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REVIEW

Indications and evidence for domiciliary noninvasive ventilation

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ABSTRACT

Introduction: Home noninvasive ventilation (HNIV) has expanded globally, with a greater evidence base for its use. HNIV improves multiple patient related outcomes in patients with chronic hypercapnic respiratory failure. Obesity hypoventilation syndrome (OHS) is rapidly taking over as the primary indication for HNIV and COPD patients who overlap with obstructive sleep apnea hypoventilation syndromes (OSAHS) and are increasingly recognized but add to the complexity of HNIV prescribing. Optimal settings vary for differing diseases, with higher inspiratory pressures often required in those with OHS and COPD, yet which settings translate into greatest patient benefit remains unknown.

Areas covered: We cover the evidence base underpinning the common indications for HNIV in COPD, OHS, neuromuscular disease (NMD), and chest wall disease (CWD) and highlight common HNIV modes used.

Expert opinion: Active screening for nocturnal hypoventilation in OHS and COPD may be important to guide earlier ventilation. Further research on which HNIV modalities best improve patient related outcomes and the right time for initiation in different patient phenotypes is rapidly needed. Worldwide, clinical research trials should aim to bridge the gap by reporting on patient-related outcomes and cost effectiveness in real-world populations to best understand the true benefit of HNIV amongst heterogenous patient populations.

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KEYWORDS
Non-invasive ventilation; hypercapnia; respiratory failure; COPD; OHS; neuromuscular disease; chest wall disease

1. Introduction

Chronic hypercapnic respiratory failure (CHRF) due to alveolar hypoventilation is a common complication that results from underlying illnesses such as chronic obstructive pulmonary disease (COPD), obesity hypoventilation syndrome (OHS), chest wall disease (CWD), and neuromuscular disorders (NMD). Home noninvasive ventilation (HNIV) was successfully introduced for the management of CHRF in the 1980s in patients with NMD [1]. The indications for home noninvasive ventilation (HNIV) have expanded across the years, with evolving ventilators that now include algorithms that estimate tidal volumes and compensate for leak [2].

1.1. Prevalence of Home Mechanical Ventilation (HMV)

Toussaint et al [3] conducted a study looking at the prevalence of home mechanical ventilation (HMV) across 24 national HMV programs between 2005–2020. They estimated the largest prevalence in Canada at 12.9 per 100,000 and documented 72% were receiving noninvasive ventilation and 18% were ventilated via tracheostomy. Their estimated overall median prevalence was 7.3 per 100,000 (1.2–47), but this is likely to be underestimated globally as in 2022, at least 12 new middle, and low-income countries were thought to be developing HMV programs [3]. High income countries are also expanding services to meet the increasing needs of patients with hypercapnic respiratory failure. This is in part due the evolving evidence on the benefits of HNIV in OHS and COPD. HMV users can be categorized by the total amount of time spent on a ventilator in 24 hours [4]; with *nocturnal use* described as 8 out of 24 hours, *discontinuous* use as 8–16 hours and *continuous* use as greater than 16 hours. Currently, HNIV is still predominantly used nocturnally only.

1.2. Indications for HNIV

A 7 year follow-up study [5] across two university hospitals and a pulmonary rehabilitation center in Switzerland ($n = 211$) evaluated the shift in HNIV prescribing across 1992–2000. From 1994, COPD and OHS became the most frequent indications for HNIV. Fifteen years later, the same group conducted a larger cross-sectional observational study [6] ($n = 489$) in 2017 over 15 years and demonstrated HNIV was initiated electively in 50% of patients and 45% in an emergency setting. COPD (including those with co-existing OSA) accounted for 45% of total set ups, OHS for 21%, and NMDs around 17%.

Large variations in services continue to exist within individual countries, and this is dependent of the location, size, and experience of different centers [7]. Mandal et al reported that [8] 67% of HMV setups in the UK for were for obesity related respiratory failure and COPD in 2013. The authors described that complex neurological conditions were managed in a smaller number of specialist weaning, rehabilitation, and home ventilation centers. Lloyd Owen et al in the Eurovent survey [7] described neuromuscular users to have the longest duration of HMV use and lung users to have the shortest. Lung

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Article highlights

- We summarize the evidence for the commonest diseases (COPD, OHS, NMD, and CWD) in regards to indications for HNIV
- Although evidence of patient benefit with NHIV is seen, we highlight this is limited by selected patient phenotypes, physiology and outcomes that are investigated in clinical trials and highlight the differences in real world patients.
- We must remember that the 'one size' approach does not meet the needs for all patients.
- We suggest that screening for clinical symptoms and physiological evidence suggestive of nocturnal hypoventilation and/or sleep disordered breathing earlier is key, such that we may better understand when HNIV is best started for patients to ensure clinically meaningful benefit.
- We highlight patient adherence to treatment remains a big challenge and that remote monitoring through automated technologies may be crucial to supporting adherence.
- Automated technologies not only need to offer monitoring but need to be able to allow machine adaptation to patients needs which may help simplify patient management pathways.
- To further support development in this area of HNIV, research must be conducted in mixed settings in real world patients, involving both higher and lower income countries, with cost-effectiveness built in as part of outcome measures.

users included patients with COPD, cystic fibrosis, bronchiectasis, pulmonary fibrosis, and pediatric patients with bronchopulmonary dysplasia. These data suggest a worse prognosis for lung users on long-term ventilation, but on the other hand, may represent lung users not having been started on HMV early enough to demonstrate an improved prognosis.

