-NIV in stable hypercapnic COPD patients. Furthermore, we will discuss the hypotheses why HI-NIV is of benefit. Finally, we will provide practical advice on how to initiate and follow-up patients on HI-NIV.

EVIDENCE OF EFFICACY OF HI-NIV IN STABLE HYPERCAPNIC COPD

The idea of HI-NIV being the mode of ventilation with which meaningful clinical benefits could be obtained stems from positive trials using higher inspiratory pressures,[12,16] as compared to negative trials using lower inspiratory pressures.[7–11,14,15] In this section, we will discuss two older trials using higher inspiratory pressures (>18 cm H_2O), the initial (uncontrolled) trials and finally the randomized controlled trials (RCT) confirming the benefits of HI-NIV in COPD.

More than 20 years ago, Meecham Jones *et al.*[12] investigated in a randomized cross-over trial whether NIV with the highest tolerated IPAP/expiratory positive airway pressure (EPAP) gradient added benefit compared to long-term oxygen alone. They included a small, well-defined group of COPD patients with a

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mean $PaCO_2$ of 55.8 mm Hg before the start of the therapy. They showed that patients on NIV had improved daytime and nocturnal gas exchange, improved sleep quality and HRQoL. With a mean IPAP of 18 cm H_2O and a low EPAP of maximum 4 cm H_2O in the spontaneous mode (S-mode; i.e. without BURR), a reduction in daytime $PaCO_2$ of 3.3 mm Hg compared to baseline values and 4.5 mm Hg compared to the period with additional oxygen alone was achieved. Interestingly, they showed a quite consistent association between improvement in nocturnal and daytime gas exchange, which seems logical, and is the essence of the HI-NIV idea: one should take care that NIV truly improves gas exchange before other (daytime) effects can be expected.

Diaz *et al.*[16] titrated NIV towards the highest tolerated IPAP, for 3 h/day, 5 days/week for a total of 3 weeks. Interestingly, EPAP was set at 2 cm H_2O. Using daytime awake NIV, they showed impressive reductions in lung hyperinflation, thereby reducing inspiratory loads, related to a concomitant decrease in hypercapnia of 8.3 mm Hg. Forced expiratory volume in 1 s (FEV_1) increased, which the authors attributed to a decrease in lung hyperinflation and thus volume recruitment, as the change in FEV_1 was accompanied by a proportional increase in forced vital capacity (FVC). Unfortunately, studies of nocturnal NIV have not been able to repeat these impressive benefits on lung hyperinflation. One might hypothesize that the daytime awake situation as compared to sleep could have a large influence on the physiological benefits of NIV. For example, being awake, patients might trigger more, have less leakage, less upper airway obstruction and, as a consequence, larger minute volumes. The study of Diaz *et al*. demonstrated that with higher, but still moderate, inspiratory pressures and low EPAP, clinical benefits of NIV could be achieved in stable COPD patients.

In 2005, Windisch *et al*. published the results of a retrospective analysis of 34 COPD patients receiving NIV with high IPAP levels and a high BURR,[22] after they demonstrated in a pilot study that NIV aimed at controlling ventilation with both a high IPAP (29.8 cm H2O) and BURR (22.9 breaths/min) was well tolerated and resulted in nocturnal normocapnia and a reduction in daytime $PaCO_2$ of 19.5 mm Hg.[21] The COPD patients in the retrospective cohort[22] benefitted extensively from HI-NIV, both in terms of improved gas exchange as well as lung function improvement. To confirm those results, the same group conducted a randomized cross-over trial in which they showed that HI-NIV improved nocturnal gas exchange more compared to previously 'low-intensity' NIV.[20] However, the study was small and relatively short-term, and did not show any extra benefits in daytime gas exchange or other clinical outcomes of HI-NIV compared to low-intensity NIV.

Although promising, these trials did not truly confirm the clinical benefit of HI-NIV. The settings used in those studies were extremely high as compared to previous studies. Furthermore, a high BURR in order to control ventilation was added for the first time. Concern has been raised regarding compliance with these high-intensity settings, although it was subsequently shown that compliance and sleep quality with HI-NIV was acceptable.[26] The necessity of the high BURR was also debated.[25] Theoretically, a high BURR could promote lung hyperinflation. It is important to recognize that HI-NIV is not defined as the highest pressures and BURR, but as 'the concept of using higher IPAP levels in addition to controlled ventilation aiming for maximal $PaCO_2$ reduction'.[24] In this respect, we are still unable to define the optimal goals on which we should titrate as we lack knowledge about mechanisms how NIV actually improves outcomes.

