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Expert Review of Respiratory Medicine

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierx20

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To cite this article: F. Soleimani, D.W. Donker, E. Oppersma & M.L. Duiverman (2024) Clinical evidence and technical aspects of innovative technology and monitoring of chronic NIV in COPD: a narrative review, Expert Review of Respiratory Medicine, 18:7, 513-526, DOI: 10.1080/17476348.2024.2384024

To link to this article: https://doi.org/10.1080/17476348.2024.2384024

Published online: 13 Aug 2024.

EXPERT REVIEW OF RESPIRATORY MEDICINE
2024, VOL. 18, NO. 7, 513–526
https://doi.org/10.1080/17476348.2024.2384024

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REVIEW

Clinical evidence and technical aspects of innovative technology and monitoring of chronic NIV in COPD: a narrative review

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ABSTRACT

Introduction: Chronic nocturnal noninvasive ventilation (NIV) improves outcomes in COPD patients with chronic hypercapnic respiratory failure. The aim of chronic NIV in COPD is to control chronic hypercapnic respiratory insufficiency and reduce symptoms of nocturnal hypoventilation, thereby improving quality of life. Chronic NIV care is more and more offered exclusively at home, enabling promising outcomes in terms of patient and caregiver satisfaction, hospital care consumption and cost reduction. Yet, to achieve and maintain optimal ventilation, during adaptation and follow-up, effective feasible (home) monitoring poses a significant challenge.

Areas covered: Comprehensive monitoring of COPD patients receiving chronic NIV requires integrating data from ventilators and assessment of the patient's status including gas exchange, sleep quality, and patient-reported outcomes. The present article describes the physiological background of monitoring during NIV and aims to provide an overview of existing methods for monitoring, assessing their reliability and clinical relevance.

Expert opinion: Patients on chronic NIV are 'ideal' candidates for home monitoring; the advantages of transforming hospital to home care are huge for patients and caregivers and for healthcare systems facing increasing patient numbers. Despite the multitude of available monitoring methods, identifying and characterizing the most relevant parameters associated with optimal patient well-being remains unclear.

ARTICLE HISTORY
Received 29 March 2024
Accepted 21 July 2024

KEYWORDS
COPD; gas exchange; monitoring; telemonitoring; noninvasive mechanical ventilation; patient-ventilator asynchrony; quality of life; sleep quality

1. Introduction

End-stage Chronic Obstructive Pulmonary Disease (COPD) may ultimately lead to chronic respiratory failure, which not only limits life expectancy but also severely impairs the patient's Health-Related Quality of Life (HRQoL) [1,2]. Although treatment options for COPD patients with chronic respiratory failure are limited, it has been shown that chronic nocturnal noninvasive ventilation (NIV), initiated in professional care environments, results in physiological and clinical benefits for these patients [3–7]. The number of patients depending on chronic NIV has been growing over the past decade [3,8–10], increasing the load on healthcare for initiation and follow-up visits. However, shortage of resources and especially healthcare personnel is regarded as a worldwide health crisis [11]. Moving NIV care to the patient's home both during the initiation period and follow-up moments will reduce cost, decreases the burden on the hospital and, above all, complies with patients' preferences [12].

Providing chronic NIV at home to COPD patients requires careful titration and monitoring to obtain and maintain adequate settings for optimal carbon dioxide (CO_2) reduction and, thereby, optimal clinical outcomes [13]. However, monitoring of chronic NIV poses several challenges. Which parameters should be monitored is still debated; while ventilator data can be automatically obtained without adding additional monitoring equipment, the necessity to substantially reduce CO_2 levels in COPD patients does require gas exchange to be monitored. However, CO_2 reduction only partially explains the gain in HRQoL that COPD patients experience when started on chronic NIV [14]. Thus, to achieve optimal ventilation in terms of comfort and clinical outcomes, it might be necessary to obtain more detailed data on the patient's respiratory effort, lung mechanics, and the interaction between the patient and the ventilator, reflected by patient ventilator (a)synchrony (PVA). Currently, it is unknown which monitored variables are related to the improvement or deterioration of a patients' clinical condition and HRQoL [14]. Monitoring at home poses the very specific challenge of being absolutely easy-to-use, practical and noninvasive without the need for professional help. Preferably, the monitoring devices should also be able to function in a telemonitoring system, enabling clinicians to monitor a patient remotely from a central hub [12].

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Article highlights

- Ventilators provide reliable data on compliance, and pressure and flow waveforms. Tidal volume, leaks, apnea hypopnea index (AHI), and patient triggered breaths as provided by the ventilators need to be interpreted with caution as there are many confounding factors in their calculation.
- Monitoring of patient-ventilator asynchrony might also be attractive in chronic NIV, as correcting for patient-ventilator asynchrony (PVA) might optimize ventilation and increase comfort. However, what the optimal method is to quantify PVA in chronic NIV is unclear; and quantification of PVA using noninvasive methods such as surface EMG needs further validation.
- Monitoring CO_2 levels nocturnally at home is feasible with transcutaneous carbon dioxide tension ($PtcCO_2$) monitoring; however, the relationship between nocturnal and daytime gas exchange in COPD is not straightforward.
- As nocturnal NIV is to a large extent provided during sleep, its intended benefit is related to sleep quality, which implies the necessity to promote research on how to monitor and improve sleep quality in COPD patients with chronic hypercapnic respiratory failure (CHRF).
- As the most important aim of chronic NIV in COPD is to improve Health-Related Quality of Life (HRQoL), patient reported outcomes should be monitored, with short and concise questionnaires.
- Initiation of chronic NIV at home with the use of telemonitoring in patients with COPD is safe, feasible, and non-inferior with regard to efficacy as compared to standard in-hospital initiation of chronic NIV. Follow-up interventions including telemonitoring of COPD patients on chronic NIV have also been shown to be feasible and might improve HRQoL and prolong the time to readmission. Technological advances in integrated and reliable data collection and analysis can enhance remote monitoring in initiation and follow-up of chronic NIV in COPD.