Rose et al [9], in a Canadian survey achieved a high survey response rate of 89% (152/171) in a total of 4,334 ventilator-assisted individuals. The most common reasons identified for NIV initiation were identified as polysomnography demonstrating nocturnal hypoventilation (57%), daytime hypercapnia (38%), and nocturnal hypercapnia (32%).

1.3. Summary

The indications for HNIV are not only expanding but the numbers of patients needing HNIV worldwide is set to increase with a need for home ventilation services to expand. Currently, the most common clinical indications for HNIV use are OHS and COPD, followed by NMD and chest wall disorders (as displayed in Table 1). The evidence underpinning individual indications for HNIV in each of these different illness will now be described in detail throughout the manuscript. We will also explore common ventilation modes for these different illnesses and the challenges limiting future effective application of HNIV.

1.4. Search strategy

We searched for publications and abstracts on PubMed and the Cochrane Database of Systematic reviews, using the keywords 'noninvasive ventilation' or 'NIV' or 'NIPPV' and 'chronic obstructive pulmonary disease' or 'COPD' or 'obesity hypoventilation syndrome' or 'OHS' or 'neuromuscular disease' or 'NMD' or 'chest wall disease' or 'CWD.' We limited the search to English publications. As this is a narrative review, for the present article, we conducted a qualitative analysis without

Table 1. Indications for HNIV across different diseases.

Medical Condition	Indications for HNIV	
Chronic Obstructive Pulmonary Disease (COPD)	Chronic Stable Hypercapnic COPD	Section 2
	Following Acute Exacerbation Of COPD with AHRF requiring NIV, with persistent hypercapnia	[14]
Obesity Hypoventilation Syndrome (OHS)	Hospitalised suspected or confirmed OHS with AHRF	Section 3
	Patients with chronic OHS who experience nocturnal desaturation or a nocturnal increase in PaCO2	[56]
	Patients with chronic OHS who experience failure of CPAP therapy by either sustained oxygen desaturation during sleep, an increase in daytime or nocturnal CO2	
Neuromuscular Disease (NMD)	**Diaphragmatic Weakness**:	Section 4
	Vital capacity < 80% predicted with any symptom of orthopnoea, dyspnoea, morning headaches, daytime sleepiness, or unrefreshing sleep	[75] and [78]
	Vital capacity ≤ 50% (FVC or SVC) predicted with or without symptoms	
	Oxygen Desaturation during sleep:	
	- **SpO2** ≤ 90% for ≥ 5% of the night	
	- **SpO2** ≤ 88% for ≥ 5 minutes	
	Hypercapnia:	
	- Daytime hypercapnia	
	- ≥ 45 mmHg on arterial blood gas	
	- end-tidal or transcutaneous PCO2 ≥ 50 mmHg	
	- peripheral venous gas ≥ 50 mmHg	
	- Nocturnal hypoventilation	
	- a 10 mmHg increase in PtcCO2 above baseline ***or***	
	- a PtcCO2 > 49 mmHg for > 10% of the total recording time ***or***	
	- PtcCO2 peak > 55 mmHg	
	Further evidence of diaphragmatic weakness defined as:	
	- Maximal inspiratory pressure (Pimax) ≤ 60 cmH20	
	- SNIP ≤ 40 cmH20	
	- Positional decrease in FVC of ≥ 20% from sitting to supine	
Chest Wall Disease (CWD)	As above (evidence of symptoms, or signs of sleep disordered breathing/diaphragmatic weakness)	Section 5 [75], [78] and [84]

*COPD- Chronic Obstructive Pulmonary Disease, AHRF- Acute Hypercapnic Respiratory Failure, OHS- Obesity Hypoventilation Syndrome, FVC- Forced Vital Capacity, SVC – Slow Vital Capacity, OSA- Obstructive Sleep Apnoea, PtcCO2-Partial pressure of carbon dioxide measured by transcutaneous monitoring, PiMax- Maximal Inspiratory Mouth Pressure, SNIP- Sniff Nasal Inspiratory Pressure.

additional assessments. The last update of the search was performed in August 2023.