Two parallel-group longer term RCT have been performed using HI-NIV in patients with stable COPD. Both trials have in common that clear gas exchange goals were set. In our own 2-year RCT,[18] we showed clinical and physiological benefits in terms of an improved HRQoL, lung function, exercise tolerance and gas exchange of adding HI-NIV to pulmonary rehabilitation in chronic hypercapnic COPD patients, as compared to pulmonary rehabilitation alone. We titrated NIV to achieve normocapnia ($PaCO_2$ < 45 mm Hg) and a partial arterial oxygen pressure (PaO_2) > 60 mm Hg during the night, measuring nocturnal exchange with repeated arterial sampling through an arterial line. Köhnlein *et al.*[17] performed a prospective, multicentre, RCT to evaluate the effectiveness of long-term HI-NIV in stable severe COPD patients compared to standard treatment. NIV was targeted to reduce baseline $PaCO_2$ by 20% or more, or achieve $PaCO_2$ values lower than 48·1 mm Hg, and they advised the use of a controlled mode with a high BURR, but also accepted the S-mode. The 1-year mortality was significantly reduced with HI-NIV (12% in the HI-NIV group vs 33% in the control group). Furthermore, $PaCO_2$, pH, SaO_2 (oxygen saturation), HCO_3^-, FEV_1 and HRQoL were significantly improved in the HI-NIV group compared to the control group. Finally, although the study of Murphy *et al.* was not performed in stable COPD patients, it is important to mention that with HI-NIV, time to the next exacerbation was increased and exacerbation frequency was reduced in COPD patients who had been admitted with a COPD exacerbation and acute (on chronic) respiratory failure.[19]

To summarize, HI-NIV seems to be beneficial in severe stable COPD patients with CHRF. Two longer term trials confirmed this benefit; in one of them NIV was additional to pulmonary rehabilitation. Although we currently should consider the evidence for chronic HI-NIV in stable COPD still as level B evidence (one large high-quality RCT,[17] one smaller RCT but with different control arm[18] and several smaller trials with variable designs[20–23]), it could be debated whether the large survival benefit in the Köhnlein *et al.*'s trial ethically allows another RCT comparing HI-NIV to 'standard' care. Nevertheless, from the studies performed, it is still unclear which settings exactly lead to the best outcomes. Even with titration to effective ventilation and a reduction in $PaCO_2$, which is necessary to achieve any benefit, it is still unclear what mechanisms precisely lead to CO_2 reduction and other clinically relevant outcomes.

MECHANISMS OF ACTION OF HI-NIV IN STABLE COPD

It is clear that there are individual differences in clinical benefits between patients using long-term NIV.

Although multiple factors are probably responsible for this variability, part of the solution might be found in a better understanding of working mechanisms in order to select patients who have a particular COPD phenotype with a particular pathophysiological derangement. In Figure 1, a schematic representation of the potential working mechanisms of HI-NIV in COPD is provided.

First, it is hypothesized that CHRF ensues once progression of the disease leads to an imbalance between inspiratory muscle capacity and the load placed on the respiratory system. Reasons for a decreased inspiratory muscle capacity are hyperinflation, leading to flattening of the diaphragm, but also intrinsic changes in diaphragm muscle fibres, such as loss of myosin content, increased oxidative stress and sacromeric injury, or the use of systemic corticosteroids contributing to a diaphragm with a decreased force generating capacity.[27] On the other hand, the load placed on the inspiratory muscles is increased due to shortening of inspiration, airway obstruction and intrinsic positive end-expiratory pressure (PEEPi).

NIV might counteract this imbalance. Indeed, NIV unloads respiratory muscle; it has been shown that surface electromyography (EMG) activity of the respiratory muscles decreases in COPD patients when using high IPAP levels.[28] However, it remains controversial whether this unloading really 'rests' fatigued muscles and improves the capacity of the respiratory system. Several studies have shown that the diaphragm of stable COPD patients with CHRF is not fatigued at all,[29] and respiratory muscle strength does not seem to improve after HI-NIV.[30] Nevertheless, NIV decreases the load placed on the respiratory system, as it improves breathing patterns, might reduce airway obstruction and counterbalances PEEPi. Therefore, the load–capacity balance might be improved leading to a more advantageous breathing pattern, more effective daytime ventilation and an improvement in symptoms and HRQoL.

