Quality of life in patients with chronic respiratory failure on home mechanical ventilation

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Shareable abstract (@ERSpublications)
Home ventilation can improve clinical outcomes for patients with COPD, obesity-related respiratory failure and neuromuscular disease. A range of modifiable and nonmodifiable factors influence its impact upon patients' health-related quality of life. https://bit.ly/3Xsak4I

Abstract

Home mechanical ventilation (HMV) is a treatment for chronic respiratory failure that has shown clinical and cost effectiveness in patients with underlying COPD, obesity-related respiratory failure and neuromuscular disease (NMD). By treating chronic respiratory failure with adequate adherence to HMV, improvement in patient-reported outcomes including health-related quality of life (HRQoL) have been evaluated using general and disease-specific quantitative, semi-qualitative and qualitative methods. However, the treatment response in terms of trajectory of change in HRQoL is not uniform across the restrictive and obstructive disease groups. In this review, the effect of HMV on HRQoL across the domains of symptom perception, physical wellbeing, mental wellbeing, anxiety, depression, self-efficacy and sleep quality in stable and post-acute COPD, rapidly progressive NMD (such as amyotrophic lateral sclerosis), inherited NMD (including Duchenne muscular dystrophy) and obesity-related respiratory failure will be discussed.

Introduction

Chronic respiratory failure arises as a consequence of an imbalance in the load and capacity of the respiratory muscle pump accompanied by ineffective change in neural respiratory drive. Disease states in which it commonly arises are COPD, obesity and neuromuscular disease (NMD). Untreated chronic respiratory failure is associated with adverse clinical outcomes, including increased risk of hospitalisation and death. This risk may be reduced by applying noninvasive ventilation (NIV) or, less commonly, invasive mechanical ventilation *via* a tracheostomy. The delivery of home mechanical ventilation (HMV) requires targeted patient selection to identify those most likely to benefit from the intervention. It is essential for HMV delivery to involve education and training for the patients and their caregivers within a clinical service model that can comprehensively support the patient, including on-site and remote clinical and technical troubleshooting [1]. HMV delivery improves clinical outcomes, but requires overcoming potential discomforts of the interface (mask or tracheostomy tube) and airway pressures and adherence to the daily HMV prescription. These clinical and technical considerations may impose a significant personal and carer burden that can detrimentally impact upon health-related quality of life (HRQoL) and perceived benefits and burdens to the patient must be balanced. Improving clinical outcomes, in particular if these are short- or intermediate-term goals such as in advanced COPD or rapidly progressive NMD, at the cost of a detrimental effect on quality of life may not be acceptable to the patient or indeed in their best interest. In this narrative review, we describe the practical delivery of HMV, explore tools that may be used to evaluate its impact on HRQoL, summarise current evidence on the impact of HMV on HRQoL in

patients with chronic respiratory failure, with a particular focus on COPD, obesity and NMD, and discuss methods that may be used to measure HRQoL in the future.

Chronic respiratory failure: pathophysiology and health perception

Pathophysiology

Chronic respiratory failure develops in COPD, obesity and NMD as a consequence of imbalance between respiratory muscle load and capacity accompanied by inadequate neural respiratory drive and a blunted ventilatory response to carbon dioxide and an increase in the arterial partial pressure of carbon dioxide (P_{aCO_2}). The associated increase in hydrogen ions is compensated by renal bicarbonate retention. The pathophysiological mechanisms through which this arises are summarised in table 1. Imbalance in the loads and capacity of the respiratory muscle pump leads to increased ventilatory demand, which may be insufficient, and is perceived by patients as breathlessness. This directly impacts upon HRQoL, as manifested by increased daytime symptom burden at rest, poorer sleep quality and impaired exercise capacity and ability to perform physical tasks to maintain independence.

Factors influencing health perception amongst HMV users

A range of modifiable and nonmodifiable factors are likely to influence patients' health perception and response to HMV. These include the underlying cause of respiratory failure, disease severity at presentation and trajectory of respiratory failure progression, clinical response to HMV, and the intersectionality of individuals' demographics. These factors, as well as the inherited or acquired nature of the disease and timing of diagnosis, impact on patients' health perception and HRQoL.

Early and accurate disease classification is imperative and NMD should be classified as slowly or rapidly progressive and inherited or acquired, since these factors will influence health perception and HRQoL (table 2). For instance, Duchenne muscular dystrophy presents in childhood and is now considered a chronic multisystem disease in which advances in respiratory, cardiac and nutritional therapeutics have extended life expectancy in recent decades [6]. In contrast, the incidence of amyotrophic lateral sclerosis (ALS) is highest in the sixth and seventh decades and death typically occurs 2–4 years after diagnosis, most commonly from respiratory failure caused by respiratory muscle weakness [7, 8]. Patients with obesity-related respiratory failure and COPD present either with acute-on-chronic respiratory failure [9, 10] or in a chronic stable state [11–13], with the acute presentation in obesity more common amongst those who live alone [12]. Clinical trials have demonstrated that HMV improves symptoms, respiratory physiology, physical activity, risk of hospitalisation and survival in patients with chronic and post-acute COPD, inherited and acquired NMD, and obesity-related respiratory failure.

TABLE 1 Chronic respiratory failure: an imbalance in respiratory muscle load, capacity and drive [2–5]			
	COPD	Obesity-related respiratory failure	Neuromuscular disease
Respiratory muscle load	• Airways inflammation and bronchospasm increasing airways resistance (RL) • Sputum retention increases airways resistance (RL) • Expiratory flow limitation results in intrinsic positive end expiratory pressure (TL) • Emphysematous lung with loss of lung elasticity (EL)	• Upper airway obstruction (RL) • Reduced chest wall compliance (EL) • Early airway closure causing intrinsic positive end expiratory pressure (TL)	• Upper airway obstruction (RL) • Sputum retention increasing airways resistance (RL) • Reduced chest wall compliance (EL)
Respiratory muscle capacity	• Lung hyperinflation impairing diaphragm contractility with preserved diaphragm strength • Impaired diaphragm contractility caused by inflammation-related proteolysis • Impaired gas exchange, increasing ventilatory demand	• Reduced respiratory muscle strength and expiratory reserve volume	• Respiratory muscle weakness • Impaired chest wall excursion
NRD	• Increased NRD inadequate for the load–capacity imbalance	• Increase NRD inadequate for the load–capacity imbalance • Blunted hypercapnic ventilatory response	• Reduced and inadequate for the load–capacity imbalance

EL: elastic load; NRD: neural respiratory drive; RL: resistive load; TL: threshold load.

TABLE 2 Classification of neuromuscular disease	
Slowly progressive	Nerve:
	• Spinal muscular atrophy
	• Post-polio syndrome
	• Guillain–Barré syndrome
	Neuromuscular junction:
	• Myasthenia gravis
	Muscle:
	• Duchenne muscular dystrophy
	• Becker muscular dystrophy
	• Myotonic dystrophy
	• Mitochondrial myopathies
	• Charcot–Marie–Tooth disease
Rapidly progressive	• Amyotrophic lateral sclerosis

Individual patients' demographics undoubtedly influence patients' engagement with HMV and the impact the intervention has on their HRQoL. However, the role of intersectionality in HRQoL amongst HMV users is poorly understood, likely as a consequence of unconscious biases within scientific research [14]. It is imperative that clinicians consider patients' sex, ethnicity, social support, level of deprivation and healthcare access, which impact upon the timing of disease diagnosis, engagement with the intervention and follow-up, and thus clinical outcomes (figure 1).