2. Indications for HNIV in COPD

The presence of hypercapnia in COPD has long been shown to be a determinant of mortality [10] and to result in an increased number of hospital admissions and morbidity in the year following hospital admission [11]. Domiciliary NIV benefits individuals physiologically by reducing diaphragmatic effort and improving tidal volumes and thus alveolar ventilation. In COPD, hyperinflation causes the inspiratory muscles including the diaphragm to operate at a shorter than normal lengths as a consequence of lung hyperinflation. This results in mechanical disadvantage as the ability of these muscles to lower intrathoracic pressure is subsequently reduced [12]. Acute NIV has been shown to reduce the risk of mortality by 46% in the management of acute hypercapnic respiratory failure as a result of COPD exacerbations [13]. Its effectiveness in the domiciliary setting is harder to prove perhaps due to varying patient phenotype, differing NIV applications and limited studies targeting a reduction in PaCO2. The European Respiratory Society (ERS) task force [14] recently published a 2023 review on the indications for NIV and have summarized evidence across two groups of COPD patients: those with *stable chronic hypercapnia* and those following an *acute episode of hypercapnic respiratory failure*.

2.1. Evidence in stable hypercapnic COPD

The 2023 ERS guidelines [14] report on a pooled analysis [15–27] across 13 RCTs evaluating NIV in stable hypercapnic COPD. This analysis showed little overall effect of NIV on mortality (relative risk (RR) 0.86, 95% CI 0.58–1.27) or hospitalizations (mean difference (MD) 1.26 fewer hospitalizations, 95% CI 0.08–2.59). Pooled analysis of 5 RCTs [17,22,25,26,28] demonstrated that NIV decreased dyspnea scores, 10 RCTs [16–18,20,23–25,28–30] improved 6 minute walk distance and 7 RCTs [15,16,18,22,25,26,28] demonstrated a higher HRQOL across variable follow-up periods of 3–12 months, which are all important individual health benefits.

Highlighting differences in NIV settings within individual studies has helped to yield information on ventilator parameters that may best influence outcomes. For example, McEvoy et al [15] showed a relatively small improvement in survival in patients randomized to NIV and long-term oxygen therapy (LTOT) vs. LTOT alone; 28 vs. 20.5 months (adjusted hazard ratio (HR) 0.63, 95% CI 0.40 to 0.99). Importantly, health-related quality of life decreased in the combined NIV/LTOT group but PaCO2 did not differ between groups. Kohnlein et al [16], demonstrated a HRQOL and significant survival benefit where a high-intensity ventilatory approach was used. This consisted of a higher tolerated inspiratory pressure (IPAP) of 21.6 cmH20 and a high back up rate (close to the patient's spontaneous respiratory rate). This was higher than the IPAP of 12.9 cmH20 used by McEvoy [15] et al. Kohnlein [16] also targeted a 20% reduction in PaCO2 from baseline and additionally observed a decrease in emergency hospital admissions per patient per year (2.2 vs. 3.1 exacerbations per patient per year). Although not in the pooled analysis, a randomized crossover study by Dreher et al [31] has shown high-intensity ventilation increases forced expiratory volume in 1 second and leads to better adherence compared to low intensity ventilation. Inspiratory pressure in this study appeared to be the main determinant of PaCO2 reduction, irrespective of respiratory rate.

Adherence has been consistently shown to improve outcomes, with a greater than 4 hour compliance in [15] associated with greater survival. In a study [32] of 213 patients with COPD who were adherent to NIV for more than 5 hours a day, Borel et al reported on improved survival in obese patients only. This suggests patient phenotypes may alter outcomes despite optimal adherence and that ventilatory parameters will still need further optimization. A meta-analysis [33] demonstrated 5 hours of HNIV use per night across 11 studies ($n = 475$) enabled a significant change in PaCO2 after 3 months of treatment. Although clinicians should try and ensure optimal adherence in patients with CHRF, we must acknowledge that variable adherence in individual users may still have a degree of clinical benefit.

2.2. Evidence for HNIV in hospitalised COPD with acute hypercapnic respiratory failure (AHRF)

The aforementioned ERS guideline document [14] has also reported on a pooled analysis across 4 RCTS [34–37] in COPD patients recovering after an episode of AHRF. This analysis demonstrated no reduction in mortality with HNIV but a reduction in exacerbations (SMD 0.19, 95% CI −0.40 to 0.01) and hospitalisations (RR 0.6, 95% CI 0.30–1.24). Dyspnoea improved using the Medical Research Council Dyspnoea Score (MD 0.8 points lower, 95% CI 1.03 lower to 6.8 higher) and HRQOL improved when using the Severe Respiratory Insufficiency Index (MD 2.89 higher, 95% CI 1.03 lower to 6.8 higher). The two largest RCTs involved in the analysis had contrasting results despite a similar trial design and primary outcome measure. Struik et al [36] randomized 201 patients to nocturnal NIV or standard treatment for 12 months. Eligible patients included those with acute respiratory failure who remained hypercapnic (PaCO2 > 6.0 kPa), following discontinuation of either invasive or noninvasive ventilation at 48 hours. This study did not show difference in survival or acute admissions at one year in HNIV users. Murphy et al [37] recruited patients with persistent hypercapnia (PaCO2 > 7kPa) at 2–4 weeks after the acute phase and demonstrated an increased time to readmission or death within 12 months. About 26% of the patients in the control group in the Struik study became normocapnic after 3 months. It is therefore plausible that due to an earlier recruitment in the Struik study, these patients represent those with lesser disease burden (i.e. more likely to have a spontaneous recovery in their PaCO2) compared to selected patients who remain hypercapnic persistently following hospital discharge. Equally, Murphy et al recruited patients with a PaCO2 > 7kPa which may have accounted for more positive responses in outcomes, yet both studies at baseline exhibited a similar mean PaCO2 (59 mmHg in the Murphy study; 59 and 58 in the intervention and control groups respectively in the Struik study).