An interesting effect of long-term NIV is its contribution to a decreased load on the system related to the positive airway pressure and its mechanical effects on the airways, such as recruiting the (small) airways, and offsetting PEEPi. Recruiting the (small) airways might prevent the related negative effects of airway obstruction on the airways, such as compression of airway epithelium triggering release of growth factors[31] and air trapping.[32,33] Interestingly, studies with HI-NIV have shown an improvement/stabilization of FEV_1 (ranging from 50 to 140 mL; see Table 1) that is currently incompletely understood and might be a result of the reversal of the pathophysiological results of airway obstruction. Moreover, a reduction in hypercapnia results in a less activated renin-angiotensin- aldosteron system (RAAS) system and thereby less fluid retention and probably airway and lung oedema, also contributing to the positive effect on FEV_1 and the reduction in inspiratory load.[34,35] Of note, these effects are very relevant as, apart from smoking cessation, therapies that truly improve lung function in these very severe COPD patients are very limited. Furthermore, the application of a certain EPAP level prevents PEEPi and the related work of breathing.[35] Finally, it has been hypothesized that HI-NIV improves ventilation–perfusion matching.[33]

A second theory states that the application of HI-NIV increases the respiratory drive,[32,36] preventing hypercapnia. Patients with CHRF seem to adopt a ventilatory strategy of rapid shallow breathing during which they deliberately allow their $PaCO_2$ to rise, probably in order to prevent respiratory muscle fatigue.[37] By improving nocturnal gas exchange and improving daytime breathing pattern, $PaCO_2$ decreases. It has been hypothesized

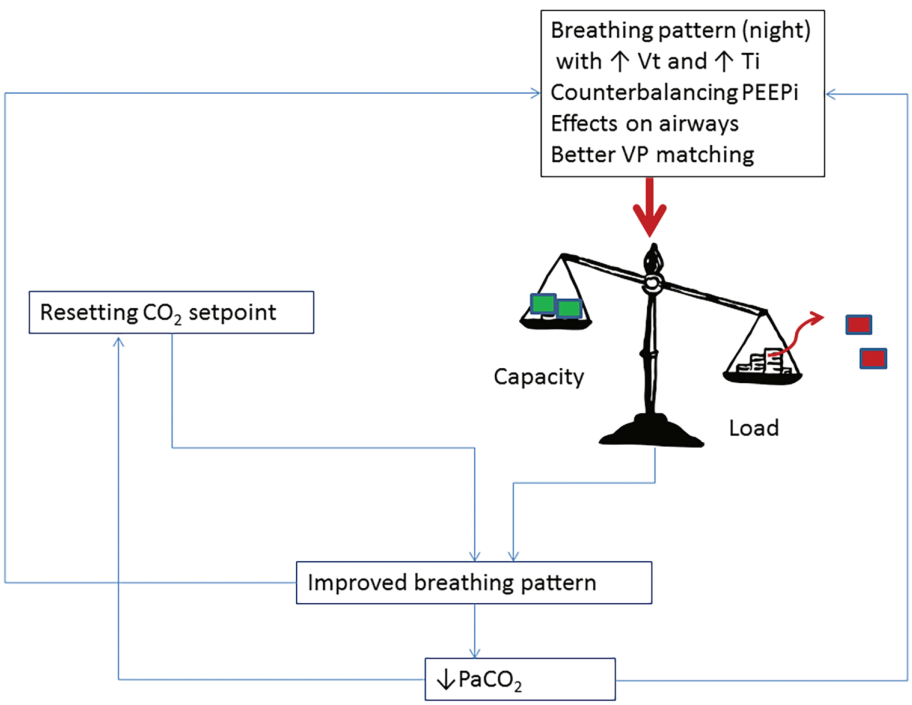

Figure 1 Theories for clinical benefits of HI-NIV in stable hypercapnic COPD. COPD, chronic obstructive pulmonary disease; HI-NIV, high-intensity non-invasive ventilation; $PaCO_2$, partial arterial carbon dioxide pressure; PEEPi, intrinsic positive end-expiratory pressure; VP, ventilation–perfusion; Vt, tidal volume; Ti, inspiratory time.

Table 1 Overview of study design, titration of NIV, ventilator settings and results of the HI-NIV studies