In this comprehensive narrative review, first, the pathophysiological background of chronic hypercapnic respiratory failure and the multifactorial working mechanisms of NIV in COPD are discussed, in order to understand more properly why advanced monitoring is relevant. Consecutively, currently available monitoring techniques for patients on chronic NIV are critically appraised, including monitoring of parameters directly provided by ventilators and derived indices, detection of PVA in long-term NIV, gas exchange monitoring, and monitoring of quality of sleep and symptoms/quality of life. Finally, we will discuss the evidence and specific aspects of telemonitoring to initiate and follow COPD patients on NIV at home. Through this explorative review, we aim to enhance the understanding of chronic NIV monitoring in COPD in order to optimize care strategies for improved outcomes.

2. Methods

As this is a narrative review, the authors (MD, EO, FS) searched PubMed using different search terms based on relevance to the selected topics/paragraphs. Also, reference lists of reviews or other relevant papers were quarried. Appropriate studies were included in the final manuscript.

3. Physiological background of chronic hypercapnic respiratory failure

COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production). Abnormalities of the airways and/or alveoli cause persistent, often progressive, airflow limitation [15] that causes a significant increase in the work of breathing [16]. In COPD patients, increased expiratory resistance leads to dynamic hyperinflation, causing an increase in inspiratory threshold loading. In addition, impaired gas exchange requires increased ventilation to enable adequate oxygen uptake and CO_2 washout. However, hyperinflation hinders ventilation by decreasing the inspiratory capacity of the chest wall and increasing the elastic load of breathing [17]. It has been shown that respiratory muscle function is impaired not only by the hyperinflation itself, but also by cellular and molecular alterations (loss of myosin content, disruption of sarcomeres) in the diaphragm of COPD patients [18], associated with the severity of airflow obstruction [17]. When the inspiratory load increases, and the respiratory pump can no longer provide sufficient ventilation to meet the metabolic demands of the body, respiratory failure occurs. Patients will be unable to remove CO_2, resulting in increased arterial CO_2 partial pressures ($PaCO_2$). Additionally, chronic hypercapnia may lead to decreased sensitivity of chemoreceptors in the brain to changes in $PaCO_2$, in turn, leading to diminished ventilatory responses and the development of chronic CO_2 retention on top of the mechanical limitations [2].

Hypercapnic respiratory failure can occur acutely during an exacerbation, or chronically during the end-stage of the disease [13,19] and is associated with increased mortality and morbidity [20,21]. In patients with advanced COPD, chronic hypercapnic respiratory failure (CHRF) leads to additional invalidating symptoms such as morning headache, and fragmented and un-refreshing sleep resulting in chronic fatigue and daytime sleepiness [13]. NIV provides ventilatory support via a facial interface, which can be for example a nasal, oronasal, or total face mask [22,23]. It has been shown that NIV in COPD patients with acute respiratory failure reduces risks of mortality and endotracheal intubation, improves gas exchange and reduces length of hospital stay and mortality [23]. Following an exacerbation, continuing NIV afterward at home in COPD patients with persistent severe hypercapnia has been shown to prolong admission-free survival [4,6]. In COPD patients with CHRF, studies have shown that lowering $PaCO_2$ using NIV improves survival [24,25] gas exchange and HRQoL [4,26–28]. The mechanisms through which NIV improves these outcomes have been hypothesized to be multifactorial and related to underlying pathophysiological mechanisms (see Figure 1). The evidence on changing lung mechanics is limited, and mainly measured during spontaneous breathing. While one previous study using daytime NIV did show that this strategy improves hyperinflation [29], more recent data from randomized controlled trials using nocturnal NIV did not measure [5], nor show persistent changes in lung volumes or lung mechanics [30]. It has been postulated that nocturnal NIV provides rest to chronically loaded respiratory muscles and increases muscle strength during the day [29,31,32]. However, it is questionable whether diaphragm fatigue really exists in chronic COPD patients [33]. Studies investigating respiratory muscle strength after a period of chronic NIV showed controversial results, without effects of NIV on the maximal inspiratory pressure or muscle force reflected by the twitch pressure [4,33]. A third

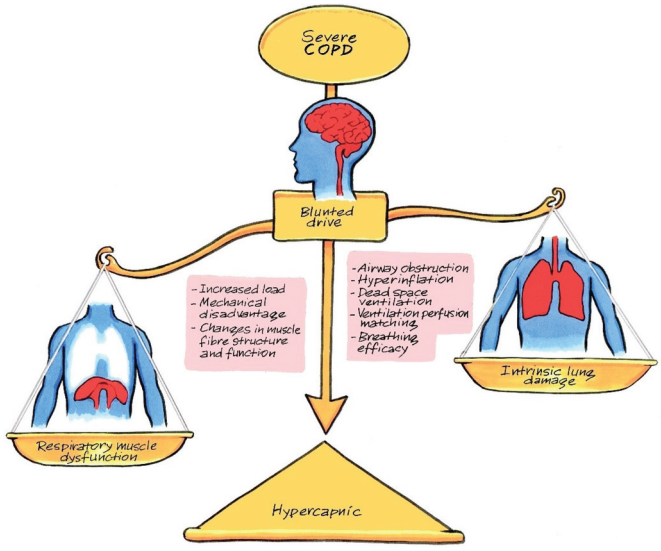

Figure 1. Multifactorial causes of pathophysiology in COPD patients with hypercapnic respiratory failure. (illustration designed by M. Duiverman and produced by Roelof Wijtsma (https://www.roelofwijtsma.nl/))

proposed mechanism might be that nocturnal NIV resets the ventilatory response to CO_2. This mechanism is difficult to investigate, as measuring this with the classical hypercapnic ventilatory response curve has limitations, especially in patients with COPD. Small sample-sized studies by Nickol et al. did show that chronic NIV might increase ventilatory sensitivity to CO_2 in patients with neuromuscular diseases, restrictive thoracic diseases and COPD, and this might explain the persistent CO_2 reduction during daytime when using nocturnal NIV [28,34]. However, the COPD patients included in this study were also frequently suffering from concomitant obstructive sleep apnea [35]. Finally, nocturnal NIV might improve sleep, reduce the number of nocturnal desaturation events and arousals, and thereby improve daytime functioning [26,33].