The prevalence of overlap of OSA in COPD patients recovering from an acute exacerbation of COPD is estimated at 46% [38]. COPD-OSA overlap patients have increased cardiovascular risk, hospitalisation due to COPD exacerbations and all-cause mortality compared to COPD patients alone [39]. Guidelines from the American Thoracic Society [40] place importance on screening patients for OSAS before starting HNIV and emphasise the importance of follow-up assessment of the underlying phenotype of sleep disordered breathing in order to better guide treatment decisions, for example the type of positive airway pressure used. The reasons for this are nicely summarised in a recent review article by Carlucci et al [41]; CPAP may be sufficient to counteract respiratory sleep disturbances and physiology, be easier to set up and cheaper to use, whereas NIV may require greater monitoring of expiratory positive airway pressures (EPAP) to avoid ineffective ventilation and ensure no worsening of lung hyperinflation in COPD.

2.3. Ventilation mode and setting in COPD

Pressure targeted NIV is widely adopted in clinical practice as research literature has traditionally used these devices. Newer modes offer volume targeted pressure support ventilation, known as average volume-assured pressure support (AVAPS). These modes may offer advantage by adapting ventilatory parameters to better manage physiological changes during sleep such as upper airway patency, changes in lung volumes, and nocturnal changes in PaCO2. The ERS [14] guidelines reference six short-term RCTS [42–47] comparing volume-assured pressure support to either fixed or high intensity bi-level pressure support ventilation. One study [46] demonstrated a small reduction in nocturnal transcutaneous carbon dioxide partial pressure (PtcCO2) with AVAPS and another [42] reported on improved sleep efficiency. However, these studies were conducted across two consecutive nights [46] and five nights [42], respectively. No study conducted across three months reported on significant improvements in HRQOL or other patient centered outcomes (self-reported tolerance or comfort) in AVAPS compared to traditional bi-level S/T mode. Disadvantages of AVAPS can include inaccurate measures of tidal volumes when excessive leak occurs and this could pose a safety concern. In patients with high respiratory drives and high tidal volumes, this mode could potentially lead to mismatching with patients' inspiratory flows. Longer term studies comparing AVAPs modes to high intensity NIV are now needed. Finally, newer ventilatory modalities that incorporate assessment and appropriate correction of expiratory flow limitation (EFL) are potential future modes that may be utilized in this patient population. EFL is characterized by the presence of a reduced expiratory flow which is not affected by increasing the expiratory driving pressure [48] Ventilatory modes that detect EFL and apply adequate positive end-expiratory pressure (PEEP) may reduce overall airway resistance and improve dynamic hyperinflation [49]. Prior work in the intensive care department has shown that EFL is common amongst ICU patients and correlates with adverse outcomes [50]. It is yet to be seen whether this is also true in the COPD population and whether using newer HNIV ventilatory modalities that adjust for EFL shows benefit in this patient population.

3. Indications for HNIV in OHS

Obesity hypoventilation is defined as daytime hypercapnia, a PaCO2 > 45 mmHg, associated with a body mass index >30 kg-m-2, without any other disorder that may explain hypercapnia. In Australia and New Zealand, OHS was reported as the most common indication for home mechanical ventilation (HMV) in 2013, affecting up to 31% of cases, with NMD prevalent in 30% and COPD in 8% [51].

OHS patients have significant load on their respiratory system due to reduced lung volumes, reduced lung and chest wall compliance, and increased airway resistance, which contribute to a higher work of breathing. In comparison to eucapnic obesity, OHS patients have a greater degree of central obesity [52]. When performing overnight sleep studies, up to 90% may have evidence of co-existent obstructive sleep apnea (OSA) but a smaller proportion (10%) can have evidence of just nocturnal hypoventilation alone [53]. In comparison to OSA alone, OHS is associated with greater risk of hospitalizations and death and increased risk of complications such as heart failure, which makes OHS more complicated to treat [54]. There is a high inpatient mortality in individuals presenting with decompensated OHS [55], hence it is important to screen earlier for sleep disordered breathing in symptomatic or at-risk patients. Hence, now guidelines [56,57] emphasise discharging OHS patients on HNIV after a single episode of acute respiratory failure requiring acute NIV. Patients often have co-existing heart failure at acute presentation and therefore accurately determining co-existing OSA and its severity at that time may be difficult.