Author and year of publication	Design	*n*	Titration of NIV	Setting IPAP/EPAP BURR	Results
Meecham Jones *et al*. (1995)[12]	Randomized cross-over, 3 months Oxygen + NIV vs oxygen	14	Maximum IPAP/EPAP gradient S-mode (no BURR) Nasal mask	18/2 —	Oxygen + NIV vs oxygen: $PaCO_2$: −4.5 mm Hg PaO_2: +6.0 mm Hg TST: +56 min % Night awake: −10% $PtcCO_2$: −9 mm Hg HRQoL SGRQ-symptoms: −10 pts SGRQ-impact: −3 pts SGRQ-total: −4 pts
Diaz *et al*. (2002)[16]	Randomized sham-controlled, 5 weeks NIV vs sham-NIV	36	Highest tolerated IPAP level S-mode FFM 3 h/day, 5 days/week for 5 weeks	18/2 —	NIV vs sham-NIV: 24 h after the NIV period: Maintained slow and deep breathing pattern $PaCO_2$: −8.3 mm Hg PaO_2: +8.3 mm Hg FEV_1: +4.1% (90 mL) RV% predicted: −36%
Windisch *et al*. (2002)[21]	Uncontrolled cohort	14	PC-mode with high BURR Nasal mask, five individual made Maximum tolerated IPAP Goal: normocapnia early morning	29.8/EPAP data not provided 22.9	HI-NIV 4 h after ending NIV: $PaCO_2$: −13.5 mm Hg PaO_2: +6 mm Hg Effects maintained over 6 months
Windisch *et al*. (2005)[22]	Retrospective cohort	34	AC-mode Nasal mask Maximum tolerated IPAP, BURR> own RR Goal: normocapnia early morning	28/EPAP data not provided 21	HI-NIV After 2 months NIV: $PaCO_2$: −6.8 mm Hg PaO_2: +6.0 mm hg FEV_1: +140 mL
Dreher *et al*. (2010)[20]	Randomized cross-over trial, 6 weeks	17	AC-mode Maximum tolerated IPAP, BURR> own RR Goal: normocapnia during NIV	29/5 18	HI-NIV vs LI-NIV $PaCO_2$ day: −3.0 mm Hg $PaCO_2$ nocturnal: −9.0 mm Hg PaO_2: NS FEV_1: +50 mL (NS) 6MWD: +14 m (NS) HRQoL SRI-SS: −0.14 pts (NS)

Table 1 Continued

Author and year of publication	Design	*n*	Titration of NIV	Setting IPAP/EPAP BURR	Results
Duiverman *et al.* (2011)[18]	Randomized controlled, comparing NIV added to PR vs PR alone, 2 years	72	ST-mode Targeted to normocapnia during the night	23/6 18	NIV + PR vs PR alone: No survival benefit No change in exacerbation frequency $PaCO_2$ day: −3.0 mm Hg PaO_2 day: +6 mm Hg 6MWD: +77.3 m FEV_1: +15 mL (= +4%) HRQoL: MRF-total: +13.4% SRI-SS: +2.9 pts (NS)
Köhnlein *et al.* (2014)[17]	Randomized controlled, 1 year, NIV + standard care vs standard care	195	ST- or S-mode Targeted to $PaCO_2$ reduction ≥20% or achieve $PaCO_2$ < 6·5 kPa	22/5 16	NIV vs standard care 1-year mortality: 12% vs 33% No change in exacerbation frequency $PaCO_2$ day: −3.0 mm Hg PaO_2: +0.5 mm Hg (LTOT, NS) 6MWD: +17 m FEV_1% predicted: +~90 mL (2.8%) HRQoL SGRQ: −6.2 pnt (NS) SRI-SS: +5.6 pnt

6MWD, 6-min walking distance; AC-mode, assist control mode; BURR, back-up respiratory rate; EPAP, expiratory positive airway pressure; FEV_1, forced expiratory volume in 1 s; FFM, full face mask; HI-NIV, high-intensity NIV; HRQoL, health-related quality of life; IPAP, inspiratory positive airway pressure; kPa, kilo Pascal; LI-NIV, low-intensity NIV; LTOT, long-term oxygen therapy; MRF, Maugeri Respiratory Failure Questionnaire; NIV, non-invasive ventilation; NS, not significant; $PaCO_2$, partial arterial carbon dioxide pressure; PaO_2, partial arterial oxygen pressure; PC-mode, pressure-controlled mode; PR, pulmonary rehabilitation; $PtcCO_2$, transcutaneous carbon dioxide tension; RR, respiratory rate; RV, residual volume; S-mode, spontaneous mode; SGRQ, St George Respiratory Questionnaire; SRI-SS, Severe Respiratory Insufficiency Questionnaire-summary scale; ST-mode, spontaneous-timed mode; TST, total sleep time.

that the resultant change in CO_2 setpoint of the chemoreflex receptors is one of the most important points of reversibility achieved by chronic NIV.

The above-mentioned principles contribute more or less to an improved breathing pattern with larger tidal volumes and a decreased breathing frequency during the day,[38] which again contributes to a better balance between load and capacity of the respiratory pump.

PRACTICAL ADVICE ON INITIATION AND FOLLOW-UP OF HI-NIV

Before commencing HI-NIV, a thorough analysis of the patient's motivation, goals, medical history and current medical situation is warranted. Unfortunately, good predictors of response and/or compliance are currently not available.