Considering the complex pathophysiology of CHRF and related, multifaceted opportunities for improvement through application of chronic NIV, it is evident that to gain insight in mechanisms, differences in individual treatment response between patients, and optimal individual titration of NIV, sophisticated monitoring of patients on chronic NIV is necessary.

4. Monitoring of ventilator data

A wealth of information is available either in raw or processed forms from modern home ventilators. A distinction can be made between parameters that are set by the caregiver, parameters that are measured within the ventilator, and parameters that are calculated or estimated from measured parameters.

All home ventilators provide reliable data on daily usage. Furthermore, pressures and flows are directly measured via a built-in pneumotachograph and related waveforms of every breathing cycle can often be retrieved and displayed on the screen of the device. Parameters like tidal volume (V_T), leakage and airway obstructions can be calculated or estimated based on these pressures and flows.

4.1. Tidal volume and leak estimation

There is variability in methods to calculate V_T and leaks, depending on the estimation algorithms of manufacturers [36]. In general, V_T can be estimated from the measured flow in the circuit, by the built-in pneumotachograph. The flow dynamics during both inspiratory and expiratory cycles is presented in Figure 2. Current home mechanical ventilators are equipped with a single-limb circuit, which leaks out the expiratory flow, called the intentional leak (F_{IL}). Besides, providing NIV inevitably comes with leakage due to insufficient closure of the face mask, called unintentional leak (F_{UL}). The remaining flow in the tube during expiration is represented in Figure 2 by the end expiratory flow ($F_{E,exp}$).

To calculate V_T, it is crucial to correct the total flow (F_T) provided by the ventilator for these leaks. The total leak flow, which is the sum of intentional leak flow and unintentional leak flow, is equal to $F_{E,exp}$, since at the end of expiration $F_{P,exp}$ is zero [37]. Using this estimated total leak value ($F_{UL+}F_{UL}$) enables estimation of V_T from $F_{P,exp}$, using the expiration equation in Figure 2.

However, bench studies have shown that V_T is underestimated up to 20% by different ventilators, mainly due to increasing and difficult-to-estimate leaks, which is even more challenging in single limb circuits with an expiratory leak port in the mask or tubing [36–38]. As obstructive breathing patterns are associated with expiratory difficulties, where F_P might be defined at nonzero flow, the detected $F_{E,exp}$ is underestimated, leading to underestimation of $F_{P,exp}$ and leak flow, and subsequently an underestimation of V_T durin\.

Besides, providing NIV inevitably comes with leakage due to insufficient closure of the face mask. This unintentional leak could be calculated by subtracting the intentional leak from

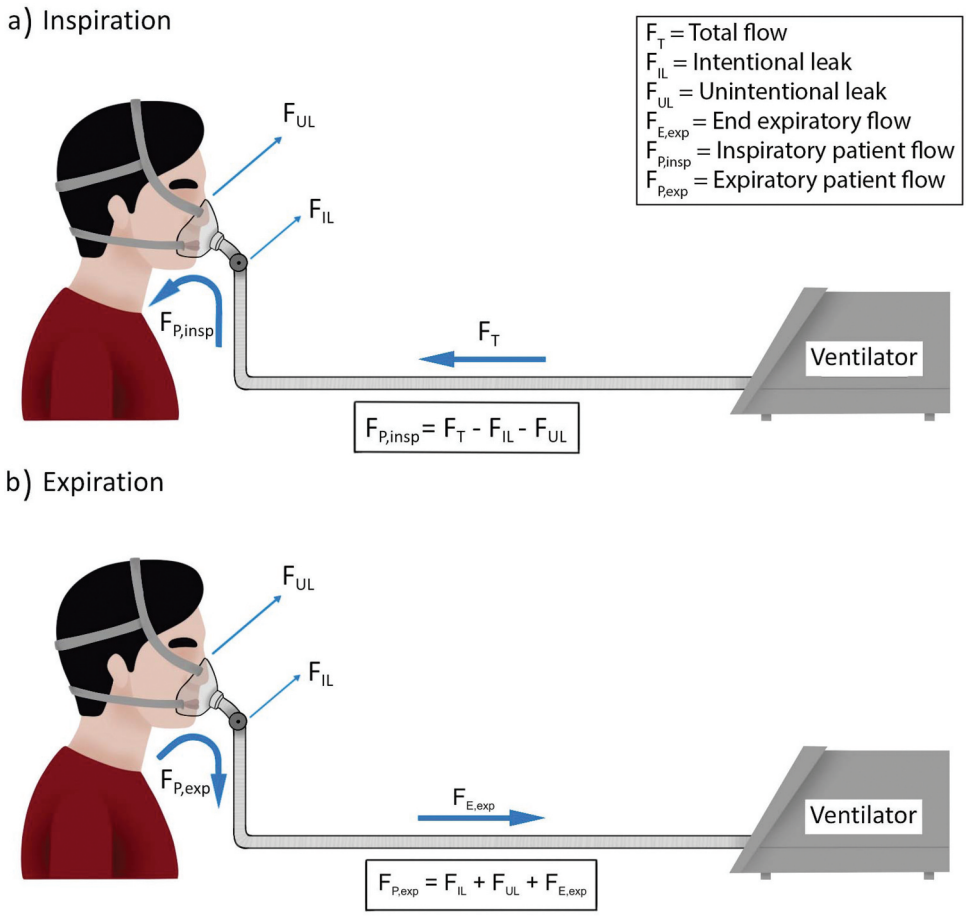

Figure 2. Schematics of flow in the ventilator circuit: a) inspiratory patient flow ($F_{P,insp}$) is calculated by subtracting the estimated intentional and unintentional leak (F_{IL} and F_{UL}) from the total flow (F_T); b) expiratory patient flow is calculated by summation of F_{IL} and F_{UL} with end expiratory flow ($F_{E,exp}$).

the total flow again at the end of expiration as patient flow is zero [37]. Sophisticated algorithms are incorporated in modern ventilators, to continuously monitor and compensate for leaks and thereby maintain the set inspiratory and expiratory pressure. However, calculating unintentional leaks at the end of expiration does not represent the whole respiratory cycle, resulting in suboptimal accuracy of V_T estimation [37]. While measuring total leaks (sum of intentional and unintentional leaks) has acceptable accuracy, measuring intentional leaks precisely is difficult, while the unintentional leakage reported from the ventilator has less accuracy [39]. Correcting leaks contributes to the accuracy of V_T calculations, and the interpretation of the apnea hypopnea index (AHI) [39] and calculation of the amount of patient triggered breaths [40].