There are no randomized control trials have that have assessed OHS patients after an episode of AHRF. Evidence on outcomes from RCTs is gained from evaluation of stable OHS patients with the largest studies conducted by Masa et al [58,59]. This group of authors performed two parallel RCTs comparing NIV and CPAP to lifestyle modifications (a control group). The first study [58] evaluated outcomes in co-existing severe OSA (defined as an apnea- hypopnea index (AHI) of ≥ 30 events per hour; $n = 221$ randomized) and the second [59] evaluated outcomes in randomized patients without severe OSA (defined as an AHI < 30 events per hour; $n = 86$ randomized). When interpreting this evidence, we must remember that included patients in the RCTs may not have had co-existent heart failure or may have already been optimized for treatment of heart failure. However, individuals presenting in decompensated AHRF with OHS patients who require HNIV often represent a more problematic group, often with co-existent acute heart failure.

In the study by Masa et al [58] evaluating OHS with co-existent OSA, NIV yielded the greatest improvement in comparison to lifestyle modification on physiological parameters such as PaCO2 and serum bicarbonate. However, this was not significantly different to the CPAP group. Thus, clinical guidelines [57] recommend using CPAP first in those with severe OSA (AHI ≥ or equal to 30 events per hour). However, this study did show some aspects of HRQOL, 6MWT, and spirometry improved with NIV more than with CPAP at two months. In addition to the short-term study [59] evaluating NIV outcomes in non-severe OSA at two months, Masa et al also conducted

a larger study ($n = 86$) over a median follow-up of 4.98 years [60] and demonstrated NIV in contrast to controls improved PaCO2, pH, serum bicarbonate, daytime sleepiness, and some HRQOL assessments. In the subgroup with high NIV adherence, the time until the first hospital admission or emergency department attendance, and mortality was longer. This continues to reinforce that concordance is key to improving patient outcomes in the management of CHRF regardless of the underlying cause.

3.1. Ventilation mode and setting in OHS

Patients with OHS have decreased lung compliance and restrictive ventilatory defect and therefore often need higher pressure support compared to other disease groups. Additionally, a high expiratory positive airway pressure (EPAP) may be needed to overcome upper airway obstruction in conjunction and a respiratory rate should be set at 2 breaths per minute less than the daytime respiratory rate helps to avoid emergence of central events.

A study by Janssens et al [61] ($n = 12$) evaluated the control of nocturnal hypoventilation in a group of stable OHS patients on HNIV for 30 months. They used a randomised cross-over design across two nights, with individuals assigned to bi-level ventilation with usual settings one night and volume targeted bi-level positive pressure ventilation on a consecutive night. They identified nocturnal PtcCO2 was better in the volume targeted group, but there was a reduction in stage 2 sleep and total sleep time. Storre et al [62] in a longer term cross over study across 6 weeks demonstrated volume targeted pressure ventilation compared to usual bi-level ventilation resulted in better nocturnal PaCO2 control (without harm to slow wave sleep) and improved disease specific HRQOL scores. These findings suggest that volume targeted modes of ventilation in OHS may be ideal as they are able to adapt to the physiological changes that occur with changes in position during sleep. The disadvantage of these modes may be that the use of higher pressures during sleep could lead to decreased concordance with NIV. Automated devices with added auto expiratory positive airway pressure (EPAP) titration have had greater positive results demonstrating similar efficacy on control of sleep disordered breathing, sleep quality but an improvement in health-related quality of life [63,64].

It is important to frequently assess the effectiveness of NIV, patient phenotypes, and the need to switch to other positive airway therapy modes at a later date in this cohort. Approximately 20% of patients will fail when switching from NIV to CPAP due to less comfort with CPAP, acute respiratory failure, or recurrence of hypoventilation [65,66]. Management of fluid and weight are also key drivers in the degree of hypercapnia in OHS and should be discussed with patients in parallel with discussions about HNIV.

4. Indications for HNIV in neuromuscular disease

The prevalence of NMD in the study by Touissant is estimated as 30 per 100,000, with around 10% suggested to be using HNIV [3]. This article does not cover the scope of different etiology of NMD but common congenital neuromuscular causes leading to respiratory failure include primary muscular dystrophies (Myotonic dystrophy, Duchenne muscular dystrophy and Becker muscular dystrophy) [2]. Other causes include spinal cord injury, inflammatory demyelinating neuropathies and myotrophic lateral sclerosis (ALS) accounts for some of the acquired NMDs resulting in patients requiring HNIV [2]. ALS warrants particular attention when considering NIV, given the difficulty that can arise in this group if they develop bulbar involvement.