In patients with cardiac failure, caution is needed when HI-NIV is initiated, as high inspiratory pressure might reduce cardiac output.[39] However, the eventual effect results from a complex interaction between potential negative and positive effects of NIV on the heart, and depends on the patient's underlying cardiac and pulmonary condition, the applied ventilatory settings and compensatory mechanisms that come into play.[40–42]

There is no consensus on how to initiate and titrate HI-NIV. Usually, HI-NIV is initiated in the hospital, although, in our opinion, this is not mandatory for success. It is important to titrate step-wise and this usually requires several days in order to achieve goals of a sufficient decrease in $PaCO_2$ with good patient comfort and tolerance.[20]

To set HI-NIV, it is advised to start with daytime practice session(s) using a spontaneous-timed mode with IPAP levels of 12–18 cm H_2O, low BURR and a low

EPAP level (Fig. 2). Then, during this first day, increase IPAP carefully, step by step, to the point no longer tolerated by the patient. With respect to the BURR, there is no consensus. Although the original papers advise to subsequently increase the BURR beyond the spontaneous rate to establish controlled ventilation,[20–23] we usually choose to set the BURR low and increase it only if nocturnal monitoring of gas exchange shows that $PaCO_2$ goals are not reached despite high IPAP levels. With high BURR, a side effect could be that patients are hyperinflated even more, leading to patient–ventilator asynchronies, discomfort and limited daytime benefits. Therefore, care in providing a sufficient expiratory time is very important. The EPAP should be set to a level where PEEPi is counter-balanced; because measuring PEEPi is difficult in patients on NIV during routine practice, it is usually set between 3 and 6 cm H_2O, values that should be sufficient for COPD patients in stable condition.[16] The occurrence of ineffective efforts can be an indication that PEEPi is inadequately balanced. However, as these events may also be provoked by, for example, leaks, caution should be taken for increasing EPAP before fitting the mask correctly, and thinking about potential negative effects of high EPAP (i.e. cardiac effects and reduction in IPAP–EPAP window).

Once an effective setting is reached that is comfortable for the patient, we advise patients to sleep with NIV. It is crucial to repeat monitoring of ventilatory data and gas exchange. Usually, it takes a couple of nights before optimal settings are reached. By monitoring our goals (improved gas exchange and comfortable NIV), we titrate HI-NIV step by step and individually.

The target of HI-NIV titration is that a $PaCO_2$ reduction/normocapnia is reached. Therefore, HI-NIV titration requires monitoring of at least gas exchange. It is interesting to note that monitoring options are expanding rapidly. We will discuss options, from simple to more advanced techniques, and give practical advice on why and how to use these monitoring options in order to optimize NIV.

Monitoring that should be available for initiation and titration of HI-NIV

Gas exchange

Gas exchange should be monitored to evaluate whether HI-NIV is effective and goals of NIV have been reached.