4.2. Apnea assessment

Upper airway obstruction could be detected by assessing the AHI index displayed by the ventilator software. The ventilator detects obstructions via algorithms based on the force oscillation technique, periodic changes of flow, or both [41]. The AHI provided by the ventilator software has shown good correlation with manually scored polysomnography (PSG) and polygraphy (PG) for stable obesity-hypoventilation patients [42,43]. In stable patients with chronic respiratory failure due to neuromuscular diseases and chest wall disorders under chronic NIV, it has been shown that AHI calculation by the ventilator software was sufficient for adjusting the ventilator settings, without the need for PG [44]. However, in the presence of excessive unintentional leaks, AHI may be unreliable. Additionally, flow waveforms might be analyzed for possible obstructive events [39]. Through a detailed inspection of flow curves, periods of flow curve flattening with maintained pressure points out toward upper airway obstructions.

4.3. Time related parameters

The assessment of time-related parameters from the ventilator, like ventilator triggers and cycling, is usually reliable [39]. Ventilators detect patient triggered breaths through the measurement of flow variations by a flow sensor in the machine [45]. Respiratory rate, and percentage of breaths triggered by the patient provided as based on ventilator software could potentially be unreliable due to low inspiratory effort, PVA and leaks [39,41].

4.4. Clinical relevance of ventilator data

Among the data captured by the ventilators, it is important to identify which parameters provided by the ventilator software are associated with clinical outcomes (21). As compliance is

a crucial element of treatment efficiency, this should be monitored closely. It is recommended that usage should be at least 5 h per day, as outcomes are proved less beneficial <5 h/day [14,46,47]. Also, NIV use >9 h/day has been shown to be associated with a higher risk to develop acute exacerbation and notably with mortality, at least in a group of very obese COPD patients with concomitant sleep apnea [48].

Moreover, as leaks reduce ventilatory efficiency, this should be checked routinely. Especially, when the flow rate is >40 L/min [49], NIV therapy is prone for excessive leaks. Excessive leakage leads to PVA, decrease in sleep quality, reduced compliance [39] and compromises the reliability of V_T estimation, as well as calculations on percentage of cycles triggered or cycled by the ventilator [36], and AHI calculations.

Another important parameter that should be routinely checked for, are upper airway obstructions, as these reduce comfort, affect ventilatory efficacy, increase leaks and may worsen outcome, as has been shown in patients with Amyotrophic Lateral Sclerosis [50]. Reducing upper airway obstructions might be rather straightforward, for example by increasing expiratory pressure, better fitting of the mask, or changing from an oronasal to nasal mask [51]. However, decreasing these obstructions can be also very complicated for example in patients with bulbar involvement of their disease, in whom imaging of the upper airway, by ultrasound and/or laryngoscopy, might be needed to titrate the pressures [52,53].

4.4.1. Prediction of exacerbations

Ventilator data could be utilized for prediction of COPD exacerbations. Studies have shown that the average respiratory rate, the percentage of respiratory cycles triggered by the patient, and the daily level of adherence, all obtained from the ventilator, might predict the onset of a COPD exacerbation [54–56]. However, the sensitivity and specificity of these parameters in predicting exacerbations was moderate and required several days of measuring. While monitoring of ventilator data can be done almost automatically and remotely by using online platforms, studies on the predictive value of more detailed ventilator data on clinically relevant outcomes are needed.

4.4.2. Future assessment of ventilator data

Currently, monitoring ventilator data is mostly based on readouts, with different ventilators providing different presentations of nightlong data. Although summary data might suffice for the majority of patients on long-term ventilation, in patients that have difficulties adjusting to the ventilator, a shift toward more sophisticated monitoring might be essential. Implementing dedicated monitoring systems that not only analyze the raw ventilator data but also provide caregivers with the ability to scroll through detailed, unprocessed information, and connect this to other parameters of ventilatory efficacy (such as gas exchange data or data on patient effort), will significantly enhance identification of any abnormalities or trends and ultimately may allow to connect these to relevant patient outcomes.

Finally, after adherence, leaks and obstructions are corrected for, a more detailed assessment of pressure and flow curves can provide insight in the interaction between the patient and the ventilator, so-called PVA.

5. Patient-ventilator asynchrony in nocturnal chronic NIV

Over the last decade, investigating the interaction between the patient and the ventilator, notably by analyzing PVA, has gained attention in patients on long-term home NIV. During NIV provided for acute respiratory failure, it has been shown that PVA impacts ventilatory efficacy and comfort [57,58]. However, in patients receiving chronic NIV, the evidence on the clinical relevance of PVA and how and when to monitor PVA is limited and needs more research. As recently surveyed, practice variation exists in the assessment of PVA during chronic NIV, based on availability of equipment and expertise [59]. To make monitoring of PVA feasible in long-term care, quantification should be standardized and automized.

5.1. Definition of PVA and how to correct

For analysis of PVA, it is important to have a clear definition of the asynchronies observed in chronic NIV. Eight different types of PVA have been defined in chronic NIV [60], see Figure 3. It has been observed that rate asynchronies, namely ineffective efforts, auto triggering and double triggering, are more prevalent than cycling asynchronies across different underlying diseases being treated with chronic NIV [61]. Figure 4 illustrates common types of asynchronies in chronic NIV. Ineffective efforts or delayed inspiratory triggering might be due to high intrinsic positive end-expiratory pressure, a low ventilator trigger sensitivity, and inadequate respiratory drive and/or effort due to diminished central drive and/or weak respiratory muscles [40,45,62–66]. Also, leaks might cause ineffective triggering. Auto triggering results from inappropriate triggering of ventilation when the patient is not attempting to initiate a breath and may be caused by a too high set triggering sensitivity, or excessive leaks [67].