Health perception is also influenced by factors modifiable by HMV, including hospital admission and re-admission, daytime fatigue and somnolence, and sleep quality. Sleep quality impacts upon an individual's ability to function during the daytime, including physical activity, concentration and memory, and impaired sleep quality is associated with poorer HRQoL in chronic respiratory disease [15]. The aetiology of sleep disturbance and sleep disordered breathing between different disease groups with chronic respiratory failure is heterogenous, which may partly explain the varied effects of NIV observed on both sleep quality and HRQoL. Sleep disturbance may additionally be compounded by anxiety and depression, which are common comorbidities in patients with chronic respiratory failure. Such patients are more likely to report difficulty falling asleep, racing thoughts at bedtime and being unable to sleep for days compared to matched controls [16].

Sleep disordered breathing is ubiquitous in obesity hypoventilation syndrome (OHS), with nearly 70% of patients having concomitant severe obstructive sleep apnoea (OSA) [17]. Effective treatment of sleep disordered breathing in OHS patients would therefore be expected to improve sleep quality, which has indeed been confirmed in comparisons of NIV and continuous positive airway pressure (CPAP) (Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ)), as well as HRQoL (Severe Respiratory Insufficiency (SRI) questionnaire, Short Form 36 (SF-36) and the visual analogue scale (VAS) for wellbeing) [9, 17]. CPAP is relatively inexpensive to set up and monitor compared to NIV. Therefore, since control of hypoventilation and sleep disordered breathing may be achieved with both NIV and CPAP in OHS, healthcare services may opt to initiate patients on CPAP either as first line therapy in patients with severe OSA who are not severely hypercapnic, or as a step down following reversal of respiratory failure with a period of NIV [18, 19]. This practice is supported by short-term data demonstrating no differences in treatment efficacy, HRQoL (SF-36 and SRI) or daytime somnolence (ESS) between CPAP and NIV as initial therapy [9], or changes in ventilatory control, HRQoL (SRI) or sleepiness (ESS and Pittsburgh Sleep Quality Index (PSQI)) when switching from NIV to auto-CPAP in OHS [20].

Different ventilator modes may be used to achieve ventilatory control, which may theoretically influence adherence and sleep quality. When using fixed pressure support ventilation, obese patients require higher pressures to overcome upper airway obstruction and achieve adequate control of hypoventilation [21]. Volume-targeted pressure support ventilation is increasingly used in OHS. This ventilator mode estimates expiratory volume and automatically adjusts delivered pressures to achieve a pre-set target tidal volume. In average volume-assured pressure support (AVAPS) mode, expiratory positive airway pressure (EPAP) and maximum inspiratory positive airway pressure (IPAP) are pre-set and IPAP is auto-titrated. In AVAPS with automated EPAP (AVAPS-AE), EPAP is auto-titrated to overcome upper airway occlusion (for example in OSA) or to offset expiratory flow limitation in COPD. These volume-assured modes have a theoretical risk of causing sleep disturbance due to delivery of variable airway pressures. This does not appear to translate clinically, with no differences observed in objective actigraphy or subjective questionnaire (ESS, VAS, fatigue severity scale (FSS)) measures of sleep quality and HRQoL (SRI summary score and all domains)
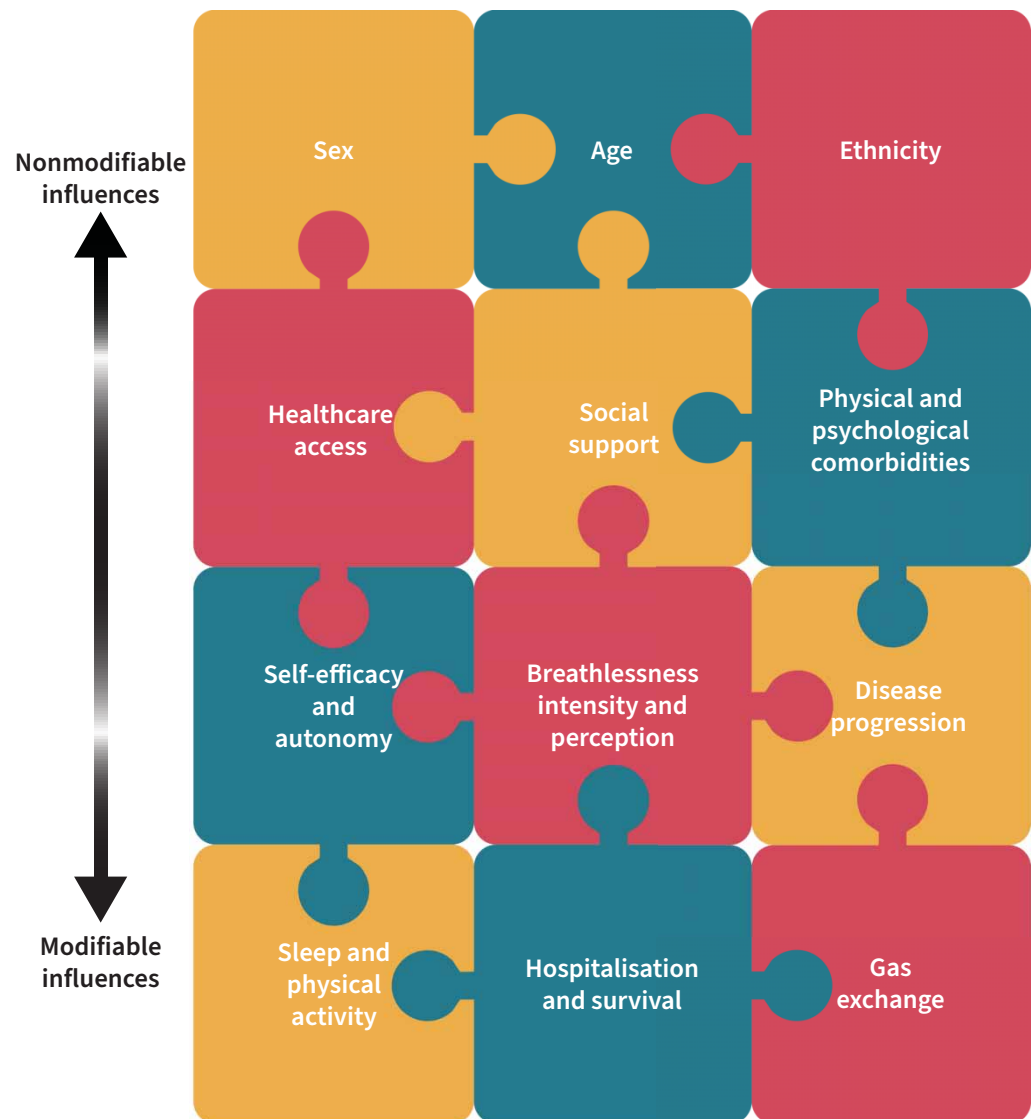
FIGURE 1 Illustration of the complexity and intersectionality of modifiable and nonmodifiable influences on health-related quality of life in patients with chronic respiratory failure, some of which may be addressed using home mechanical ventilation.