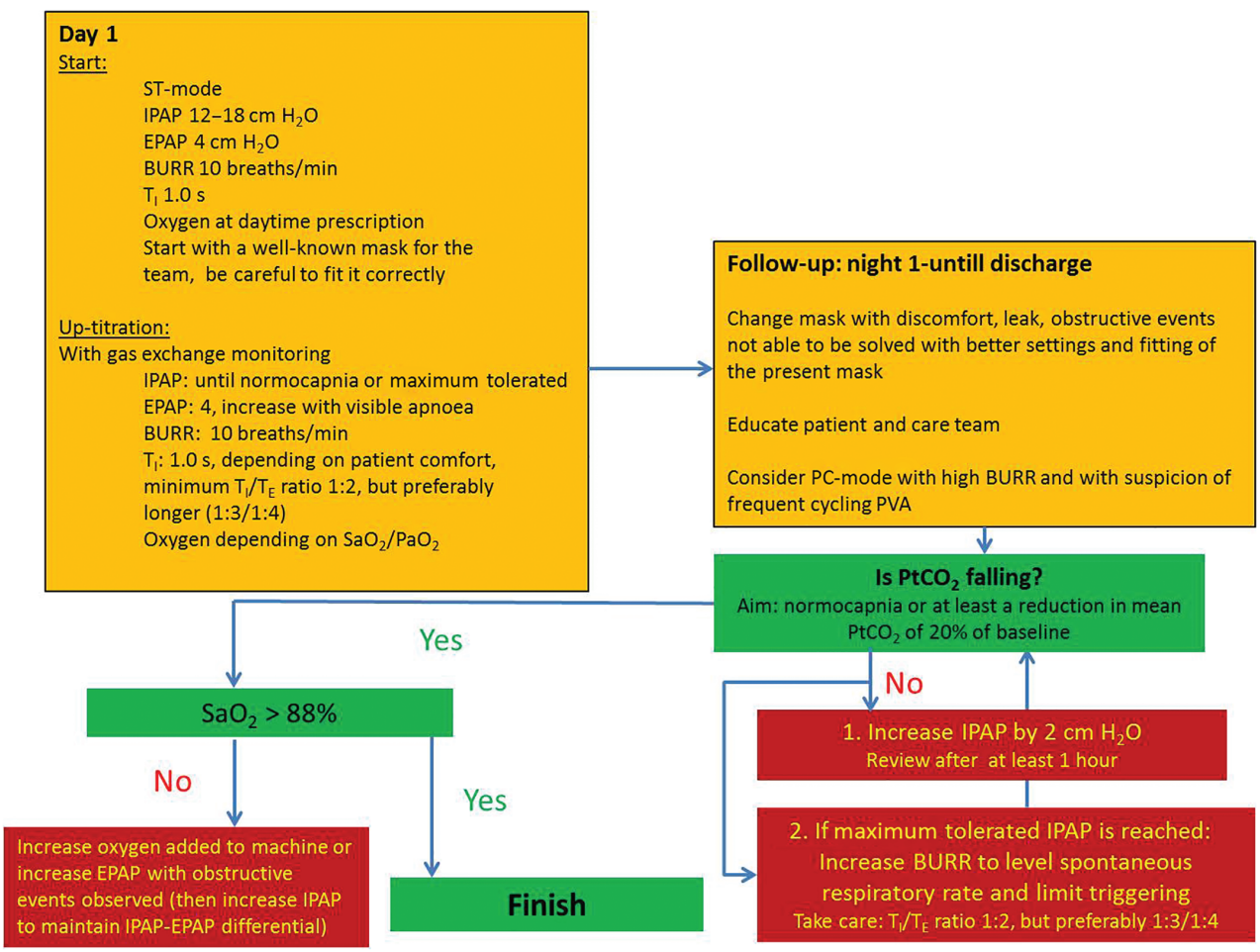

Figure 2 Ventilator set-up for high-intensity NIV at the Home Mechanical Ventilation (HMV) centre Groningen. BURR, back-up respiratory rate; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; NIV, non-invasive ventilation; PaO_2, partial arterial oxygen pressure; PC-mode, pressure-controlled mode; $PtcCO_2$, transcutaneous carbon dioxide tension; PVA, patient–ventilator asynchrony; T_E; expiratory time; T_I, inspiratory time; SaO_2, oxygen saturation; ST-mode, spontaneous-timed mode.

Although normocapnia during wakefulness is the ultimate goal, this might not be a realistic goal in patients with severe COPD in whom daytime $PaCO_2$ rises after ceasing nocturnal ventilatory support. To adequately judge ventilatory efficacy, and to guide optimal adjustments of settings, nocturnal monitoring is necessary.

Pulse oximetry is a simple, easy way to detect oxygen desaturation.[43] However, the specificity of the detection of nocturnal desaturation as a marker of nocturnal respiratory events is low and not reliable when patients use additional oxygen.[44] Nocturnal carbon dioxide measurements are therefore needed to assess the quality of alveolar ventilation. The 'gold standard' to measure this is to retrieve repeated samples of arterial blood via an arterial line. However, arterial cannulation is uncomfortable, expensive and demands continuous monitoring by trained personnel, in most hospitals only available in high care units. Early morning sampling of $PaCO_2$ is also less appropriate, as this is always after arousal and a period of spontaneous awake breathing, which does not reflect overnight $PaCO_2$.[43] Capillary blood gas is an alternative for arterial blood gases, but still cannot be measured continuously during the night. A non-invasive way to assess carbon dioxide pressures continuously is by measuring end-tidal carbon dioxide tension ($PetCO_2$) or transcutaneous carbon dioxide tension ($PtcCO_2$).[43,45–49] However, measuring $PetCO_2$ is not a reliable measurement for $PaCO_2$ in COPD patients because of large dead space ventilation. In contrast, $PtcCO_2$ values are comparable to arterial (gold standard) values in COPD patients.[50] Therefore, we advise using nocturnal $PtcCO_2$ to monitor HI-NIV gas exchange goals, both during the initiation period as well as during patient follow-up. Extending the ability to monitor gas exchange transcutaneously at home with an easy-to-use home or in-built ventilator module with telemonitoring capabilities would be an significant improvement in the care of today's and future patients on chronic NIV.

Ventilator monitoring

Many ventilatory devices contain sensors and built-in software that provide information about compliance, settings and estimated values of tidal volume, leaks, breathing frequency, minute ventilation, percentage of breaths triggered by the patient and the apnoea–hypopnoea index (AHI) over an extended period. These parameters can help identifying abnormal nocturnal events, and in some cases, the causes of these events. Notably, the parameters provided depend on the type of device used, with many parameters recorded not yet validated by independent studies.