Sleep related hypoventilation occurs due to progressive respiratory muscle, in particular, diaphragmatic weakness, which is caused by bilateral degeneration of phrenic nerve motor neurons in ALS [67]. Low peripheral oxygen saturations are a late feature of respiratory failure and the clinical history is critical to eliciting symptoms suggestive of symptomatic sleep disordered breathing or daytime hypercapnia. Often overnight PtcCO2 monitoring may be needed to investigate for the presence nocturnal hypercapnia, even if an overnight oximetry, sleep polygraphy or polysomnography does not identify evidence of sleep disordered breathing. Thirty percent of patients will manifest hypercapnia if sleep studies only capture pulse oximetry [68]. Carlucci et al have summarised the definition of nocturnal hypoventilation as either i) a 10 mmHg increase in PtcCO2 above baseline, ii) a PtcCO2 > 49 mmHg for > 10% of the total recording time or iii) a PtcCO2 peak >55 mmHg [41]. Daytime hypercapnia is often a late clinical sign of hypoventilation in this group yet there remain challenges to patients performing accurate PtcCO2 measurements overnight [69,70]. Alongside overnight physiological studies, patients should be monitored for diaphragmatic weakness and have regular monitoring of respiratory muscle strength including sniff nasal inspiratory pressures (SNIP). A maximal inspiratory pressure (Pimax) ≤ 60 cmH20 or SNIP ≤ 40 cmH20 constitute indications to start ventilatory support. In the absence of these, a positional decrease in FVC of ≥ 20% from sitting to supine or a FVC of less than 50% predicted is used [56]. The presence of OSA is associated with a worse prognosis in ALS [71]. OSA has been shown to be more prevalent in males with ALS and less prevalent in those with preserved bulbar function [72].

It is important to remember that NMD patients can develop both inspiratory and expiratory muscle weakness and that scoliosis can contribute to the restrictive ventilatory defect in patients with neuromuscular disease. Secretion clearance may be impaired first before the development of respiratory failure in those with predominant expiratory muscle weakness [72]. Therefore, often NMD patients may need cough augmentation in conjunction with HNIV.

There has only been one RCT in patients with ALS; this study randomized 92 patients with ALS and daytime hypercapnia and orthopnea to NIV or standard care [73]. This study demonstrated greater survival in the NIV group compared to controls (219 vs. 171 days). Timely ventilation is therefore deemed an important therapeutic option to prolong life span in ALS, an advanced disease where focus is not necessarily on just longer life, but better quality of life. This same principle applies to other NMDs and Moss et al [74] found in 355 patients with MND, that 90% of patients were glad they had chosen HMV and would do so again.

Hansen-Flaschen et al [75] have published a 2023 practical guide to the management of HNIV in adults with chronic neuromuscular disease highlighting the key indications for initiation as demonstrated in Table 1, and also further recommendations for troubleshooting problems that may arise with HNIV in this group of patients.

4.1. Ventilation mode and setting in NMD

Oronasal masks for HNIV initiation in NMD may induce upper airway obstruction [76], this occurs more commonly in ALS than in other NMD and can impact on long-term outcomes [77]. Bourke et al, however, reported on improvement of HRQOL quality in ALS patients using HNIV with bulbar dysfunction [73]. Therefore, recommended strategies to overcome this issue [78] include: changing to a nasal mask, adjusting bed position (with the use of a pillow), increasing the EPAP levels, and titration assisted with video-laryngoscopy. Secondary life support ventilators devices should be offered if ventilatory support is required for more than 10 hours in the day [78] and mouthpiece ventilation is indicated in those with sufficient bulbar function and orofacial strength [79], but this is likely to become ineffective in ALS patients earlier than other NMDs [80].

5. Indications for HNIV in chest wall disease (CWD)

Rib abnormalities such as thoracoplasty or trauma resulting in fractured ribs and a flail segment can lead to acute respiratory failure. Scoliosis and less frequently kyphosis with severe deformity can cause severe ventilatory failure but conditions such as Ankylosing Spondylitis rarely do [81]. Hypercapnia develops when the force generated by the respiratory muscles is ineffective against the extra load that is imposed on them from reduced chest wall compliance.

Significant clinical experience in HNIV for chest wall disorders has accrued since Ellis et al in 1988 [82] compared nocturnal ventilation by nasal CPAP or nasal NIV in patients with severe thoracic kyphoscoliosis ($n = 7$). They demonstrated either intervention improved clinical measurements of respiratory function (daytime ABGs, lung volumes and muscle strength) and quality of sleep. A retrospective study [83] of kyphoscoliosis patients compared those who had received long-term oxygen therapy (LTOT) alone ($n = 15$) in comparison to LTOT and HNIV ($n = 18$) in combination and demonstrated a higher 1 year survival in the combined LTOT/NIV group. Indications to start HNIV mirror NMD guidance including symptoms, hypercapnia i.e. a PaCO2 of more than 45 mmHg, signs of diaphragmatic weakness or overnight oximetry demonstrating oxygen saturations < 88% for 5 consecutive minutes [75,84].