in superobese (body mass index (BMI) >40 mg·kg^{-2}) patients in chronic respiratory failure randomised to either fixed pressure support or AVAPS ventilation [12]. Similarly, AVAPS-AE has been compared to fixed-pressure support ventilation in OHS, with no between-group differences in polysomnographic indices or subjective measures (ESS, RSQI, VAS) of sleep quality or HRQoL (SRI) observed [22]. In both cohorts of obese and super obese, comparable ventilatory control was achieved with fixed-pressure support, AVAPS and AVAPS-AE. It should be noted that there is currently no evidence base guiding the implementation of volume-targeted ventilation as a first-line ventilatory mode [23, 24]. There is increasing recognition of COPD-OSA overlap syndrome, where control of both hypoventilation and abolition of expiratory flow limitation and upper airway occlusion may be required. Nonrandomised data demonstrate that, in COPD-OSA patients established on fixed pressure support HMV, switching to AVAPS-AE is not associated with short-term changes in polysomnography indices of sleep quality after 6 weeks; however, subjective sleep comfort (VAS) improved following mode transition [25]. Furthermore, there were no changes in gas exchange or disease-specific HRQoL measures, including the COPD Assessment Test and the SRI questionnaire. These preliminary data indicate the safety and efficacy of using automated HMV modes in COPD-OSA; however, prospective randomised trials are warranted to understand the effects of different methods of delivering positive airways pressure therapy in this cohort.

The underlying cause of respiratory failure likely influences the psychological impact of the diagnosis and need for HMV. Patterns of HMV setup in different disease categories have evolved over the last two decades. Data from the 2001 Eurovent survey, which included 21 526 HMV users from 16 countries, classified the aetiology of chronic respiratory failure into neuromuscular (which was the largest category), lung/airways disease and thoracic cage disorders, which included OHS [26]. 20 years later, data on 1746 patients from two European specialist ventilation units demonstrate that the underlying disease affecting 30% of HMV users is OHS, with NMD (23%) and obstructive airways disease (19%) accounting for the next largest disease categories [27]. In patients with COPD and progressive NMD, the cause of chronic respiratory failure is progressive and irreversible in nature. Thus, once daytime hypercapnia arises, the need for ventilation is lifelong and may be associated with the accumulation of additional physical disabilities. Patient-centred therapeutic aims when initiating NIV in these patients thus depend on the underlying aetiology of respiratory failure, with the aim of sustaining HRQoL in rapidly progressive disease (such as ALS) and improving it with other conditions (such as COPD or obesity) [28]. This is less true of obesity-related respiratory failure, which is theoretically reversible when patients are provided with lifestyle, pharmacological, rehabilitation and surgical support, where appropriate and available.

Autonomy, the ability to make and enact informed decisions about individuals' healthcare, is directly associated with HRQoL. Decision making regarding medical interventions must take patients' preferences and priorities into account. These may relate to the practicalities of engaging with HMV, including technical issues surrounding novel medical devices, as well as the restrictions or burdens it may impose upon patients' home setup, ability to eat, communicate and travel, as well as the impact on bedpartners, relatives and caregivers. Qualitative interviews reveal that the increased dependence on others precipitated by HMV, surveillance by carers and the reliance on technology can also impede autonomy [29]. Furthermore, HMV users commonly express a preference to remain in their home environment, rather than a care facility, to promote independence and normalisation of their lives as much as possible [30]. Interestingly, a study undertaken by KLINGSHIRN et al. [31], which sought to explore differences in care quality between HMV delivered in private homes and shared living communities, found no quantitively ascertained HRQoL differences (SRI summary score and all subdomains). This discrepancy may reflect the limitations of current questionnaires in identifying nuances of the psychological impacts of HMV.

Assumptions and judgements may be made by healthcare professionals regarding patients' HRQoL based on their level of disability, which may influence medical decision-making and information provided on therapeutic options [32]. This discordance can detrimentally impact upon patients' satisfaction with their healthcare providers and autonomy and could lead to breakdown in professional relationships between patients, their caregiver and healthcare professionals [33]. Interviews with HMV users reveal the feeling of being compelled to commence NIV. In some, this was due to the desire to sustain life and so HMV initiation was deemed a necessity, not a choice [34]. Conversely, others describe implicit pressure from family or healthcare professionals to accept HMV and subsequently feeling trapped by the machine [35]. Autonomy impairment, as perceived by healthcare professionals, has been shown to impact around 50% of COPD patients on HMV and is associated with poorer HRQoL, using the SRI [36]. It is important to recognise the limitations in quantitative measures of quality of life that do not necessarily capture individuals' ability to engage with activities important to them. These may include social visits with friends, completing higher education, attending sporting or religious events and eating at restaurants [37], which should be enquired about during HMV initiation decision-making conversations. The impact of economic implications associated with HMV use must also be acknowledged, including formal costs of increased electricity usage, care support and travel to regular hospital appointments, as well as informal care costs [38].

Self-efficacy refers to individuals' confidence in their capacity to undertake behaviours that lead to desired outcomes and is a mechanism through which effective disease education and self-management can be promoted [39]. Self-efficacy may be lower in patients with higher disease burden and poorer self-efficacy is associated with worse HRQoL, as measured using the EuroQol-Five Dimensions-Five Levels (EQ-5D-5L) and the EuroQol-Visual Analogue Scale [40]. Data routinely collected from ventilators, including adherence, leaks, apnoea–hypopnoea index (AHI) and ventilatory parameters, may be used to optimise patients' HMV interfaces and settings remotely and potentially avoid future respiratory deterioration and emergency healthcare attendance. Interestingly, however, additional support provided through daily telemonitoring using simple physiological observations and symptom reporting may impair self-efficacy and lead to excess healthcare utilisation [41].

Anxiety is a common comorbidity in chronic respiratory disease and is independently related to HRQoL [42]. HMV appears to have a beneficial effect on anxiety, as quantified using the anxiety component of the

SRI, with greatest improvements observed in patients with OHS and restrictive thoracic disease and more modest improvements in those with COPD and NMD 12 months post-setup. This is corroborated by qualitative interview data, in which HMV users report multidimensional improvements in HRQoL. These include both physical benefits, including renewed vitality, more refreshing sleep and fewer morning headaches, as well as psychological improvements relating to a renewed sense of being, safety and a diminished fear of death [30]. Disease education, including explaining the rationale for HMV and its intended benefits, is important in how acceptable HMV is deemed by patients. Additional psychological support, in the form of a specialist cognitive behavioural therapy programme on awareness and control of physical and emotional symptoms, has been shown to improve HMV adherence as well as HRQoL compared to educational videos [43].

Evidence of improvement in symptoms, physiology, healthcare utilisation and survival

To assess the trajectory of change in HRQoL in the three patient groups, we have focussed on those clinical studies, both observational and clinical trials, which demonstrate that HMV improves symptoms, respiratory physiology, physical activity, hospitalisation and survival.