Data on compliance provide important information. It is thought that a threshold number of hours daily use is necessary to obtain clinical benefits (at least 5 h daily use).[13] However, increasing nightly use may also predict COPD exacerbations.[51] Furthermore, interrupted patterns of ventilation or an overall decreased use may indicate inappropriate settings, adverse effects or patient discomfort.[43,51,52] Both situations should alert the clinician to a potential problem with NIV. In the future, compliance monitoring might be an important parameter in the follow-up of patients, although further studies should provide evidence for improved outcomes and cost-effectiveness of such strategies.

Data on tidal volume, leaks, breathing frequency and AHI are estimated parameters and when interpreting these data one should be aware of the drawbacks. For example, most ventilators tend to underestimate the tidal volume delivered, especially when high IPAP levels are used,[53,54] so no hard conclusions should be based on this. Furthermore, although high leaks could indicate poor mask fit, influencing the effectiveness of ventilation and quality of sleep,[55–57] not all devices estimate leaks in the same way influencing the reliability of leak estimation with different devices.[53,58,59] Lastly, the reliability of the AHI provided has only been assessed for a few ventilator models.[60]

In conclusion, compliance data should be used especially during follow-up of patients using HI-NIV. Other data provided by the ventilator may be of value; however, the usefulness, reliability and validity of most parameters require further evaluation.

Extended monitoring

In addition to the above-mentioned mandatory monitoring of patients treated with HI-NIV, more extensive monitoring possibilities have been investigated over the last decade. In general, although some of these methods are promising, an important question that should be addressed is whether this extensive monitoring improves patient-related outcomes.

Patient–ventilator asynchrony

Monitoring patient–ventilator asynchrony (PVA) helps to identify abnormal respiratory asynchronous events during the night. Although it seems attractive to monitor these events and correct them, there is controversy whether this leads to improved clinical outcomes. A recent pilot proof-of-concept clinical trial showed a trend towards greater improvements in daytime $PaCO_2$, HRQoL and sleep quality when using simple gas exchange monitoring compared to advanced monitoring.[61] Moreover, it was shown that the presence of PVA do not necessarily affect outcomes in patients with CHRF.[62,63] Conversely, Adler *et al.*[64] showed that actively titrating NIV to minimize PVA and sleep-disordered breathing decreased morning dyspnoea and increased patient comfort.

There are multiple methods available to monitor PVA non-invasively. The most extensive way is to use full polysomnography (PSG).[65,66] However, since PSG is time-consuming and expensive, this is only feasible when a sleep analysis is needed anyway. Another approach is to use flow and airway pressure waveforms.[67,68] However, detection of PVA based solely on flow and pressure waveforms is difficult.[67] An easier and more precise method to detecting PVA is to compare pressure waveforms with the patients' own respiratory activity measured with surface EMG[28,63] or thoracoabdominal movement measurements (plethysmography).[67–69] An example of surface EMG combined with airway pressure to detect an ineffective effort is shown in Figure 3.

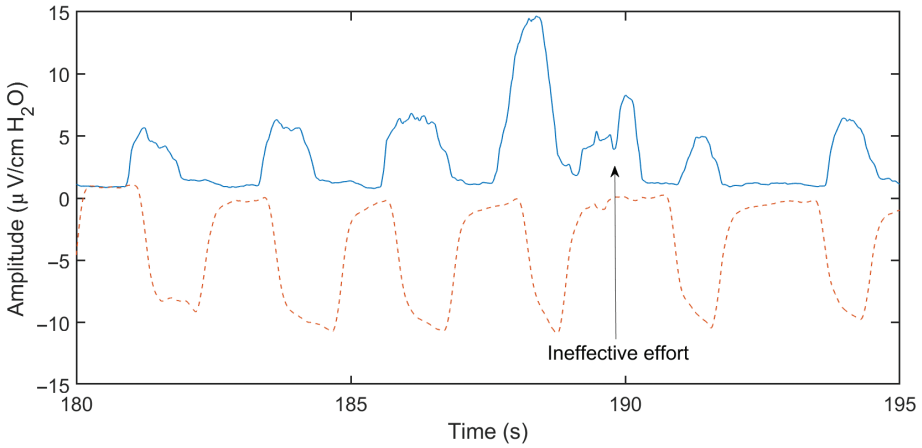

Figure 3 Example of the use of surface electromyography of the diaphragm (——) together with airway pressure (- - - -) to access an ineffective effort.