Double triggering or multiple triggering, which is the delivery of two or more breaths with a single patient effort, is usually due to a prolonged patient effort not being matched with the ventilator's inspiratory time. This might be the case when the inspiratory time is set too short and/or insufficient assistance is provided during that inspiration. Double triggering often occurs with premature or early cycling meaning that the ventilator cycles from in- to expiration too early, so before the patient's effort ends, and can be solved by increasing the pressure support or increasing inspiratory time, the latter especially in patients with low compliance of the lungs or chest wall.

Relatively rare intracycle asynchronies as under assistance and overshoot indicate distortions of the flow and pressure curves with respect to the set inspiratory pressure, and thereby represent a mismatch between the patient effort and the support [60]. Lastly, phase asynchronies might occur, i.e. either premature or delayed cycling. Delayed cycling, where the ventilator cycles from in- to expiration too late, usually arises from setting a flow trigger that does not match the underlying disease. For example, in patients with

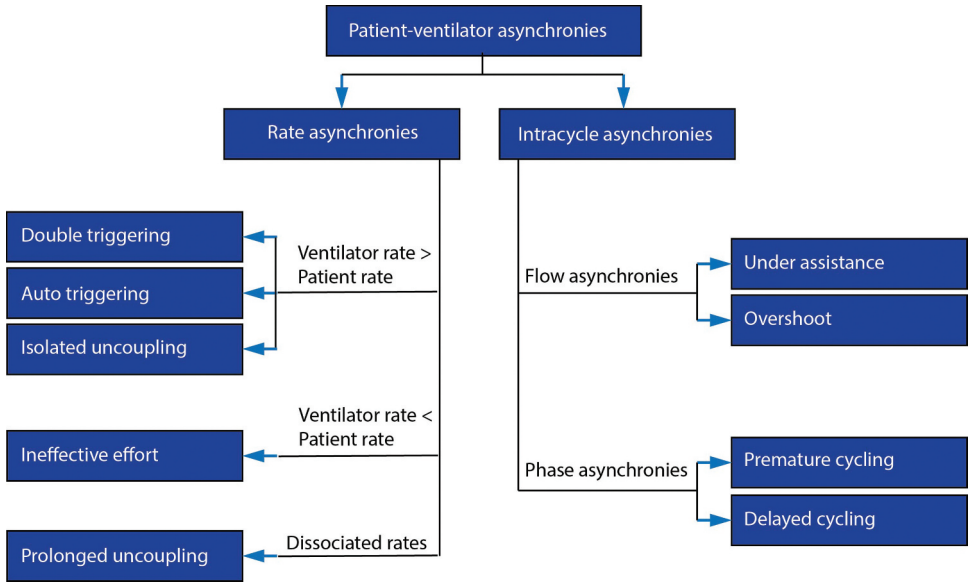

Figure 3. Overview of different types of patient-ventilator asynchronies.

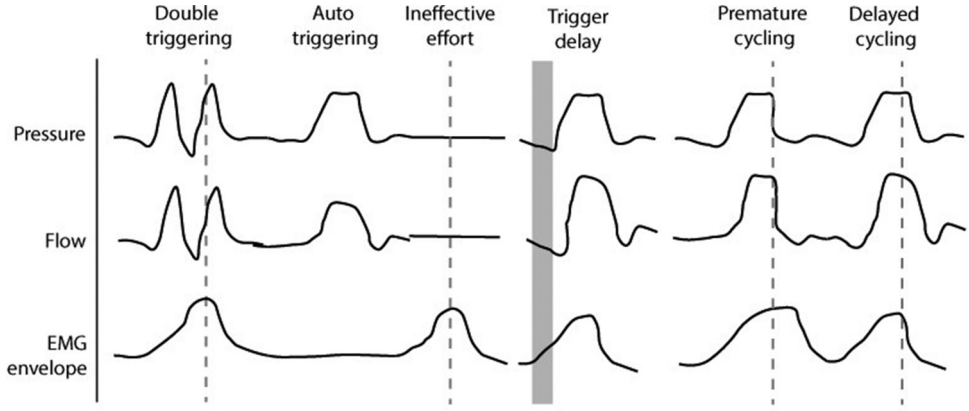

Figure 4. Representation of patient-ventilator asynchronies that are most common in chronic nocturnal NIV, with pressure, flow and EMG envelope tracings. Dashed lines show relevant time points where patient and ventilator are asynchronous, shaded area shows muscle activity without ventilator support.

COPD, the high lung compliance and expiratory flow limitation, due to airway collapse, might lead to a less steep flow reduction from peak inspiratory flow, leading to prolonged inspiratory flow once the flow trigger has been set at a too low percentage of peak flow. This has detrimental effects, as a too long inspiratory flow limits expiratory time and makes patients prone for dynamic hyperinflation [68].

5.2. Analysis of PVA in NIV

5.2.1. Ventilator data

Several methods are described to analyze PVA in chronic NIV. The first method is using only data provided by the ventilator. In a multicenter study, looking at ventilator pressure and flow tracings from patients on NIV for patients with acute respiratory failure, it was observed that the sensitivity to detect asynchronies was low, even in experienced hands. PVA were difficult to recognize and categorize in comparison with assessing PVA by additionally analyzing patient effort through assessing electrical activity of the diaphragm [69]. Automation can advance the assessment of PVA compared with visual analysis. In a recent study, flow and pressure waveforms have been scored using SyncSmart software for asynchronies. In cases where the respiratory rate was not excessively high, the automated software outperformed the experts in scoring asynchronies [70].

5.2.2. Electrical activity of the respiratory muscles

The second method to investigate PVA is the assessment of neural respiratory drive, by measuring respiratory muscle electrical activity. This method is a more direct way of assessing the patient's own effort, and thus might be of additional value in assessing the synchrony between the patient's effort and the ventilator's response. In invasive mechanical ventilation, numerous studies have shown the value of measuring the electrical activity of the diaphragm through an esophageal catheter [71,72]. Quantification of PVA using the electrical activity of the diaphragm has shown better sensitivity in comparison with only analyzing pressure and flow of the ventilators [69,73].