COPD

a) In chronic stable hypercapnic patients with preserved exercise capacity and low exacerbation frequency, HMV in addition to oxygen therapy has been shown to improve all-cause survival compared to standard care [11].
b) In post-acute patients with persistent severe hypercapnia following an acute exacerbation with decompensated respiratory failure requiring acute NIV, HMV with home oxygen therapy increases the time to readmission or death compared to home oxygen therapy alone [10].

Obesity

Obesity-related respiratory failure in superobese patients with hypercapnia secondary to OHS and severe OSA have shown improvement in overnight and daytime carbon dioxide levels with CPAP, pressure support ventilation with a back-up rate and volume-targeted pressure support ventilation either started as an inpatient or outpatient [44–46]. These improvements in gas exchange and lung function are accompanied by changes in HRQoL and sleep quality, with no differences observed between pressure-targeted and volume-targeted modes of ventilation [12, 47].

NMD

HMV has been shown to improve survival in congenital neuromuscular and restrictive chest wall disease [27, 48–50]. ALS patients have demonstrated improvement in survival in patients with orthopnoea, nocturnal hypoventilation, respiratory muscle weakness without severe bulbar impairment, with or without daytime hypercapnia, compared to conventional medical care when treated with HMV [51].

HMV is conventionally initiated on an inpatient basis, involving patient and caregiver education and training, interface selection and acclimatisation. Setup and follow-up may involve long-distance travel to a specialist centre, which requires patient and caregiver time and resources to transport required medical equipment. Emerging data support outpatient and domiciliary setups, which may achieve comparable control of hypoventilation without additional cost implications [13, 52], and advances in remote ventilator monitoring may facilitate fewer in-person follow-up visits.

HRQoL assessment tools for HMV users

Clinicians must consider the burden of complex medical interventions, such as HMV, on patients' day-to-day life. The concept of shared decision-making and patient-centred care is far from a new concept [53] and clinicians must be cognisant of HMV patients' and caregivers' perspectives, values and preferences to enhance HMV setup and early and long-term adherence. This approach is embedded into clinical trials and clinical practice, with patient involvement in research design, delivery and dissemination considered standard practice [54]. Information can be gathered using measurements that explore patients' perception of their symptoms and the impact of their condition on physical and psychological wellbeing (patient-reported outcome measures, PROMs). Evaluating patients' healthcare experiences (patient-reported experience measures, PREMs), including accessibility, hygiene of facilities, staff friendliness, confidence in the clinicians and being listened to, improves the quality of clinical services [55]. PREMs are infrequently reported in clinical trials of HMV. However, limited data indicate that HMV training with effective communication from clinicians, tangible symptomatic improvement and interface comfort can improve patients' well-being as well as HRQoL and HMV adherence [56].

An important part of clinicians' work is to explain in detail and contextualise the important healthcare decisions that patients may face. For this, and the delivery of patient-centred care, the patient and their carer need to actively engage and consider their decision to start and adhere to HMV as starting HMV, delayed starting of HMV and declining HMV will have different but important long-term consequences. The clinical benefits of HMV reported by the clinician to the patient must be balanced with the perceived treatment burden to the patient, which will be considered by the patient often in discussion with their family and carers. The consequences of this decision will be important to the patient, their family and caregivers and will also have implications on primary, secondary and emergency care [57].
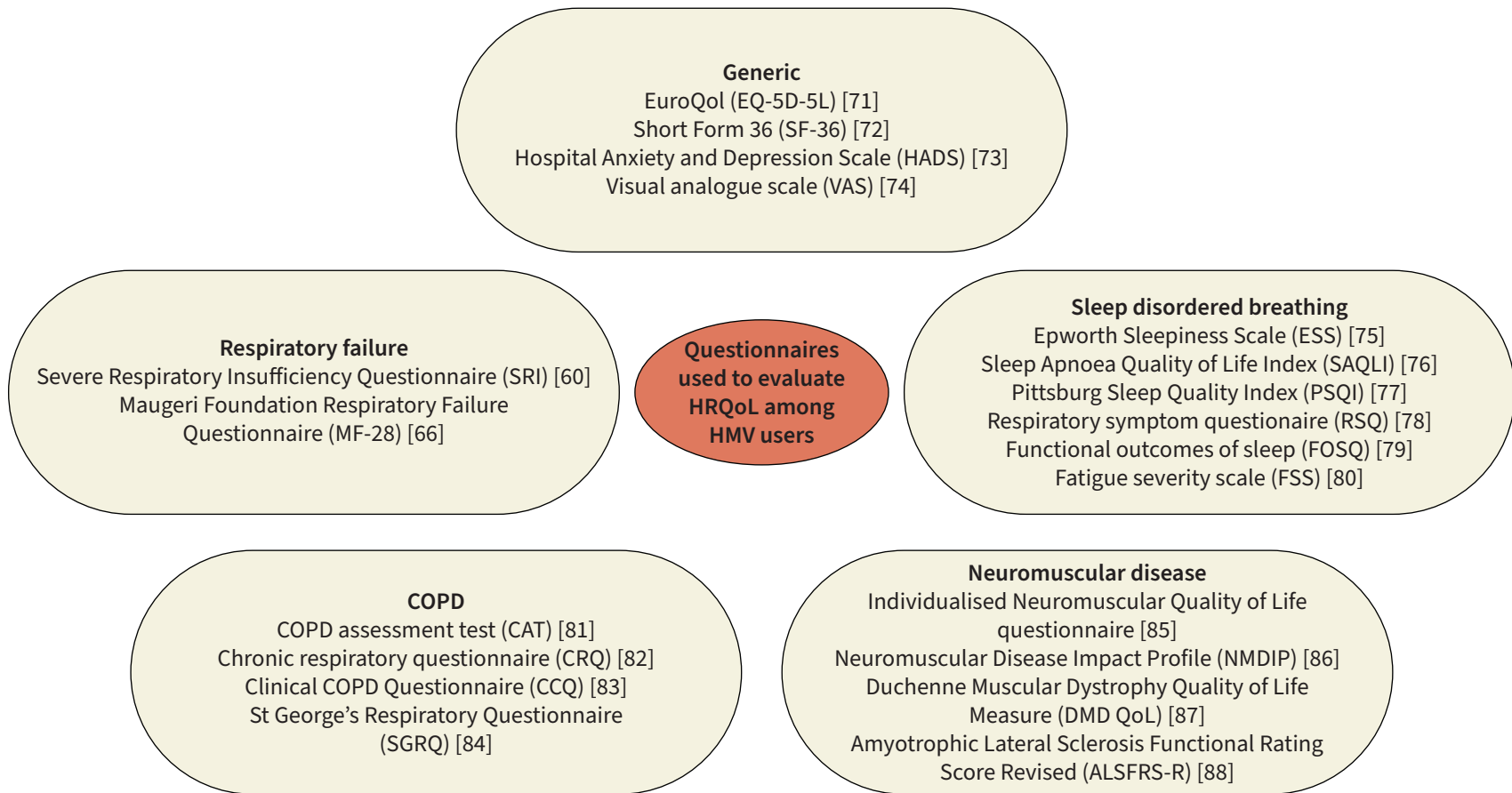
HRQoL among HMV users is evaluated with quantitative questionnaires at baseline then at regular intervals post-setup. A host of generic and disease-specific questionnaires are implemented in research, as summarised in figure 2. Generic tools, such as the SF-36 and EuroQol-5D, are used in health economics to determine intervention cost-effectiveness [58, 59]. The SRI questionnaire is a tool that was specifically developed to quantify HRQoL in stable patients receiving HMV [60]. It comprises seven subscales using 49 questions that are ranked on a five-point Likert scale, with higher scores indicating better HRQoL [61]. The SRI has satisfactory psychometric properties amongst HMV users and is sensitive to change in patients with stable COPD, obesity-related respiratory failure, NMD and restrictive chest wall disease [62]. It has also been validated specifically for COPD patients requiring long-term oxygen therapy and those requiring HMV [63, 64]. A minimum clinically important difference has not been defined for all disease groups, but a five-point change has been proposed for HMV users with severe stable COPD [65]. The Maugeri Foundation Respiratory Failure Questionnaire (MF-28) is a 28-item set which was developed amongst patients with chronic respiratory failure [66]. Whilst the emphasis of the SRI is more closely related to anxiety and depression, the MF-28 focuses on activities of daily living and includes an evaluation of perceived physical and cognitive function [67]. It is discriminatory in patients with chronic respiratory failure and related to patients' general health perception without a floor or ceiling effect.

