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REVIEW

Long-term noninvasive ventilation in COPD: current evidence and future directions

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ABSTRACT

Introduction: Long-term noninvasive ventilation (NIV) is an established treatment for end-stage COPD patients suffering from chronic hypercapnic respiratory failure. This is reflected by its prominent position in national and international medical guidelines.

Areas covered: In recent years, novel developments in technology such as auto-titrating machines and hybrid modes have emerged, and when combined with advances in information and communication technologies, these developments have served to improve the level of NIV-based care. Such progress has largely been instigated by the fact that healthcare systems are now confronted with an increase in the number of patients, which has led to the need for a change in current infrastructures. This article discusses the current practices and recent trends, and offers a glimpse into the future possibilities and requirements associated with this form of ventilation therapy.

Expert opinion: Noninvasive ventilation is an established and increasingly used treatment option for patients with chronic hypercapnic COPD and those with persistent hypercapnia following acute hypercapnic lung failure. The main target is to augment alveolar hypoventilation by reducing $P_a\text{CO}_2$ to relieve symptoms. Nevertheless, when dealing with severely impaired patients, it appears necessary to switch the focus to patient-related outcomes such as health-related quality of life.

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COPD; long-term noninvasive ventilation; respiratory failure; telemedicine; outpatient setting; quality of life; lung function

1. Introduction

Chronic obstructive pulmonary disease (COPD) can manifest as a hypoxemic respiratory failure (type 1 respiratory insufficiency) and/or hypercapnic respiratory failure (type 2 respiratory insufficiency) [1]. Previous clinical trials have shown that long-term oxygen therapy has a survival benefit in patients with chronic hypoxemic respiratory failure [2,3]. On the other hand, long-term noninvasive ventilation (NIV), applied via mask, is a validated treatment strategy for patients suffering from chronic hypercapnic respiratory failure, which can arise from various underlying disorders including COPD, neuromuscular diseases (NMDs), obesity hypoventilation syndrome (OHS) and chest wall disorders [4]. All of these disease entities are characterized by reduced inspiratory muscle capacity and/or an increased load placed on the respiratory system, which results in alveolar hypoventilation and hypercapnia with the associated complex of symptoms [5]. Noninvasive or invasive mechanical ventilation can then be initiated in order to restore the balance between load and capacity, as well as to increase alveolar ventilation. Indeed, patients with an underlying NMD or chest wall disease have shown dramatic improvements in survival, health-related quality of life (HRQoL) and respiratory symptoms, once long-term ventilation has been provided [6–10].

However, these effects have long remained controversial in relation to COPD patients suffering from chronic hypercapnic respiratory failure. Nevertheless, clear improvements in survival and HRQoL, as well as a reduction in hospitalization rate have now become evident in COPD patients when NIV is aimed at maximally reducing the partial pressure of carbon dioxide ($P_a\text{CO}_2$) [11,12]. Discussions concerning the use of long-term NIV for COPD and other diseases are contentious, and many of the associated topics require reconsideration and will hence form an essential part of future trials. Such topics include:

- Newly emerging ventilation modes and the extent of their usefulness
- The impact of long-term NIV on patient-related outcomes and HRQoL
- Developing efficient expert healthcare settings in order to increase the quality of care in a cost-effective manner
- Implementation of E-Health (especially telemonitoring) for individualized therapy control and improved patient follow-up
- Further outcome parameters that depict physiological changes for successful therapy
- Pathophysiological phenotyping of the patient collective that benefits most from NIV therapy

Article highlights

- Long-term NIV therapy has critical significance both in COPD patients suffering from symptomatic chronic respiratory failure, and in those with persisting hypercapnia after acute hypercapnic respiratory failure.
- The overall goal is to augment alveolar hypoventilation witnessed by a reduction in $P_a\text{CO}_2$ in order to reduce symptoms such as severe dyspnea, sleep-disordered breathing, and further hypercapnia-related symptoms.
- In COPD patients, long-term NIV should be carried out by High-intensity NIV strategy capable of augmenting ventilation and thereby normalizing $P_a\text{CO}_2$ for at least 5 h per day. Individual titration is essential and it should be aimed for normocapnia.
- The rise in the number of patients who require long-term NIV could lead to so-called bottlenecks in health care expertly arranged out-patient settings and the use of telemonitoring are promising solutions that are simultaneously capable of promoting an improvement in the quality of care.
- Numerous technological developments have taken place in the past decades, thus improving the means of NIV application. However, when dealing with a severely impaired patient collective, it appears necessary to switch the focus to patient-related outcomes and search for solutions that ultimately improve HRQoL.