5.1. Ventilation mode and setting in CWD

Patients often need high peak inspiratory pressures of 20–25 cmH20, and a short response time for triggering is usually needed in view of the rapid breathing that occurs in patients with chest wall disease. A recent meta-analysis [85] included controlled, non-controlled, and cohort studies evaluating respiratory outcomes in HNIV in individuals with slowly progressive NMDs or chest wall disorders. This study ($n = 16$ studies, 176 participants; 113 with NMD, 63 with CWD) demonstrated NIV intensity was not associated with improved PaCO2 except in individuals with CWD and in those with the most severe baseline hypercapnia. Overall, this study demonstrated that the amount of daily usage rather than intensity was key to improving hypoventilation in this population reinforcing again that adherence is key to improving outcomes.

6. Conclusion

Despite a growing population of patients who meet the indications for NIV, evidence is limited by differences in phenotypes, physiology and outcomes investigated in trials. CHRF often goes unrecognised in the first instance, in all patient groups meeting indications for HNIV. Equally, there may be delays in detecting co-morbid disease such as OSA which appears to worsen prognosis in COPD, OHS, and NMD. Therefore, we must start to look for clinical symptoms and physiological evidence suggestive of nocturnal hypoventilation and/or sleep disordered breathing earlier, such that we may better understand when HNIV is best started. Above all though, HNIV is only as effective as much as it is used, and therefore, patient adherence remains key to improving outcomes across all underlying causes.

To enhance clinical effectiveness of HNIV, patient comfort, and adherence, we need to understand which modalities best enhance patient outcomes in the long term and how best to use telemonitoring to aid clinicians in supporting patients in sleep and ventilation services. With expanding services in high income countries, and the set-up of services in low-income countries, this looks likely to improve in the future but requires a cohesive approach from clinicians and researchers worldwide.

7. Expert opinion

We have described the current and up-to-date evidence on the indications, uses, and benefits of HNIV. However, several challenges remain prior to global adoption of HNIV in this patient population. Firstly, the occurrence of differing phenotypes within each disease group, meaning creating a 'one size fits all' approach is difficult. Most studies published to date have been performed in Western and developed countries and given the heterogeneity of the diseases, it is likely that different populations will have different predominant phenotypes and thus different HNIV requirements.

Secondly, prior work has shown that a nations' economy is closely linked with HMV service development [3]. Work by Lloyd-Owen et al [7] showed that the estimated prevalence of HMV in Eastern European countries was as low as 0.1 per 100,000, compared to 6.6 in Western Europe. While reliable data is lacking, it is probable that other low-middle income countries in the Africa and Asia have similar data. Encouraging these nations to invest in an HMV service requires demonstration of significant benefit; however, research in this field is currently lacking. Thirdly, it is important to note, that

resources are also limited in higher income counties and the intense management and monitoring that occurs in clinical trials can make it prohibitive for centers to actively screen for patients or expand services. A large number of centers initiate HNIV in the inpatient setting, requiring hospital admission for several nights with daily titration [86]. However, given the burden imposed on an already stretched healthcare system, several studies have investigated the role of HNIV set-up in the outpatient setting. Indeed, Duiverman et al [87] have shown significant cost benefit in home initiation of HNIV when compared to hospital initiation. Other studies [64] have showed no difference in cost and equivalent outcomes when comparing inpatients versus outpatient set up. However, outpatient set up of HNIV is feasible and may result in a cost saving. A major limitation of some of these studies has been the intense monitoring that has been used within the study, limiting real-world applicability. Embracing automated technologies and wearable devices that adapt to patients' needs as well as monitoring patients on HNIV will simplify the outpatient pathways and no doubt reduce the cost burden. This in turn is likely to encourage global adaptation of HNIV. For example, using an automated NIV device which titrates pressures according to patient need and feeds this back to clinicians remotely, can lead to virtual support of clinics and reduce face-to-face consultations. Moreover, devices that monitor residual events and hypoxia could be used as part of patient telemonitoring with adequate alarm systems in place. Mobile phone applications can also give more control to patients with pre-set targets. These targets could include 'duration of HNIV', 'residual AHI' and 'concordance percentage'. These applications could also have motivational messaging to encourage the patients to continue, improve use and call for help. These future applications can simplify the management pathways of these patients. To bring about change, future studies need to be conducted in mixed settings, involving both higher and lower income countries, with cost-effectiveness, built in as part of outcome measures, to understand the realistic prospect of setting up HNIV in the 'right' patient population for that country and understand the cost implications. Study designs should be as simple as possible and aim to reflect real clinical practice in that area. Therefore, parallel and adaptable trial designs are needed.