For home NIV, however, these techniques cannot easily be applied in its current form and alternative methods should be considered. Surface electromyography (EMG) of the respiratory muscles is considered a noninvasive surrogate marker of neural respiratory drive [74]. Analysis of surface EMG of parasternal muscles compared to pressure and flow curves of the ventilator showed a notable 79% occurrence of PVA among 28 patients with different disorders, as they were initiating home mechanical ventilation [61]. Using this method, a wide variety of PVA was identified to be prevalent in chronic NIV, including ineffective effort, auto triggering, double triggering, multiple triggering, premature expiratory cycling, delayed expiratory cycling and auto cycling.

5.2.3. Respiratory inductance plethysmography (RIP)

The third method used to quantify PVA is by using RIP, using elastic belts to detect thoracic and abdominal expansion, thus representing patient effort. Some ventilators are equipped with integrated poly(somno)graphy functionalities, enabling addition of RIP belts that could be used for synchronous data collection along with flow and pressure waveforms of the ventilator allowing to have a measure of patient's respiratory effort [75]. However, poly(somno)graphy is not widely available in the home setting, is expensive and RIP might not be sufficiently sensitive to detect the patient's effort, especially in the more obese individuals and patients suffering from neuromuscular diseases, in whom chest wall movements might be limited and paradoxical abdominal movements might occur [76].

5.3. The clinical relevance of monitoring PVA

The evidence on the clinical relevance of monitoring PVA in chronic NIV is unfortunately limited. In a small study performed by Adler et al., they managed to reduce morning breathlessness or deventilation dyspnea by correcting for PVA using a diagnostic PSG, and adjusting the ventilator settings accordingly [75]. The group of Ramsay et al. did show that PVA were prevalent during the initiation of NIV (in a broad group of patients with different underlying diseases), but there was no correlation with clinical outcomes like gas exchange [61]. However, more recent data by Arrestad et al. did show that there might be a relationship between the occurrence of PVA and experienced HRQoL in patients on long-term home NIV [77].

Current clinical data on monitoring of PVA in home NIV are limited and there is no consensus about the way to measure and analyze it. The most important reason is that the available techniques of mainly visual counting are very time-consuming and there is an obvious lack of automation [78]. Although, there has been progress in the transfer of an almost unlimited amount of (raw) data from home to an online platform, validated, broadly available algorithms for automatic detection of PVA using different monitoring parameters in home NIV are currently lacking. Also, adding measurements of patient effort (invasive EMG or plethysmography) is not easily applied in the home situation. The measurements are too cumbersome to perform in patients and also pose considerable problems for caregivers to use at home when patients are also needing to adjust and get used to their ventilator. To further advance the field, there is a need for a) more evidence on the exact magnitude of the consequences of patient effort and different types of PVA on clinical outcomes and ventilatory efficacy in long-term NIV, b) more integrated monitoring, and c) automated algorithms to detects PVA from the different signals.

6. Monitoring gas exchange

In COPD patients, relevant patient-centered outcomes, like survival and HRQoL have been shown to improve only if hypoventilation was adequately reversed [8], i.e. when a substantial reduction in CO_2 levels was achieved. Therefore, to ensure effective chronic NIV, gas exchange monitoring is essential.

Monitoring gas exchange in chronic NIV could be achieved via different methods, but there is no consensus on when and how to monitor. Daytime monitoring of gas exchange might not reflect hypoventilation occurring during the night [44,79,80]. Especially, in patients with a limited ventilatory capacity, where CO_2 levels might rise during the day despite correct nocturnal ventilatory support. Nevertheless, in a small group of patients with CHRF due to COPD, Windisch et al. showed that patients might be able to sustain the benefits [81]. Unfortunately, the relationship between nocturnal and daytime gas exchange levels in COPD patients with chronic NIV is not well understood.

6.1. Blood gas analysis

Monitoring gas exchange during chronic NIV demands that the technique is easy to use, and feasible for at-home measurement. Blood gas sampling (either arterial, capillary or venous) is usually not feasible in the home setting, as an expensive device and caregivers with experience in blood sampling are needed. Although arterial blood gas analysis is the gold standard, taking a venous blood gas is usually easier and less painful compared to an arterial sample. Another alternative is capillary blood gas analysis. For pH and $PaCO_2$, earlobe capillary blood gas analysis is regarded as a substitute for an arterial blood gas analysis. However, capillary blood gas analysis is less accurate for PaO_2 results, especially in patients in hypoxemic COPD patients [82].

A big disadvantage of blood gas sampling is that it is a snapshot, and results might be influenced by the exact moment and circumstances under which the sample is taken. Therefore, having noninvasive continuous monitoring of gas exchange has advantages. Although end-tidal carbon dioxide tension ($EtCO_2$) is often easy to measure, this has important drawbacks. First, EtCO2 monitoring is not reliable in the patient under NIV, mainly because of intentional and unintentional leakage. Second, in COPD patients [82], $PaCO_2$ is evidently underestimated due to dead space ventilation [83,84]. Therefore, measuring $PtcCO_2$, is more useful [85–87]. Nocturnal monitoring of $PtcCO_2$ has been shown to be feasible also at home in high correlation with arterial blood gas analysis for CHRF patient utilizing NIV [88,89].

6.2. Pulse oximetry

A recent survey showed [59] that many clinicians use peripheral oxygen saturation measured by pulse oximetry (SpO_2) to monitor chronic NIV. SpO_2 monitoring is easy, and many techniques including wearables have been developed to measure SpO_2 at home. However, reliability of SpO_2 use is questionable in monitoring chronic NIV. With only SpO_2 monitoring hypoventilation might be missed [44]. Furthermore, in patients with COPD, additional oxygen supplementation might result in fairly acceptable SpO_2 levels while hypercapnia is remaining.

7. Sleep quality during nocturnal chronic NIV

7.1. Clinical rationale

Patients with CHRF frequently report poor sleep quality, represented by symptoms of sleepiness and fatigue during the day, and resulting in a significant impact on the quality of life [90]. It has been shown that during sleep the neural drive to breath is reduced, resulting in sleep-associated hypoventilation [91]. Moreover, the force generating capacity of the diaphragm of COPD patients is usually affected, especially in case of severe hyperinflation. In these patients, as the accessory respiratory muscles on which they usually rely are completely relaxed during REM sleep, severe COPD patients are extremely prone to REM-related hypoventilation. This might be wrongly considered as concomitant sleep apnea, as a sleep study will count repeated hypopneas during REM sleep. Finally, there is debate about the prevalence of concomitant sleep apnea in patients with COPD. In general, the prevalence seems to be equal to the general population, and dependent on the specific COPD phenotype. Furthermore, the more severe the COPD, the less prevalent upper airway obstructions are [92]. This cascade of events during sleep worsens respiratory failure, cardiovascular and other co-morbidities, and ultimately survival [93].