- Arriving at a large database on methods of applying long-term NIV by means of multinational registers

The aim of the review is to provide a comprehensive overview of the latest scientific findings in these areas and to discuss them in the context of the current recommendations and developments.

2. Pathophysiology of chronic hypercapnic respiratory failure in COPD

The regulation of respiration is a rather complicated process with manifold interactions, governed by the respiratory center located in the brain stem. The respiratory center is influenced by changes in the partial pressure of arterial oxygen ($P_a\text{O}_2$), $P_a\text{CO}_2$, and pH, as well as by signaling from mechanoreceptors located in the lung and chest wall [13] (Figure 1).

Changes in the sensitivity of ventilatory responses to $P_a\text{CO}_2$ and $P_a\text{O}_2$ are the main causes of reduced ventilation during sleep. For this reason, tidal volume is reduced during sleep, especially during the rapid eye movement (REM) phase [14,15]. In addition, general muscle hypotension occurs during REM sleep, and given that the diaphragm is the only respiratory muscle not affected by this process, respiration depends solely on diaphragmatic contractions. Therefore, patients who are dependent on accessory respiratory and intercostal muscles – such as COPD patients – may experience significant hypoventilation during REM sleep, with increased dead space ventilation, reduced tidal volume, and subsequent hypercapnia. Secondly, muscle hypotension leads to increased upper airway collapse, with a subsequent increase in airway resistance. As a result, REM sleep is often associated with transient deoxygenation and increased $P_a\text{CO}_2$ in patients with respiratory failure. Therefore, measurements of sleep quality are of particular importance in patients with an increased risk of nocturnal hypoventilation [16–18]. A screening for comorbid obstructive sleep apnea syndrome should be performed

Figure 1. Flow diagram of respiratory pump actions and its malfunctions.

Abbreviations: CNS: Central nervous system; PNS: Peripheral nervous system

before NIV therapy is started. Sufficient studies on whether a polysomnographic (PSG) measurement is necessary for the titration of NIV are missing, so that it is currently assumed that a PSG is not absolutely necessary with carefully established individual NIV. Further studies are needed to determine the additional therapeutic benefit of such diagnostic procedures [19].

When the imbalance between load and capacity of the respiratory system increases, daytime hypercapnia also ensues

(Figure 2). This load is caused in particular by a shortening of inspiration, airway obstruction, dynamic hyperinflation and the pre-stretching of the thorax. On the other hand, capacity of the ventilatory pump is affected in particular by systemic muscle atrophy, possible ventilator-induced diaphragmatic dysfunction, and the change in diaphragmatic alignment when the diaphragm flattens as a result of emphysema. At this point, patients suffer not only from symptoms such as dyspnea, but also from reduced sleep quality and symptoms

Figure 2. Causes of ventilatory insufficiency in COPD.

Abbreviations: PEEP: Positive end expiratory pressure; VIDD: Ventilator-induced diaphragmatic dysfunction.

Figure 3. Depiction of respiratory insufficiency symptoms such as dyspnea, edema, headaches, conjunctival redness, daytime tiredness, and tendency to fall asleep.

such as morning headaches, daytime tiredness, and the tendency to fall asleep (Figure 3) [20]. The type and severity of the symptoms dramatically affect HRQoL. These discernible effects of hypoventilation not only depend on the underlying disease itself, but also on the course of the disease, the patient’s own view of his or her situation, and previous life experiences [21].