In conclusion, the value of PVA monitoring has still to be proven. A future field of interest for PVA monitoring might be in the prevention and treatment of specific side effects and ventilatory problems. Although most techniques are still time-consuming because of a lack of automation, in the future an easy-to-use small EMG monitoring device might become realistic and of value in achieving comfortable optimal HI-NIV.

Sleep quality

Ventilation can improve sleep quality[70,71] or impair it due to respiratory events.[65,67,72] Additionally, the stage of sleep can significantly influence ventilation in patients with respiratory insufficiency.[45] Titration under PSG provides a precise analysis of different mechanisms involved in persisting nocturnal respiratory events and could improve sleep quality, by reducing the number of these events.[71,73] However, performance of a PSG without careful ventilator titration will not improve sleep quality.[74] For most centres, a full PSG is not feasible on a routine basis, as it is expensive and time-consuming.

Telemonitoring

With more extensive monitoring tools available and the desire to manage patients in their own homes, e-health solutions are emerging. Once easy and reliable monitoring and transfer of ventilatory data, gas exchange data and other parameters from the home to the clinical setting are available, even HI-NIV initiation, titration and optimalization should be possible at home.

In this respect, two different solutions have to be addressed: (i) the replacement of in-hospital initiation of chronic NIV and (ii) (partial) replacement of in-hospital follow-up with the use of home telemonitoring. The initiation of NIV at home has been investigated by Hazenberg *et al.*, although not in patients with COPD.[75] They found a comparable, or even improved, $PtcCO_2$ and HRQoL in patients who were initiated on NIV at home compared to patients initiated in the hospital.[75] Moreover, there was a cost reduction of 3000 Euros per patient using home-initiated NIV.[75] Currently, we are performing a study evaluating the effectiveness of initiating COPD patients on HI-NIV at home. Our experience is that home NIV initiation is (at least) feasible and hopefully our data will show that it is as effective as in-hospital initiation.

Follow-up of chronic NIV patients with the use of telemonitoring has been investigated in a few studies,[76,77] with contradictory results. Vitacca *et al.*[76] showed that nurse-centred teleassistance decreased hospitalizations, urgent general practitioner consultations, acute exacerbations and costs, especially in COPD patients. On the contrary, Chatwin *et al.*,[77] using a comparable protocol and patient group as Vitacca *et al.*,[76] showed that telemonitoring made no difference in time to hospital admission, did not improve quality of life and increased hospital admissions and home visits, compared to standard care. As with all telemonitoring possibilities, it is important to understand what is being monitored and how it should be responded to by patients and clinicians. Once clear goals are set, for example to prevent hospitalizations or replace hospital visits, this approach may be a very attractive management option especially for very disabled patients with CHRF. Overall, more prospective studies are needed to assess the effectiveness of telemonitoring on both patient-centred outcomes as well as cost-effectiveness.

CONCLUSION

There is sufficient evidence that HI-NIV improves outcomes in stable COPD patients with CHRF. In order to preselect those who will benefit most, we need to gain better insights into the mechanisms underlying how HI-NIV works. Practically, HI-NIV setting is 'personalized medicine', targeting normocapnia or a maximal reduction in $PaCO_2$. To achieve this, reliable awake and nocturnal gas exchange monitoring are needed. Ventilator data can assist with monitoring of compliance, with cautious interpretation of leak, tidal volumes and residual respiratory events. Other monitoring possibilities, such as PVA monitoring, are promising but first need to be addressed in the context of specific ventilatory or clinical problems.

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Abbreviations: 6MWD, 6-min walking distance; AC-mode, assist control mode; AHI, apnoea–hypopnoea index; BURR, back-up respiratory rate; CHRF, chronic hypercapnic respiratory failure; EMG, electromyography; EPAP, expiratory positive airway pressure; FEV_1, forced expiratory volume in 1 s; HI-NIV, high-intensity NIV; HRQoL, health-related quality of life; IPAP, inspiratory positive airway pressure; NIV, non-invasive ventilation; $PaCO_2$, partial arterial carbon dioxide pressure; PaO_2, partial arterial oxygen pressure; PC-mode, pressure-controlled mode; PEEPi, intrinsic positive end-expiratory pressure; $PetCO_2$, end-tidal carbon dioxide tension; PR, pulmonary rehabilitation; PSG, polysomnography; $PtcCO_2$, transcutaneous carbon dioxide tension; PVA, patient–ventilator asynchrony; RCT, randomized controlled trial; RR, respiratory rate; S-mode, spontaneous mode; SGRQ, St George Respiratory Questionnaire; SRI-SS, Severe Respiratory Insufficiency Questionnaire-summary scale; ST-mode, spontaneous-timed mode; T_I, inspiratory time.

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