NIV is aimed at reducing hypoventilation, hence it is logical to provide it during the night. However, it has also been reported that NIV can have a negative impact on sleep quality, particularly in cases of patient – ventilator asynchrony or leakage [82]. Fortunately, studies have also shown that NIV improves sleep quality, with increases in both slow-wave and REM sleep and beneficial effects on the Respiratory Disturbance Index, daytime sleepiness and HRQoL [94].

7.2. Monitoring sleep quality

Multiple techniques have been described in literature to monitor sleep quality, both subjective and objective, ranging from sleep quality questionnaires to the gold standard being the highly complex nightlong PSG [84]. As chronic nocturnal NIV is applied in a home setting, monitoring sleep quality requires easy and objective measures other than the full PSG.

Questionnaires can be used to report patient experiences and outcomes. In the Severe Respiratory Insufficiency (SRI) questionnaire, which will be further discussed in the next section of this review, a specific sleep section is included to assess sleep quality. The Pittsburgh Sleep Quality Index is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval to distinguish good and poor sleepers [95–97]. However, the Sleep Quality Index showed varying scores in different studies in COPD patients, potentially due to varying comorbidity burden in different COPD subgroups [98], which complicates using these questionnaires to objectively assessed sleep quality under NIV.

More objective and easy-to-use technology is emerging with the rise of wearable technology, including aspects of the full PSG [99] For example, oxygen saturation and its pulse wave amplitude can be monitored to assess sleep fragmentation [84]. In modern watches, actigraphy is often implemented to quantify sleep or wake by measuring body movements, although specific sleep stages cannot be classified. However, data is lacking on analysis and interpretation of sleep quality, in terms of sampling frequency and signal averaging, and how these are related to NIV and its settings to improve quality of sleep [84].

8. Patient reported outcomes

As COPD is often a progressive disease and at the stage of CHRF, a disease with a limited life expectancy, one of the main goals of chronic NIV is to reduce the patient's symptoms and improve HRQoL. Monitoring patient-reported outcomes as a complement to clinical and physiological improvements is thus essential in chronic NIV monitoring.

There is an extensive number of questionnaires available assessing HRQoL in patients with COPD. Disease-specific questionnaires, like the St. George's Respiratory Questionnaire (SGRQ), the Clinical COPD Questionnaire (CCQ), and the COPD Assessment Test (CAT) cover the main symptoms that COPD patients encounter, like dyspnea, cough and sputum production. However, for patients that suffer from CHRF, symptoms of hypoventilation influence their HRQoL, and capturing these symptoms (like headache, fatigue, complaints of bad sleep), is important to get a broad view on HRQoL in these patient groups. Therefore, multiple questionnaires have been developed and validated to measure patient-reported outcomes and HRQoL (see Table 1) for patients with CHRF. The SRI questionnaire, originally developed in Germany [100], is now widely available in many languages [107–115], and has been used in multiple chronic NIV trials to assess patient-reported outcomes [5–7]. Recently, even an online application has been developed and validated, which has been shown to be not inferior compared to the paper format [116]. The Maugeri Respiratory Failure (MRF-28) is another HRQoL questionnaire developed for CHRF patients, but studies have shown that the SRI is more sensitive to change [117]. However, as both the SRI and MRF-28 questionnaires have been developed for research purposes, they are both quite long, and therefore might be too cumbersome to use in daily life. Recently, a short 11-item questionnaire was developed assessing both symptoms as well as comfort with NIV therapy, the S^3NIV [101]. Also, this questionnaire has been translated and validated in other languages [118,119].

Table 1. Overview of questionnaires.

Questionnaire	Aim	# items	Scoring	Reference
HRQoL questionnaires developed for patients with CHRF				
SRI	HRQoL	49	0–100*	[100]
S^3NIV	Symptom and NIV assessment	11	0–10*	[101]
MRF28	HRQoL	28	0*–42	[102]
Disease-specific COPD questionnaires				
CCQ	Health status	10	0*–6	[103]
CAT	Health status	8	0*–40	[104]
SGRQ	HRQoL	50	0*–100	[105]
CRQ	HRQoL	20	0–100*	[106]

Aimed score indicated by *. Abbreviations: Severe Respiratory Insufficiency (SRI), Maugeri Respiratory Failure (MRF28), Clinical COPD Questionnaire (CCQ), COPD assessment test (CAT), St. George's Respiratory Questionnaire (SGRQ), chronic respiratory questionnaire (CRQ).

9. Telemonitoring

It is crucial to monitor chronic home ventilation at the patient's residence. Digital technology allows caregivers to remotely access ventilator data and various other parameters. Over the past decade, several studies have demonstrated the benefits of telemonitoring for both the initiation of chronic NIV at home [120,121], including patients with COPD [122,123], and for ongoing monitoring of patients on chronic NIV [124].

During the initiation phase of home NIV in COPD telemonitoring of ventilator and transcutaneous gas exchange data has been found to be feasible, safe and equally effective as in-hospital initiation, as well as cost-effective [122]. Additionally, remote monitoring of follow-up data shows promise by enabling caregivers to detect deterioration or exacerbations promptly, potentially preventing further decline or hospitalizations [54,55,124] A recent randomized controlled trial from China has shown that an intervention, consisting of an educational program, scheduled additional and unscheduled as needed contacts with caregivers, and daily telemonitoring of ventilator data, improved HRQoL and reduced the time to readmission compared to standard care during follow-up in patients recently being started on home NIV [124]. However, as this intervention was more extensive than only telemonitoring, and its additional effect is clearly dependent on the existing standard of care, further research is absolutely needed to confirm the benefits of telemonitoring during follow-up. Furthermore, it remains unclear which parameters or combination of parameters should minimally be assessed during telemonitoring of patients on home NIV to improve outcomes relevant to patients, like survival, HRQoL and re-admission rates. While most research focuses solely on ventilator data, further research is needed to investigate whether this alone is sufficient for accurately adjusting NIV settings to adapt to changing patient conditions and prevent deterioration or exacerbations. Furthermore, to enable remote monitoring of different parameters, technological progress should be made with regard to integration of data and simplification of monitoring technology for home use.