3. Treatment effects of NIV in COPD patients with chronic hypercapnic respiratory failure

The aim of NIV is to augment alveolar ventilation so that elevated $P_a\text{CO}_2$ levels are reduced (Table 1) during both NIV application and consecutive phases of spontaneous breathing [22,23]. Furthermore, another fundamental outcome parameter in COPD

Table 1. Typical blood gas analysis findings in patients with acute and/or chronic respiratory failure.

	Acute	Chronic	Acute on chronic
pH	↓	↔	↓
$P_a\text{CO}_2$	↑	↑(↑)	↑↑
HCO_3^-	↔	↑	↑

patients with chronic hypercapnic respiratory failure is lung function, as this is severely impaired in advanced stages of disease [16] and is associated with prognosis, even in end-stage COPD [24]. On one hand, NIV bears the potential to stabilize lung function, while on the other, it runs the risk of dynamic hyperinflation, ventilator-

induced lung injury, and discomfort of the patient, which must be avoided to prevent an even further burden on severely impaired patients [25–28].

In terms of clinical outcome parameters, it needs to be emphasized that although many treatment strategies, including NIV, bear the potential to improve physiological parameters, symptoms, and/or exacerbation rates, there are only a few observations derived from long-term trials showing a survival benefit. Moreover, it remains to be seen whether there are other unknown therapeutic effects associated with NIV in particular. Further studies must take place to determine the appropriate target parameters and therefore better understand the effects of NIV at a physiological level.

4. Ventilator settings for long-term NIV in COPD

Finding the correct ventilator settings is essential for successful NIV treatment. Previous studies that used inadequate ventilator settings for reducing $P_a\text{CO}_2$ in COPD patients with chronic hypercapnic respiratory failure also failed to show other potential benefits of NIV, such as a gain in HRQoL or survival benefit [29–38]. These trials used ventilator settings similar to those normally applied to correct alveolar hypoventilation in patients with NMD or thoracic restrictive disorders and ‘healthy lungs.’ However, it is important to note that considerably different pressure settings are often needed to achieve a clinical benefit in COPD patients. The so-called high-intensity NIV (HI-NIV) was first described for chronic hypercapnic COPD patients in 2009 [25], and refers to a specific

ventilatory approach by which NIV settings are aimed at maximally reducing $P_a\text{CO}_2$ values in order to reach normocapnia [39]. To achieve this goal, HI-NIV requires ventilator settings to be increased in a stepwise manner up to the maximum level that is tolerated by the patient, or to the level at which a substantial reduction in $P_a\text{CO}_2$ or even normocapnia is achieved. In 2010, the feasibility of HI-NIV in COPD was shown in comparison to a control group undergoing low-intensity NIV, as were clear benefits in physiological parameters, the most important of which was nocturnal $P_a\text{CO}_2$ [27]. After this small, short-term physiological trial was published, more evidence emerged to suggest that HI-NIV is capable of improving important physiological parameters such as blood gases and lung function, as well as HRQoL and long-term survival [11,26]. As a consequence, an increasing trend toward the use of HI-NIV can be detected throughout the literature published over the last decade, particularly in COPD patients (Figure 4) [11,12,27,40–46]. Further improvements leading to an overall-bettered outcome are developments in the engineering of the ventilator, more comfortable mask interfaces, and an overall improved organization of care and follow-up.

4.1. New technologies in long-term NIV: sense or nonsense?

Only a few studies exist that compare pressure-controlled and volume-controlled ventilation modes. Although no differences in daytime blood gas levels or sleep quality were reported

Figure 4. Graph showing the mean inspiratory pressure levels used across a period of 3 decades in COPD patients receiving home NIV.