Previous studies have traditionally excluded older individuals and patients with co-morbidities such as sleep apnea and heart failure. COPD has been traditionally associated with cachexia from respiratory muscle atrophy-induced dysfunction, but the average BMI in clinical trials of COPD may not be reflective worldwide given the evolving obesity epidemic. A large number of these patients will have an 'overlap' syndrome with OSA or OHS, and therefore studies describing benefit or lack of, in 'pure' or single disease conditions does not reflect the reality of clinical practice. This creates a disparity between the study sample and the real world intended population. Indeed, the prevalence of OSA in a COPD population ranges from 2.9–65.9%, and is by no means insignificant [88].

We have still not fully understood who benefits from HNIV. Whilst there is clearly a mortality benefit in some patients, this does not translate to everyone, and few studies have demonstrated both a morbidity and mortality benefit alongside patient reported benefit. We therefore need easier ways to phenotype and endotype patients in order to target therapy. This is perhaps even more important in low-middle income countries where resources are limited. Furthermore, although a recent systematic review on NIV in palliative care [89] indicated NIV improves breathlessness and quality of life in patients with end-stage lung diseases, this review included only quantitative studies. Breathlessness treatments, however, require further qualitative analysis from patient, carer and healthcare professionals perspectives in order to evaluate their effectiveness centered around patient related outcomes.

Lastly, alternative therapies are now emerging such as nasal high flow oxygen (NHFO) that have been shown to have benefit in patients with stable hypercapnic COPD in regard to reduction of moderate-severe exacerbations and health-related quality of life across a year [90]. One retrospective study [91] compares HFOT initiated for home use or in a post-acute re-enablement facility across a mixed patient population (chronic airway disease, interstitial lung disease, pulmonary hypertension, lung cancer and neuromuscular disease). This study demonstrated a reduction in the number of respiratory exacerbations in those initiated on HFOT via tracheostomy, rather than via a nasal cannula. However, a physiological study [92] has evaluated the effects of high flow oxygen therapy through a tracheostomy interface (tHFOT) and demonstrated no impact on neuro-ventilatory drive and work of breathing in patients at high risk of weaning failure, in an intensive care unit setting. The authors suggest the lack of positive physiological effects in this cohort was due to the fact that the benefit of HFOT arises from the mechanism of carbon dioxide washout, mainly from the nasopharyngeal anatomical dead space. However, this is bypassed when HFOT is applied via tracheostomy. Therefore, this therapy still requires further research on effect upon physiological parameters and patient related outcomes in those with severe COPD and other lung diseases before its implementation into clinical practice and within a domiciliary setting. This will ensure its optimal use in the right patient population. The Danish European Society [93] have published indications for its use, including hypoxic COPD patients who meet long-term oxygen therapy criteria and have had up to two or more severe acute exacerbations. They have reserved recommendations in the hypercapnic COPD population to alternative use where patients are unable to tolerate HNIV.

Ultimately, the main goal in all diseases is prevention. Therefore, future work needs to focus on identifying which patients will progress and develop hypercapnia. Most patients with OHS are picked up at a much later stage, usually once admitted following decompensation. It may be too late at this point to impact upon long-term outcomes. Identifying early hypoventilation is critical, but we currently do not have an easily accessible way to do this. Using overnight transcutaneous CO2 monitoring is expensive and has technical challenges, and using overnight oximetry is perhaps not sensitive enough. Developing newer modalities with different analysis

methodologies are important in simplifying diagnosis. Prospective cohort studies, following large numbers of patients, are needed to identify which factors predispose to hypercapnia. This would enable earlier treatment intervention in a targeted population, potentially preventing hospital admissions and improve mortality. However, an issue with this approach is likely to be tolerability and concordance to the device. Asymptomatic patients have reduced concordance, as they are less likely to see any 'real time' benefit. It is probable that greater use of NIV overnight leads to greater benefit and a likely limitation of prior studies is concordance, which may be too low to realize the true benefit.

It is important to add, that other preventative strategies are also vitally important. Smoking cessation and cleaner air to prevent COPD development and a global public health drive to improve lifestyle decrease obesity rates is critical for the reduction in OHS.

It is important to remember, that while we have some evidence for the utility of HNIV in some chronic diseases, we have limited evidence in other disease processes for which data is urgently needed. This includes patients with interstitial lung disease and end-stage bronchiectasis which are highly prevalent globally. While Aliberti et al [94] investigated the role of NIV in ILD patients in acute respiratory failure and Flight et al (2012) [95] looked at HNIV efficacy in a population of cystic fibrosis patients, larger randomized controlled trials are necessary in these fields to guide future clinical practice. Finally, in an ever-growing world of increasing technology, never has there been a better time to introduce remote monitoring in these patients. Empowering patients with objective measures that show improvement, may lead to improved concordance. Fully automated technology that can adapt to patients' underlying physiology, monitor their residual disease and change settings accordingly which will improve patient outcomes and ease financial burdens on ever stretched healthcare systems.

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