Dimensions that are not consistently captured in questionnaires are the impact of HMV on sleep quality, intimacy and self-efficacy, which all impact upon HRQoL. Nocturnal symptoms, such as breathlessness, cough and sleep disordered breathing likely contribute to the high prevalence of subjective and objective indices of sleep disturbance among HMV patients with COPD, obesity and NMD and specific enquiries during clinical encounters should be undertaken to evaluate the impact of HMV on sleep quality [68, 69]. Other aspects to consider when using such questionnaires are patients' educational attainment and cognitive function, since increasing evidence indicates that HMV users have impaired cognitive function when starting HMV, which improves with ongoing adherence [70].

Qualitative research has also been used to investigate patients' and their caregivers' experiences of HMV, typically employing purposive sampling and completion of semi-structured interviews to explore various aspects of HMV delivery. These may include barriers and facilitators to HMV adoption and adherence, technical needs and support [89] and the impact of HMV on household members and caregivers [90]. Common methods of analysing interview transcripts include thematic analysis, in which data codes are used to identify emerging themes [91], and framework analysis, in which data are organised by predefined constructs, summarised in a structured matrix output [92].
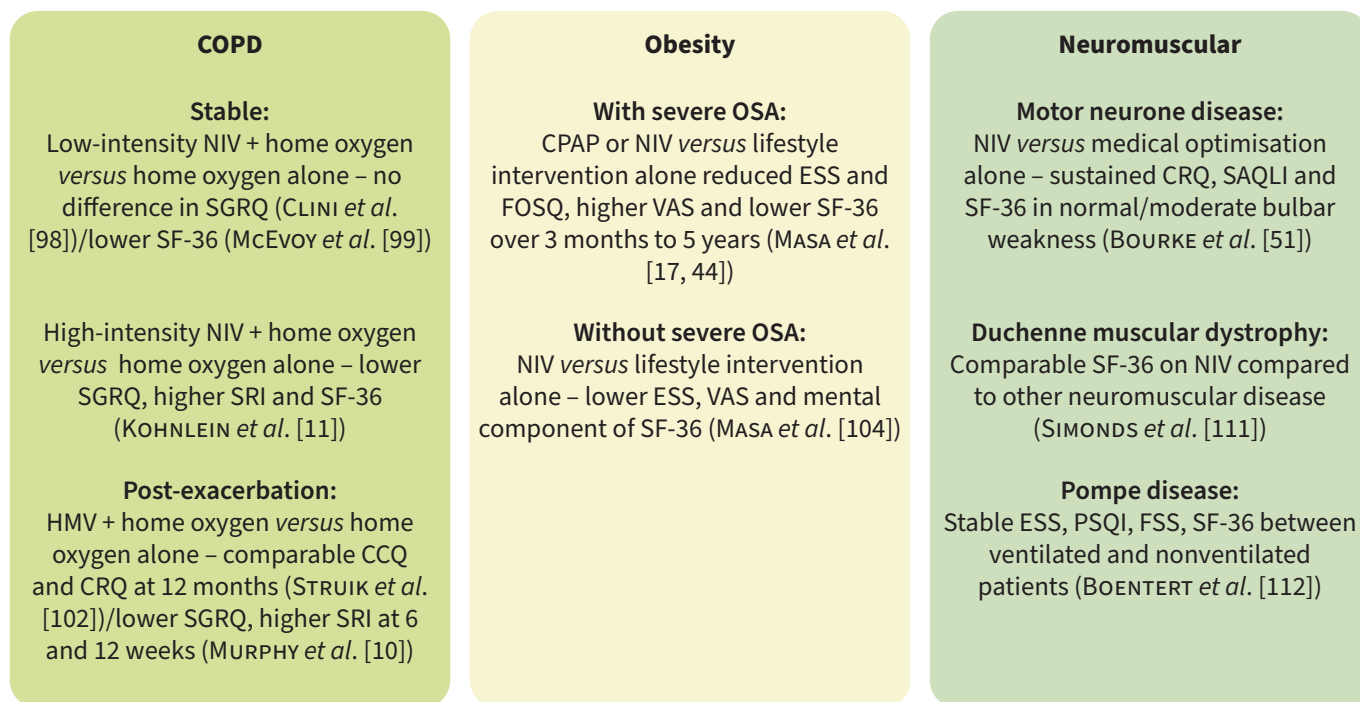
Impact of HMV on HRQoL

Baseline HRQoL and response to treatment are influenced by the underlying cause of respiratory failure. The reasons for this are multifactorial, likely relating to speed of disease progression, increased ventilator dependence, diminution in autonomy, physical and psychological comorbidities, and social factors [27, 50, 62]. Interestingly, changes in HRQoL following HMV initiation do not appear to correspond with disease severity, physiological improvements in gas exchange or advantageous clinical outcomes [21, 93]. There are currently few studies that have prospectively evaluated the trajectory of HRQoL amongst HMV users in the long term. It may be hypothesised that progression of the primary disease causing respiratory failure and comorbidities would lead to a cumulative deterioration in symptoms and HRQoL. In the short and medium term, data indicate that HMV confers a stabilisation of HRQoL in COPD and OHS [10, 94]. The mortality rate amongst HMV users after setup is high, particularly amongst those with COPD and rapidly progressive NMD with a median survival of 1.1 and 2.7 years, respectively, as reported in a recent multicentre European study [27, 50]. Amongst survivors, HRQoL appears to remain stable between setup and 5-year post-setup evaluation [95]. Data reporting HRQoL amongst HMV users in the final phase of life are limited. Limited questionnaire data and experiential evidence indicate that respiratory symptom burden is high and patients have a greater dependence on their ventilator to achieve effective gas exchange as well as alleviate breathlessness [96, 97]. This imposes burdens upon patients, through more limited verbal communication, interface-related discomfort and ventilator alarms which may disrupt sleep and