Abbreviations: IPAP = Inspiratory positive airway pressure; '90 = 1990

[26,47], pressure-controlled ventilation is by far the most commonly used NIV mode today, due to better patient compliance, pressure stability, and relatively better leak compensation [26]. One major disadvantage of pressure-controlled ventilation is that it does not guarantee minimal tidal volume, resulting in hypoventilation; this particularly holds true during sleep due to changes in position or obstruction of the upper airway. However, new ventilatory modes that allow automatic adjustment of ventilation parameters in relation to dynamic changes in respiratory mechanics (for example, during changes in body position) have now been introduced. Modern modes potentially allow an optimal combination of the advantages associated with each of the two NIV modes, without the negative aspects [48]. Techniques known as adaptive or auto-titrating modes have been developed to achieve these objectives. It is anticipated that automatic identification of appropriate settings for a selected patient would allow NIV to be performed in non-specialized centers, thereby supporting widespread use of this technique. On the other hand, there are certain complications and pitfalls associated with these types of hybrid modes [48]. The lack of sufficient evidence means that no clear recommendation can be made at this point in time, and additional prospective studies need to be performed.

5. Current evidence

The road to finding evidence that supports the use of long-term NIV in COPD patients has been long and unsettled. Initial international trials could not demonstrate any benefits of long-term NIV in this patient cohort [29–31,33,49]. Nonetheless, the first edition of the German guidelines for home mechanical ventilation (HMV, published in 2009/2010) [50] still recommended the use of NIV in COPD-related chronic hypercapnic respiratory failure based on positive feedback from the clinical practice setting; however, this contradicted international scientific opinion at the time. In the last decade, more and more publications arose and with an increasing foundation of evidence, long-term NIV became clinical practice for COPD patients with chronic hypercapnic respiratory failure, in many countries.

Therefore, there was a need for establishing a consensus across Europe and embodying this in a guideline. A European task force was founded in 2017 for this purpose. Within the framework of this European Respiratory Society (ERS) task force, 15 international clinical experts, as well as additional experts from the fields of statistics and methodology, collaborated to develop a scientific evaluation of long-term NIV in COPD with conclusive clinical recommendations. The European guidelines for long-term NIV were published in the European Respiratory Journal in 2019 [51], and are based on a specific grading system (GRADE system – grading of recommendations, assessment, development, and evaluation).

The GRADE procedure is a strict rating method that focuses on evidence resulting from large randomized-controlled trials. After defining four PICO questions (target population-intervention-comparator-outcome) of relevance, a large literature search across five of the largest databases was performed in order to address the topics at hand. The retrieved data sets

were rated by the task force members, who ranked the certainty of evidence from ‘very low’ to ‘high,’ in order to establish levels of evidence and, ultimately, recommendations. Two indications for long-term home NIV were defined: (i) chronic stable hypercapnic COPD patients and (ii) persisting hypercapnia following an episode of acute exacerbation (2–4 weeks post-exacerbation). Due to the lack of high-quality scientific data, only low level of evidence could be given for many questions raised.

6. Quality of life in patients receiving HMV

The majority of patients with chronic hypercapnic respiratory failure have no real chance of being cured. These patients usually suffer from a terminal illness with objectively severe limitations to their everyday life, which leads to a lower HRQoL than that of the normal population [52,53]. Fortunately, daily clinical practice (and research) in the field of long-term NIV in COPD is becoming increasingly focused on not only prolonging life, but also enriching it and improving HRQoL.

HRQoL forms an individual entity, and previous trials have shown that it does not correlate strongly with physiological parameters [43]. However, if applied in the correct way, long-term NIV bears the potential to improve HRQoL [9,11,12] on both short- and long-term scales [40], although scientific results have not always been consistent in this context [11,12,36,38] (Table 2). This could be due to the fact that the studies in question were performed in different countries and thereby different health-care systems, potentially creating an underlying bias. Reconsideration of living situations and psychological and psychosocial influences on HRQoL is urgently needed, especially in COPD patients suffering from multiple comorbidities. Qualified test methods are required to determine HRQoL and individual therapeutic effects on different psychological patterns.