10. Conclusion

End-stage COPD is a disease characterized by complex pathophysiology, with an imbalance between the high respiratory load and a diminished capacity of the respiratory muscles and blunted drive may lead to CHRF. It has been shown that nocturnal NIV in these patients prolongs admission-free survival, improves gas exchange and increases quality of life. However, the complicated underlying pathophysiology implicates that monitoring of these patients receiving NIV requires sophisticated methods enabling to optimally tailor their ventilatory support. Although ventilators provide a wealth of continuous time-series data, the readouts that are available for routine care are highly condensed and summarized, potentially missing information. Measuring PVA might be relevant, but requires standardized definitions on acquisition and analysis, to be further investigated for its clinical relevance. Normalization of hypercapnia is considered to be the primary marker of effective ventilation, although measurement is not standardized, and the relationship between gas exchange, ventilator output data, and clinical outcomes is not straightforward in COPD. Sleep quality requires attention in COPD patients receiving nocturnal NIV, as the interaction between sleep and receiving NIV is unclear but considered important for the patient reported outcomes. To have a clear view of patient wellbeing, HRQoL needs to be assessed through appropriate questionnaires. With all the data modalities recorded and analyzed for optimal patient outcomes, telemonitoring and automation of the chronic NIV may result in fewer hospital visits and enhance the treatment process.

11. Expert opinion

Advanced monitoring of chronic home NIV in patients with severe COPD is absolutely necessary. This is because adjusting and maintaining optimal ventilator settings in a disease with various phenotypes, different underlying mechanisms leading to CHRF, and of continuously changing patient and disease condition over time is challenging but crucial to improve success rates and personalize treatment and care. Ideally, monitoring, titration, and adjustments should be carried out at home as much as possible, and telemonitoring holds promise for achieving this in the future.

Ventilator data are typically easy to monitor as they are automatically provided by the ventilator output. However, it is important to be aware of how these data are obtained, as several parameters are calculated based on different algorithms provided by manufacturers. Moreover, it is questionable whether monitoring only ventilator data is sufficient for titrating and optimizing chronic NIV in the long term. In COPD,

to ensure effective ventilation, gas exchange monitoring is at least necessary in addition to ventilator data.

Monitoring PVA is a new area of research in the field of chronic NIV in COPD. While it has been shown that correcting asynchronies leads to better patient-related outcomes in acute respiratory failure, this relationship is still unclear in chronic NIV. More research is needed to investigate technology that enables automatic and reliable calculation of PVA and its correlation with clinical outcomes, such as NIV success rates and comfort.

The primary goal of chronic NIV in COPD is to reduce symptoms of nocturnal hypoventilation and improve HRQoL. Therefore, more advanced monitoring should ultimately lead to improved patient-reported outcomes. Future research is needed to demonstrate the feasibility of advanced monitoring at home as well as its value in improving patient-reported outcomes. Additionally, there is an urgent need for integrated monitoring systems that are easy to use and can track several physiological parameters simultaneously. Future research on monitoring of patients on chronic NIV should focus on investigating which monitored parameters or combination of parameters predict deterioration and other important goals, like survival and patient reported outcomes. Until now, specificity and sensitivity of single parameters to detect deterioration have been shown to be only moderate [55]. Probably, a combination of parameters or a combination of trends in monitored parameters might be more promising. Machine learning might be a promising method to investigate these patterns and develop valuable algorithms. There is an exponentially growing body of evidence on artificial intelligence (AI) in the field of mechanical ventilation on the ICU, where huge data collections can often be gathered from the ventilator and monitoring equipment, often automatically. AI has been mainly used for prediction of strategies to wean patients from mechanical ventilation [125]. In the field of home mechanical ventilation, AI is completely new, as the collection of data is not standardized and the amount of data collected is now far too limited. For AI to advance to clinical chronic NIV care, we need dedicated research on bigger datasets of monitored variables, preferably for the different types of underlying diseases as both predicting variables/algorithms and goals might be different. By international collaboration and by developing a framework for collecting (tele)monitored data (preferably through automatic transfer from clouds for example), we should be able to collect large amounts of high-frequency data collected under different conditions and in different geographical areas [126], also enabling research with AI. Eventually, by integrating artificial intelligence (AI) algorithms with advanced respiratory monitoring or telemonitoring systems, healthcare providers might achieve real-time analysis of patient data, enabling early detection of complications and personalized adjustments to ventilation settings.

Funding

This paper was not funded.

Declaration of interest

F Soleimani does not have any conflicts of interest, financial or otherwise, to disclose. D Donker provides research consultancy to Maquet Critical Care AB, Solna, Sweden and is involved in a research cooperation with Sonion BV, Hoofddorp, the Netherlands. All financial compensation for these activities is paid to the University of Twente, no personal fees are received. E Mos-Oppersma and M Duiverman received a research grant from NWO (NOCTIVENT trial) with co-funding from Löwenstein BV, Vivisol Nederland BV and Sencure BV. M Duiverman received additional grants and personal fees from Vivisol BV (fee for lecture), grants and personal fees from RESMED LtD (fee for lecture AND grant for RECAPTURE trial, ClinicalTrials.gov NCT03053973), grants and personal fees from Philips BV (RECONSIDER trial funded by the Dutch Lung Foundation with in-kind co-funding of Philips; Longfonds grant nr 5.2.15.057JO, registered at ClinicalTrials.gov NCT02652559), travel grant and fee for lecture from Breas, fee for a lecture from Chiesi, Astra Zeneca, Novartis and a Research grant from Fisher&Paykel (High-TeC trial funded by a public–private partnership of Health-Holland/Dutch Lung Foundation, with co-funding of Fisher and Paykel LtD, and Vivisol BV; registered at ClinicalTrials.gov NCT03564236). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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