Generic
EuroQol (EQ-5D-5L) [71]
Short Form 36 (SF-36) [72]
Hospital Anxiety and Depression Scale (HADS) [73]
Visual analogue scale (VAS) [74]

Respiratory failure
Severe Respiratory Insufficiency Questionnaire (SRI) [60]
Maugeri Foundation Respiratory Failure
Questionnaire (MF-28) [66]

Questionnaires used to evaluate HRQoL among HMV users

Sleep disordered breathing
Epworth Sleepiness Scale (ESS) [75]
Sleep Apnoea Quality of Life Index (SAQLI) [76]
Pittsburg Sleep Quality Index (PSQI) [77]
Respiratory symptom questionaire (RSQ) [78]
Functional outcomes of sleep (FOSQ) [79]
Fatigue severity scale (FSS) [80]

COPD
COPD assessment test (CAT) [81]
Chronic respiratory questionnaire (CRQ) [82]
Clinical COPD Questionnaire (CCQ) [83]
St George's Respiratory Questionnaire
(SGRQ) [84]

Neuromuscular disease
Individualised Neuromuscular Quality of Life
questionnaire [85]
Neuromuscular Disease Impact Profile (NMDIP) [86]
Duchenne Muscular Dystrophy Quality of Life
Measure (DMD QoL) [87]
Amyotrophic Lateral Sclerosis Functional Rating
Score Revised (ALSFRS-R) [88]

FIGURE 2 Questionnaires used to evaluate the impact of home mechanical ventilation (HMV) on health-related quality of life (HRQoL) [60, 66, 71–88].

COPD	Obesity	Neuromuscular
Stable: Low-intensity NIV + home oxygen *versus* home oxygen alone – no difference in SGRQ (CLINI *et al.* [98])/lower SF-36 (MCEVOY *et al.* [99]) High-intensity NIV + home oxygen *versus* home oxygen alone – lower SGRQ, higher SRI and SF-36 (KOHNLEIN *et al.* [11]) **Post-exacerbation:** HMV + home oxygen *versus* home oxygen alone – comparable CCQ and CRQ at 12 months (STRUIK *et al.* [102])/lower SGRQ, higher SRI at 6 and 12 weeks (MURPHY *et al.* [10])	**With severe OSA:** CPAP or NIV *versus* lifestyle intervention alone reduced ESS and FOSQ, higher VAS and lower SF-36 over 3 months to 5 years (MASA *et al.* [17, 44]) **Without severe OSA:** NIV *versus* lifestyle intervention alone – lower ESS, VAS and mental component of SF-36 (MASA *et al.* [104])	**Motor neurone disease:** NIV *versus* medical optimisation alone – sustained CRQ, SAQLI and SF-36 in normal/moderate bulbar weakness (BOURKE *et al.* [51]) **Duchenne muscular dystrophy:** Comparable SF-36 on NIV compared to other neuromuscular disease (SIMONDS *et al.* [111]) **Pompe disease:** Stable ESS, PSQI, FSS, SF-36 between ventilated and nonventilated patients (BOENTERT *et al.* [112])

FIGURE 3 Health-related quality of life outcomes in clinical trials evaluating home mechanical ventilation (HMV) in patients with COPD, obesity and neuromuscular disease [10, 11, 17, 51, 98, 99, 102, 104, 112]. CCQ: Clinical COPD Questionnaire; CPAP: continuous positive airway pressure; CRQ: Chronic Respiratory Disease Questionnaire (higher score indicates better health); ESS: Epworth Sleepiness Scale (higher score indicates worse sleep quality); FOSQ: Functional Outcomes of Sleep Questionnaire (higher score indicates worse sleep quality); FSS: fatigue severity scale; NIV: noninvasive ventilation; OSA: obstructive sleep apnoea; PSQI: Pittsburgh Sleep Quality Index (higher score indicates worse sleep quality); SAQLI: Sleep Apnoea Quality of Life Index (higher scores indicate better health; SF-36: Short Form 36 (higher score indicates worse health); SGRQ: St George's Respiratory Questionnaire (higher score indicates worse health); SRI: Severe Respiratory Insufficiency Questionnaire (high score indicates better health); VAS: visual analogue scale (higher score indicates better health).

cause distress, as well as onto family members and caregivers, which may related to end-of-life decision-making as well as the financial implications of caregiving [96, 97]. The following sections will describe the far-reaching effects of HMV on patients' HRQoL, divided into themes specific to the underlying cause of respiratory failure, specifically COPD, obesity-related respiratory failure and NMD (figure 3), and those common to all HMV users, including sleep quality, psychological impact on patients and their caregivers, as well as a description of location of HMV setup and long-term invasive mechanical ventilation.

Disease-specific effects of HMV on HRQoL
COPD
The impact of HMV on global scales of HRQoL in COPD is heterogenous and appears to relate to clinical stability the time of initiation and HMV prescription. Several studies have evaluated the impact of HMV in stable hypercapnic COPD patients, with HRQoL measures included as secondary end-points. Trials implementing low-intensity ventilation (low pressures, low back-up rate) with home oxygen therapy have demonstrated either no HRQoL benefit, using St George's Respiratory Questionnaire (SGRQ) at 12- and 24-months post-setup [98] or a potentially deleterious impact on general and mental health, as quantified using SF-36, and worsened confusion and vigour, based on the profile of mood states at 12 months [99]. Of note, neither study demonstrated improvements in clinical outcomes with HMV with respect to either hospitalisations or survival. Conversely, a high-intensity approach targeting reduction in P_{aCO_2} appears to confer both clinical benefits (admission-free survival), as well as HRQoL, with better adherence in the high-intensity arm, indicating that patients are better able to tolerate interventions that improve their HRQoL [100]. This manifests as improvements in global scores of HRQoL, using general respiratory and disease-specific tools (SGRQ and SRI), and improvements in general health perception, quantified using SF-36 [11]. Explanations for differences in HRQoL outcomes between low-intensity and high-intensity strategies in stable COPD patients remain speculative. Hypotheses include high inspiratory pressures driving greater expiratory flow at the start of expiration and subsequently resulting in a reduction in lung

hyperinflation, improved symptoms and clinical outcomes, and higher pressures directly influencing the airways, possibly through reducing airway oedema, which manifests as increased forced expiratory volume in 1 s and P_{aCO_2} reduction, which is not observed using a low-intensity approach [100, 101].

During acute exacerbations of COPD, a proportion of patients develop acute respiratory failure. Following a period of acute support with mechanical ventilation, hypercapnia resolves in a large proportion of patients during in-hospital and post-discharge recovery. The two multicentre randomised controlled trials evaluating the effects of HMV with home oxygen compared to home oxygen alone following an episode of acute hypercapnic respiratory failure during COPD exacerbation requiring acute mechanical ventilation were the RESCUE and HOT-HMV trials [10, 102]. In RESCUE, total and subdomain Clinical COPD Questionnaire and Chronic Respiratory Questionnaire (CRQ) scores improved in both intervention and control arms over the 12-month follow-up period, with a trend toward improved SRI. However, HMV with home oxygen therapy appears to have conferred benefits in symptom burden, sleep quality and social relationships, quantified with the SRI. In HOT-HMV, early HRQoL benefits (SRI and SGRQ) were observed amongst HMV users at 6- and 12-weeks post-setup, but these were not sustained at 6 or 12 months. The question as to the usefulness of SRI as an HRQoL measurement tool during post-exacerbation recovery remains.