Questionnaires have been developed to objectify HRQoL in order to better understand the patient’s perspective (patient-related outcomes – PROs [54]) and address this question scientifically. HRQoL is a multidimensional construct and includes physical, functional, psychological, and social aspects [52,55–57]. HRQoL questionnaires can be either disease-independent or disease-specific [56,57]. Disease-independent questionnaires enable the comparison between different collectives, albeit with limited sensitivity. In contrast, disease-specific instruments assess HRQoL in a defined disease or condition, and are therefore essential if therapy-related changes need to be reflected. Various disease-specific questionnaires have been developed for COPD over time (COPD Control Questionnaire – CCQ [58], Chronic Respiratory Questionnaire – CRQ [59], and St. George Respiratory Questionnaire – SGRQ [60]). Questionnaires have also been developed to specifically assess HRQoL in patients with chronic respiratory failure (Maugeri Foundations Respiratory Failure Questionnaire – MRF-28 [61], Severe Respiratory Insufficiency Questionnaire – SRI) [62].

The SRI questionnaire has particularly gained acceptance in the more recent trials published on NIV in COPD [63]. This questionnaire was especially developed for patients with severe respiratory failure arising from various underlying

Table 2. Summary of long-term (≥ 1 year follow up) randomized-controlled trials and their findings on health-related quality of life.

Trial (year)	n	IPAP/IPAP	Design	Difference in HRQoL (Treatment effects)
Clini et al. [36]	86	14/2 cmH ₂ O	Parallel-group (oxygen)	2-year: SGRQ: no difference MRF: 7.1 (95% CI: 0.13–4.07; $p = 0.04$)
McEvoy et al. [38]	144	13/5 cmH ₂ O	Parallel-group (oxygen)	1-year: SGRQ: no difference SF-36: deterioration observed in two subscales (GH, MH)
Duiverman et al. [42]	66	23/6 cmH ₂ O	Parallel-group (pulmonary rehabilitation)	2-year: MRF: –13.4 (95% CI –22.7– –4.2; $p = 0.005$) CRQ: no difference SRI: Improvements observed in one subscale – <i>physical functioning</i> : 10.7% (95% CI 3.8–17.6; $p = 0.003$)
Köhnlein et al. [11]	195	22/5 cmH ₂ O	Parallel-group (standard care)	1-year: SGRQ: 6.2 (95% CI: 0.7–11.8; $p = 0.03$) SRI: 5.6 (95% CI: 0.1–11.1; $p = 0.04$) SF-36: improvements observed in one subscale (GH)
Struik et al. [43]	201	19/4 cmH ₂ O	Parallel-group (standard care)	1-year: MRF: no difference CRQ: no difference SRI: Improvements in subscales <i>attendant symptoms & sleep</i> : 8.7 (95% CI: 1.9–15.4) $p < 0.05$ <i>social relationships</i> 8.4 (95% CI: 2.4; 14.5) $p < 0.05$
Murphy et al. [12]	116	24/4 cmH ₂ O	Parallel-group (oxygen)	6 weeks: SRI: 4.9 (95% CI: 0.4–9.3; $p = 0.03$) SGRQ: no difference 3 month: SRI: no difference SGRQ: –4.3 (95% CI: –8.4– –0.2; $p = 0.04$) 1 year: SRI: no difference SGRQ: no difference [#]

HRQoL: Health-related-quality-of-life; CRQ: Clinical Respiratory Questionnaire; GH: General health subscale of the SF-36; MH: Mental health subscale of the SF-36; MRF: Mageri Foundation Respiratory Failure item set; of patients randomized and followed; SF-36: MOS 36-Item short-form health survey; SGRQ: St. George's Respiratory Questionnaire; SRI: Severe Respiratory Insufficiency Questionnaire; IPAP/EPAP: Inspiratory/expiratory positive airway pressures; # Difference Adjusted for baseline values

diseases, and is therefore suitable for evaluating treatment effects in this cohort [55]. In the corresponding validation study, high psychometric values for reliability and validity were demonstrated for SRI. These findings were later confirmed in a consecutive trial in COPD patients [52].

6.1. Future trends in quality-of-life research

In order to use HRQoL assessment as a primary endpoint in clinical trials, a minimal clinical important difference (MCID) is required. The minimal clinical difference is already known for the SGRQ and SF-36 [60,64–66], while an MCID of ~5 points was just recently shown for the SRI.

The applicability of the questionnaires is essential so that they can be adapted to the specific needs of the patient cohort concerned. The availability of questionnaires in the patient's native language is also invaluable. The language availability and other characteristics of the questionnaires most commonly used in NIV RCTs to measure quality of life are summarized in Table 3.

An additional key aspect of future trends in this area of research is the digitalization of questionnaires for easier use in clinical practice. An application for a smartphone or tablet is available for different HRQoL assessment tools, such as the SF-36 and recently SRI, which can also be used in studies by transferring the data after patient approval (Figure 5). A web application system was developed for scoring the SGRQ, which also enables digital data input and direct evaluation

(e.g. for scientific studies) [67]. According to data from a validation study of the SRI application, this particular digital approach is advantageous to the conventional method of

Table 3. The most common instruments used in RCTs to assess quality of life in patients treated with noninvasive ventilation.

Questionnaire	Characteristics	Languages	Items	Availability	App
SRI [50,53,59]	Specific tool for assessing health-related quality of life in patients with chronic respiratory insufficiency	15+	49	https://www.pneumologie.de	Yes
SGRQ [58,82]	Disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airway disease.	77	50	sgrq@sgul.ac.uk	Yes*
SF-36 [83,84]	Survey of general health status for healthy reference populations and specific disease groups.	170+	37	https://www.optum.com	Yes

* web application for Apple, Microsoft and Linux systems.

Figure 5. SRI application.

Abbreviations: SRI: Severe Respiratory Insufficiency Questionnaire

paper questionnaires, because missing data input is completely avoided [68].

Some of the above-mentioned questionnaires have the disadvantage of being too complex due to the large number of questions needed to capture the different dimensions of HRQoL. This can then make the transition from study findings to daily clinical practice difficult. In this regard, the recently validated S^3 -NIV questionnaire provides a simple tool for assessing NIV-related domains for clinical practice, based on a simple scoring algorithm and a limited number of items ($n = 11$) [69]. Simplifying the method of measuring HRQoL

can then make it possible to assess Patient-related outcomes in daily clinical practice.

7. In-patient vs. outpatient set-up for NIV

There are currently no scientific data available on the exact number of patients receiving invasive or noninvasive ventilation therapy. A European evaluation (EuroVent) conducted 15 years ago counted more than 21.500 (6.6/100.000) patients with chronic respiratory failure who were receiving HMV [70]. Two recently published analyses also highlighted that the

actual number of patients receiving HMV is much higher than that derived from the results of the EuroVent survey [71,72].

Based on these findings, and taking into account the ever-increasing incidence of COPD patients, it can be assumed that the number of patients on HMV will continue to rise. However, this is occurring in the face of declining healthcare capacities worldwide, due to an aging population and increasingly complex treatment regimes. A continuous increase in the number of patients on mechanical ventilation will therefore pose a major challenge to the health-care system. In addition, this group of patients is at high risk of hospital-transmitted diseases [73]. Therefore, transferring the patient from in-hospital to outpatient care is preferable, as long as the advantages of the latter are carefully weighed up against those of the former. Regarding the feasibility of outpatient care for patients on HMV, several recent studies have shown that initiation of therapy and outpatient control is possible in patients with neuromuscular diseases [74–78] and COPD patients [45,79]. The extent of blood gas improvement and HRQoL gain with NIV was similar in patients initiated and controlled in outpatient care versus those who were admitted to in-hospital care for initiation and controls [9]. This is an important observation, since outpatient care can indeed reduce the costs and complications associated with hospitalization [73], although the latter has not yet been investigated and should be the focus of larger studies in the future.

It is important to note that adequate structural management of outpatient care also brings the benefits of the outpatient sector in terms of ongoing doctor-patient contacts and a firm doctor-patient relationship. This is particularly important for building the trust required for actions such as setting a therapeutic limit or perhaps even terminating therapy, if it shows to lead to uncontrollable side effects or no subjective benefit. In addition, outpatient care structures could form the intersection between several care actors and consequently form the basis of a care model, which would address not only treatment monitoring but also homecare and education of the patient.