Currently, HMV-related improvements in HRQoL in COPD patients with chronic respiratory failure are best observed in the stable population. Shorter-term unsustained changes in HRQoL are observed post-HMV set-up period in patients recovering from an episode of acute hypercapnic respiratory failure who have persistent chronic respiratory failure [10]. Additionally, there is indirect evidence that both exacerbation history and anaemia substantially influence HRQoL, as quantified using the SRI [103]. Additional factors, such as the poorer clinical outcomes (risk of hospital readmission and survival), the potentially more limited scope to alleviate symptoms or improve exercise capacity, and the psychological impact of post-exacerbation setup on autonomy in this cohort may need to be considered and evaluated. Further investigation into current measures used to assess HRQoL in the post-exacerbation period are thus warranted.

OHS

Early observational data indicated that NIV improves breathlessness, sleep quality (FOSQ) and daytime sleepiness, which were subsequently explored in randomised controlled trials [104, 105]. The Pickwick Project was a long-term clinical trial that compared the effects of lifestyle modification, CPAP and NIV in OHS, defined as obesity (BMI $\geqslant 30$ kg·m^{-2}) with daytime hypercapnia. Patients with and without severe OSA (AHI $\geqslant 30$ events per hour) were evaluated separately. Masa et al. [17] identified that both CPAP and NIV are associated with short-term improvements in sleep quality (using the ESS and FOSQ) and both physical and mental wellbeing (based on SF-36 and a VAS). These benefits are also present in obese subjects without comorbid severe OSA (polysomnographic AHI $\geqslant 30$ events per hour), in whom home NIV is associated with greater short-term improvements in patient-reported tiredness and refreshing sleep, as well as objective indices of sleep quality, including AHI, arousal and desaturation indices and nocturnal oxygenation [94]. In the long term, the Pickwick Project identified that there were no differences in indices of HRQoL or sleep quality, using the SF-36, ESS or FOSQ between NIV and CPAP in obese patients with chronic respiratory failure and severe OSA over 5 years [44].

NMD

Respiratory failure in ALS is inevitable and HMV is an essential part of treatment 30 months after symptom onset [106]. The nonspecific presentation of the disease commonly results in late diagnosis and patients are often initiated on HMV shortly after receiving the diagnosis. HMV likely confers a survival advantage in patients with ALS following the development of respiratory failure (orthopnoea with maximal inspiratory pressure <60% predicted or daytime hypercapnia), particularly in those without severe bulbar weakness [51]. However, it can be difficult to establish in patients with moderate and severe bulbar weakness and these patients demonstrate lower treatment adherence than those with normal or mild impairment of bulbar function [107]. This may be due to difficulties obtaining an adequate seal leading to mask leaks, which are noisy and uncomfortable, and pooling of upper airway secretions in the interface.

The impact of HMV on HRQoL in ALS is variable, and likely related to bulbar function. Studies of patients with rapidly progressive NMD are challenging to perform for ethical and practical reasons. The landmark clinical trial by Bourke et al. [51] used HRQoL, specifically the SF-36 mental component summary and Sleep Apnoea Quality of Life Index (SAQLI) symptoms domain (given the expected decline in physical function), as the primary outcome. Patients with normal or moderate bulbar weakness who received HMV were found to maintain better HRQoL than those who received standard medical care alone, quantified in all total and domain scores for the CRQ and SAQLI, and the SF-36 domains of mental

health, energy vitality, general health perception, emotional and social function and the physical component summary. HMV-related improvements in HRQoL in those patients with severe bulbar weakness were less pronounced, with improvements observed in only the CRQ dyspnoea and SAQLI daily functioning, social isolation and symptoms components. Interestingly, those patients who received NIV had 50% lower rapid eye movement sleep than controls, indicating more sleep disruption, but this was not reflected in subjective measures of sleep quality. Prior work by the same group identified that the peak improvement in HRQoL was achieved 3–5 months after HMV initiation [107]. In contrast, a prospective cross-sectional evaluation which explored predictors of HRQoL in ALS identified that need for mechanical ventilation, as well as disease severity, reduced social activities and comorbid anxiety or depression, were associated with worse HRQoL [108]. This poorer HRQoL amongst patients with more severe disease appears to be positively influenced by HMV, with improvements in ALS Assessment Questionnaire 5 and EQ-5D-5L scores reported by PESESCHKIAN et al. [109] at each disease stage. The limited data available thus indicate that there is likely a cohort of patients in whom HMV will enable a plateau or decelerated decline in HRQoL. Patients with preserved bulbar function are most likely to benefit, likely as a consequence of improved interface fit, which permits minimisation of leak and optimal delivery of positive airway pressures. An individualised approach with respect to patients' needs and preferences regarding place of ventilation setup, interface selection, ventilator settings and secretion management should improve both survival and HRQoL [110].

There are few clinical trials evaluating the impact of HMV in slowly progressive NMDs. Observational data in Duchenne muscular dystrophy indicate that HMV does not impede patients' ability to participate in education and social activities and that SF-36 domains of health perception, social function, physical and mental function and mental health are comparable to scores from patients with scoliosis and post-polio syndrome [111]. HRQoL data prospectively collected from patients with adult Pompe disease, which is an inherited glycogen storage disease that causes progressive myopathy, indicate potentially detrimental effects of HMV in this cohort [112]. Patients established on HMV during study participation had a longer disease duration and had correspondingly higher levels of physical disability and resting breathlessness than those who were not ventilated. Despite comparison of different disease stages, no differences were observed in sleep quality, fatigue or mental health (quantified with PSQI, FSS, ESS and SF-36) between ventilated and nonventilated patients. However, those patients who also required daytime ventilation were observed to have lower HRQoL, poorer sleep quality and more intense fatigue. Furthermore, daily time spent on ventilation was inversely related to the physical and mental components of the SF-36. Observational data has demonstrated that nocturnal HMV does not adversely impact upon the patients' abilities to continue with daily activities that are important to them. However, the need for daytime use of HMV may adversely affect HRQoL.

Elderly population

Eligibility criteria for HMV clinical trials typically exclude elderly patients due to the likely introduction of confounding factors that may influence study outcomes, notably physical comorbidities, cognitive impairment and age-related changes in sleep patterns and architecture. Data on the effects of NIV in older patients are therefore lacking. A prospective evaluation undertaken by TISSOT et al. [113] sought to evaluate trends in HRQoL and sleep following NIV initiation for chronic respiratory failure and compared outcomes between elderly (aged 75 years and above) and younger patients. They identified a higher prevalence of OHS amongst the elderly and stability of HRQoL measured with SF-36 between HMV setup and 6 months post-setup in contrast to the improvements in all SF-36 domains observed in younger patients. Comparable improvements in sleep quality, measured with ESS and PSQI, were observed in the older and younger patients, as was reduction in P_{aCO_2}.