However, it should be noted that this varies greatly between countries, based on the differential organization of healthcare systems. In a system where outpatient and in-patient medicine is highly interlinked and outpatient care is already established, costs will be lower than those in countries where outpatient care structure is limited and needs to be developed from scratch, and where the geographical distances between outpatient centers and patients are extensive. In near future, telemedicine could serve as an alternative solution for the establishment of an outpatient care structure, even in regions with challenging conditions.

8. Telemonitoring

Ventilators for HMV can be equipped with a remote monitoring device that enables supervision over particular treatment from a distance. This can enable physicians in specialized centers to monitor settings and adherence to therapy in the home environment of the patient and potentially even adapt settings accordingly [80]. It is important to first distinguish between these remote options: telemonitoring is, by

definition, restricted to the follow-up of data from a distance. As soon as an intervention is involved, this action is referred to as ‘teletherapy,’ or more broadly speaking, ‘telemedicine.’ At a time when many new terms are arising, distinct and correct wording is especially important for ensuring that scientific consensus is established. Two different situations can be distinguished in the home NIV setting; firstly, remote monitoring/medicine can assist with the timely follow-up of patients on long-term NIV; secondly, remote monitoring/medicine can be used to initiate NIV at home.

Over the last decade, several studies have investigated the effect of follow-up telemonitoring in patients with COPD, and a few have focused on the population of COPD patients with chronic hypercapnic respiratory failure [81]. In a randomized cross-over trial by Chatwin et al. 39 patients with severe COPD who used either LTOT or NIV (84%) were randomized to extensive telemonitoring of physiological parameters and symptoms, or to standard care; however, no benefits of either approach were found during a 6-month period in terms of time to hospital readmission or HRQoL [82]. However, telemonitoring is a multi-faceted process that requires the establishment of a self-management plan for the patient. Other studies focused on the potential early prediction of exacerbations by machine readouts through telemonitoring [83]. The development of a sound algorithm which can detect the physiological changes/parameters that correctly predict poorer outcomes is critical to the success of these telemonitoring follow-up studies. Therefore, future trials need to assess the occurrence of physiological deviations from the norm in this patient collective, before robust parameters for the early detection of exacerbation can be identified. Using this approach, follow-up telemonitoring might lead to personalized treatment, selecting patients that need more care or a different type of therapy to that planned earlier. Furthermore, it could also avoid unnecessary care in patients who do fine on their own without a lot of control visits.

The appeal of telemedicine is its potential use in the establishment of long-term NIV. This makes it an attractive alternative to an in-patient NIV set-up, which otherwise places a large burden on healthcare facilities. In a Dutch randomized-controlled trial conducted in hypercapnic COPD patients, the possibility of initiating NIV at home with supplementary telemedicine care was investigated; the authors not only found this to be feasible, but also reported a substantial reduction in costs of over 50% compared to those associated with the initiation of NIV in an in-patient setting [45].

In summary, despite these positive results it remains difficult to find conclusive and decisive reasons that argue for or against telemonitoring. This is partly due to the lack of relevant long-term trials and partly because there is a multitude of possibilities for applying telemonitoring solutions. Furthermore, in terms of NIV in COPD patients, there still is no clear consensus on the required ventilator settings, the choice of interface, application modes, ventilation rationale, or what the usual care of these patients consists of in general, irrespective of telemonitoring, which is why it is difficult to find consensus for ‘standard-therapy’ [81,84]. There are substantial differences throughout Europe in terms of what is considered to be standard care, which is why the results from one country are not

necessarily applicable to another. Nevertheless, in view of the challenges faced by the constant increase in patient numbers and the concurrent need to reduce healthcare costs but increase safety, telemedicine might certainly be an attractive option for tackling these issues.

9. Phenotyping – avoiding over- and under-use

In the process of defining the type of patient that benefits the most from NIV, the only clue that we have is that patients suffering from severe hypercapnia (>50 mmHg) who are initiated on HI-NIV appear to benefit most from this sort of therapy [51], at least with respect to CO₂ reduction. Further trials are required to investigate the phenotype of COPD patients and determine whether PaCO₂ really is the best – or merely a surrogate – parameter for the physiological expression of another mechanism that underlies improvements in survival and HRQoL. Furthermore, it would be interesting to investigate how to better distinguish between patients who respond well to therapy and those who respond poorly, and whether the variety of comorbidities that are often associated with COPD patients play a significant role.

It should also be noted that in some cases there may be unnecessary prescription of NIV, since this therapy is frequently initiated after acute exacerbations without reexamining recovery [79,85]. An outpatient setting provides the opportunity for short-term control visits that serve to reassess the NIV indication 2–4 weeks after exacerbation [79]. Additionally, it is of crucial importance not only to avoid an unnecessary prescription, but also not to miss an initiation of NIV therapy according to the guidelines. Here, very different approaches have been observed in different European countries. In the Netherlands, for example, the initiation of NIV only takes place in specialized centers, whereas in Germany, prescription of NIV can in theory be done by any licensed physician, without any expertise in ventilation therapy necessary. This is where a structured care system is essential to ensure proficient initiation and control of the therapy by taking into account the indication criteria and possible side effects.

10. Expert opinion

Recent trials have provided a sufficient base of evidence to suggest that long-term NIV is beneficial to patients with COPD in terms of physiological and patient-related outcomes. Patients undergoing long-term NIV treatment appear to benefit from the treatment itself, as well as the improved care package they usually receive, once instituted on long-term NIV. An apparent prerequisite for this is that NIV needs to be delivered in a way that maximally reduces chronic hypercapnia. Nevertheless, several issues still require ongoing attention. Firstly, a clear understanding of the physiological effects of NIV is necessary, in order to better comprehend the numerous interactions taking place at physiological, cellular, and molecular levels, and to select the patient that would benefit the most from this type of therapy. This, in turn, requires further research into the selection of optimal outcome parameters. There remains a necessity, to further comprehend which benefits we want to achieve, who to ventilate and when to initiate NIV. Given that current developments

point to an ongoing increase in the number of patients with HMV it is important to avoid overuse of this therapy, so as to prevent ‘bottlenecks’ in the medical care of a patient collective that is severely in need, but in the same time not risk underuse. Secondly, technological advances in the care and follow-up of severe COPD patients have emerged that serve to address this capacity issue. Telemonitoring and the establishment of specialized outpatient settings are such developments that promise to deliver helpful solutions. The last few years have been characterized by technological advancements in ventilator settings and modes, as well as in software and hardware developments. Although these technical solutions have the potential to increase cost-effectiveness and improve care, it is crucial to readdress the approach to treating severe cases of COPD so that the main focus is on the actual patient. Therefore, it is of utmost importance that we concentrate on patient-related outcomes and restructure therapies with the aim of delivering benefits in HRQoL. This, in turn, forms the basis for an effective, individualized care concept.

10.1. Five-year view

Studies carried out over the last few years in COPD patients with chronic hypercapnic respiratory failure have focused on finding the right settings for NIV, as well as the optimal time to initiate it. After a consensus is finally finding its way into an increasing number of guidelines, a glimpse into the future presents new tasks and new challenges.

- New developments, particularly advances in telemedicine, will be the focus of interest in coming years. In order to make these technologies more widely accessible, it is essential to use a common collaborative platform. In this respect, close collaboration between sectors will be required for further progress. Reliable data structures also need to be developed.
- Up until now, the type of patients that benefits the most from NIV has not been clearly identified. This question urgently needs to be addressed, as it can also help clinicians to avoid the initiation of therapy in cases where it will not only be less effective, but may also even increase the patient’s suffering. It also needs to be determined whether laboratory parameters such as CO₂ are sufficient, or simply serve as surrogates for not entirely understood physiological processes. It is of particular importance to establish a better insight into aspects of the intrinsic patient world and their actual concerns, including those at the end of life, to improve the overall standard of care.
- Based on existing scientific registry data sets such as those found in oncology, appropriate structures will be set in motion to accommodate the increasing number of patients. A large database also offers the future possibility of developing individualized therapy strategies, since a ‘one-size-fits-all’ principle cannot be applied to the COPD-chronic hypercapnic respiratory failure patient group. Moreover, ethical and economically acceptable care models need to be established.

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