Location of HMV setup

Initiation of HMV is conventionally undertaken in the inpatient setting, which typically requires hospital admission for several nights to titrate and optimise titration settings to achieve adequate ventilatory control. Given the burdens this imposes onto stretched healthcare resources and upon symptomatic patients in chronic respiratory failure, studies evaluating HMV setup in outpatient and home environments have been undertaken. DUIVERMAN et al. [52] evaluated home initiation using transcutaneous CO_2 ($TcCO_2$) and remote monitoring and titration of ventilator settings in stable hypercapnic COPD patients as compared to conventional inpatients setup. They observed improvements in disease-specific HRQoL in both groups at 6 months post-setup and the home setup was confirmed as noninferior with respect to P_{aCO_2} reduction. Furthermore, home-based setup incurred half the costs of inpatient setup. In OHS, MURPHY et al. [13] randomised patients to receive protocolised NIV setups either as an inpatient using a nurse-led protocol using fixed pressure support ventilation or in the outpatient department with a trained doctor, nurse or physiotherapist using AVAPS-AE ventilation, with both approaches targeting P_{aCO_2} reduction. HRQoL,

measured with the EQ-5D-5L, improved in both groups at 3 months, and there were no between-group differences in sleep quality, based on actigraphy and VAS for sleep quality and comfort, or the primary outcome of cost-effectiveness. The Dutch Homerun study compared home and inpatient NIV setups using fixed pressure support ventilation in patients with neuromuscular or chest wall disease [114]. The home setup was achieved using $TcCO_2$ measurement and remote ventilator monitoring and comparable P_{aCO_2} reductions were achieved in both groups. HRQoL was measured at baseline and 6-months using the Hospital Anxiety and Depression Scale, MF-28, SRI and SF-36 and no between-group differences were observed in any total or component scores. Finally, VOLPATO et al. [43] compared HMV setups for motor neurone disease patients in outpatient and home environments. In both environments, patients received a minimum of eight 2-h sessions with a respiratory therapist, which included education on secretion clearance and NIV acclimatisation. An early benefit in HRQoL (SF-36) was observed in the home setup group at 2 months, which was not sustained at 6 months, and the general health SF-36 domain was better in home-setup patients at 6 months. At study completion, were no between-group differences in P_{aCO_2} (the primary outcome) or in caregiver burdens, as measured using the caregiver burden inventory. From current data, it thus appears that it is feasible to establish stable patients on HMV outside the conventional inpatient setting, in either the outpatient department or home. Home or outpatient HMV setups appear to be cost-effective compared to inpatient initiation and is associated with comparable ventilatory control and HMV adherence. Furthermore, questionnaire evaluation indicates that outpatient setups are qualitatively acceptable to patients and generally perceived as a positive experience, with sufficient time given for education and acclimatisation [56].

Invasive mechanical ventilation

A proportion of patients in chronic respiratory failure receive invasive mechanical ventilation. This may have been inserted electively, following careful decision making, or in the emergency setting of an acute presentation of respiratory failure, sometimes before the aetiology of hypercapnia has been diagnosed. There are significant geographic variations in the prevalence of long-term invasive mechanical ventilation, with particularly high numbers observed in Canada and Japan [115, 116]. This may be consequence of complex and interacting factors relating to healthcare infrastructure, financial reimbursement, healthcare practitioners' attitudes and patients' deference and family support [117]. It is interesting to note that surveys of motor neurone disease patients from America (where tracheostomy ventilation is uncommon, with numbers comparable to the United Kingdom [118, 119]) and Japan have highlighted that Japanese patients were more likely to oppose invasive and 24-h NIV and one-fifth of patients in each country supported the idea of tracheostomy ventilation [120].

The impact that invasive ventilation has on an individuals' HRQoL is likely influenced by the underlying cause of chronic respiratory failure, baseline level of disability and pre-existing comorbidities [121]. Studies comparing outcomes in COPD and NMD patients receiving long-term invasive ventilation highlight much poorer HRQoL indices in COPD patients [122]. Whilst neuromuscular patients are more likely to require more intense nursing support for higher levels of physical disability, patients with COPD report poorer overall HRQoL and lower satisfaction regarding their ability to mobilise, communicate and engage in social activities. Poignantly, surveys indicate that, if given the choice of tracheostomy ventilation again, 43% of COPD patients and 18% of neuromuscular patients would decline, preferring certain death. These data highlight the necessity of engaging in conversations regarding advanced care planning early to ascertain patients' priorities and preferences in advance of acute deteriorations, under which circumstances patients' choices may be challenging to ascertain and invasive ventilation may be initiated to preserve life whilst more information is gathered from relative and caregivers.

Impact on relatives and caregivers

Household members are directly impacted by the introduction of HMV for patients. This may initially be through disruption in the sleeping environment from the bulk and noise of equipment and, in the case of progressive diseases, may lead to an increasing role in HMV setup, delivery and troubleshooting. As such, it is important to provide appropriate education and training to patients' caregivers regarding the underlying cause of respiratory failure, the rationale for HMV and importance of adherence, as well as technical aspects of HMV delivery [90]. Multidisciplinary support from specialist physiotherapists, nurses, dieticians and occupational therapists may be necessary where patients require assistance with secretion management, including delivery of upper airway suctioning or mechanical insufflation–exsufflation, gastrostomy feeding and aids for mobility and activities of daily living. Healthcare professionals should also be sensitive to the potential perceived intrusion of this additional support into the privacy in the family home and the psychological impact of transition to medicalisation of the home [123, 124]. Furthermore, healthcare professionals should explore and co-ordinate patients' and household members' wishes regarding their roles in delivery of specific aspects of care, since some may prefer all aspects to be

delivered by professionals, whilst others may wish to be part of care with support [125]. Providing support, whether that be emotional or healthcare-related, is associated with caregiver burdens, which is well-described in the NMD population [126]. Clinical trials into psychological and peer support for informal caregivers are ongoing (ClinicalTrials.gov identifier: NCT04695210).

Conclusion

Mechanical ventilation may be delivered in the home using either noninvasive or invasive techniques to support patients with chronic respiratory failure. This most commonly affects patients with COPD obesity and NMD. HMV may be associated with physical discomfort and psychological burdens but can improve clinical outcomes, including risk of respiratory deterioration, hospitalisation and survival. Clinical studies have demonstrated that HMV can improve or stabilise HRQoL and sleep quality in patients with chronic respiratory failure secondary to COPD, obesity and NMD. However, it is important to consider the impact it has on patients' autonomy and caregiver wellbeing and offer appropriate education and support where needed.

Points for clinical practice

- HMV is an evidence-based treatment for chronic respiratory failure and improves clinical outcomes and symptoms in COPD, obesity and neuromuscular patients with chronic respiratory failure.
- HRQoL may be impacted upon by treatment with HMV and this can be quantified in research studies and clinical practice using general and disease-specific questionnaires and interviews.
- Clinical studies demonstrate that HMV can improve or stabilise HRQoL in patients with chronic respiratory failure.
- The impact of HMV on patients' sleep quality, autonomy, social interactions and on their caregivers must be considered, with appropriate support offered where necessary.

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