Update on clinical trials in home mechanical ventilation

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Home mechanical ventilation (HMV) is an increasingly common intervention and is initiated for a range of pathological processes, including neuromuscular disease (NMD), chronic obstructive pulmonary disease (COPD) and obesity related respiratory failure. There have been important recent data published in this area, which helps to guide practice by indicating which populations may benefit from this intervention and the optimum method of setting up and controlling sleep disordered breathing. Recent superficially conflicting data has been published regarding HMV in COPD, with a trial in post-exacerbation patients suggesting no benefit, but in stable chronic hypercapnic patients suggesting a clear and sustained mortality benefit. The two studies are critiqued and the potential reasons for the differing results are discussed. Early and small trial data is frequently contradicted with larger randomised controlled trials and this has been the case with diaphragm pacing being shown to be potentially harmful in the latest data, confirming the importance of non-invasive ventilation (NIV) in NMD such as motor neurone disease. Advances in ventilator technology have so far appeared quicker than the clinical data to support their use; although small and often unblinded, the current data suggests equivalence to standard modes of NIV, but with potential comfort benefits that may enhance adherence. The indications for NIV have expanded since its inception, with an effort to treat sleep disordered breathing as a result of chronic heart failure (HF). The SERVE-HF trial has recently demonstrated no clear advantage to this technology and furthermore detected a potentially deleterious effect, with a worsening of all cause and cardiovascular mortality in the treated group compared to controls. The review serves to provide the reader with a critical review of recent advances in the field of sleep disordered breathing and HMV.

Keywords: Non-invasive ventilation (NIV); sleep disordered breathing; chronic respiratory failure

Introduction

Mechanical ventilation in the home is not a new idea. Over half a century ago, individuals with polio led the challenge of maintaining mechanical ventilation outside of institutions. Limited data are available on the number of patients with chronic respiratory failure treated outside of hospital. A European survey in 2005 reported that almost 22,000 patients with chronic respiratory failure were receiving home mechanical ventilation (HMV) with either non-invasive ventilation (NIV) or invasive ventilation (1). In this study, the estimated prevalence of HMV in Europe was 6.6 per 100,000 people. An accurate count of the number of patients receiving HMV in the US is unknown (2).

Differing drivers have fuelled demand for HMV: rising costs of hospital care, the advent of commercially available non-invasive masks and positive-pressure ventilators, the rise in obesity and the desire of individuals to maintain

a quality of life (QOL) at home (3). Questions remain regarding patient benefit in a number of groups and this review describes some of the recent completed and ongoing studies that have sought to shed light on this growing field.

Chronic obstructive pulmonary disease (COPD)

The empirical appeal of treating chronic respiratory failure in patients with COPD and physiological data from small single centre studies (4,5) has led to continued enthusiasm for HMV despite disappointing data from large clinical trials (6,7). The reasons for the failure to translate physiological data from small studies performed in highly specialist centres, to improved clinical outcomes in large multicenter trials, has largely been attribute to study design, rather than failure of the intervention. Further impetus for definitive clinical trials has been provided by increasing data suggesting that high intensity ventilation, targeting CO_2 clearance, has beneficial effects over the standard low pressure ventilation (8,9).

There have been two recent high impact, well designed studies, examining the role of HMV in COPD (10,11). These two studies have each examined a different patient population, one stable chronic hypercapnic COPD and the other post-acute exacerbation, and are as such complementary to each other.

COPD—stable hypercapnic

Köhnlein *et al.* (11) investigated the effect of long-term NIV, targeted to markedly reduce hypercapnia, on survival in patients with clinically stable (4-week run-in period) advanced COPD (Global Initiative for Chronic Obstructive Lung Disease, GOLD stage 4). The study was an open label, multicenter, randomized controlled trial (RCT), in patients with a $PaCO_2$ of ≥7 kPa and pH >7.35, originally powered for 300 patients. NIV was targeted to reduce baseline $PaCO_2$ by at least 20% or to achieve $PaCO_2$ values <6.5 kPa. Over a 7-year period [2004–2011] across 36 respiratory units in Germany and Austria, 195 patients were randomly assigned to NIV (n=102) or control (n=93). The primary outcome was 1-year all-cause mortality. Settings (data available in 83%) included mean inspiratory positive airway pressure (IPAP) 22±5 cmH$_2$O and expiratory positive airway pressure (EPAP) 5±2 cmH$_2$O with adherence (data available in 47%) 5.9±3.1 hours/day.

The trial was terminated early as the mortality reduction in the intervention arm was greater than expected and a change in national guidelines occurred, which recommended NIV in this patient group thus rendering further recruitment unfeasible. One-year mortality was 12% in the intervention *vs.* 33% in the control group; hazard ratio (HR) 0.24, 95% confidence interval (CI) 0.11–0.49; P=0.0004; number needed to treat to prevent one death: 5. QOL (assessed by the St George's Respiratory Questionnaire summary score) improved more in the intervention group (6.2 points, 95% CI 0.7–11.8, P=0.0289). Notwithstanding the problems of recruitment to such clinical trials, the protracted time to recruitment and lack of information on numbers screened raises the issue of selection bias (12). Although reported as having a low incidence of admissions over the year in both groups, the 2.2±10.2 admissions per patient in the NIV and 3.1±5.4 admissions per patient in the control group would classify them as frequent exacerbators (13). Interestingly, only three patients in the control arm received NIV during the year (indication was $PaCO_2$ >10 kPa, irrespective of pH). Furthermore, the cohort enrolled into the study had preserved exercise capacity despite their very severe COPD, with a 6-minute walk test (6MWT) of 227±121 m in the NIV group and 250±145 m in the control. This is in stark contrast to those patients enrolled into the RESCUE trial, in whom the incremental shuttle walk test results were not reported, as the patients were so frequently unable to perform it (10). The data from this study suggests that when NIV is applied to effectively reduce $PaCO_2$ in stable COPD patients with a preserved exercise capacity and moderate hypercapnia, a significant survival benefit can be obtained.

COPD—post-acute exacerbation

In acute hospital admissions of COPD complicated by hypercapnic respiratory failure, NIV reduces hospital deaths and complications associated with invasive ventilation and length of hospital stay (14). However, patients who have required an admission with decompensated respiratory failure have a poor prognosis over the following 12 months (15). The RESCUE trial (10), an RCT from the Netherlands, was designed to assess if the addition of HMV improved patient outcomes in this high risk group. The trial primary outcome was respiratory admission-free survival. In total 201 patients were enrolled following an acute exacerbation of COPD, complicated by respiratory acidosis requiring treatment with NIV, to receive domiciliary NIV or standard care. Patients were GOLD stage 3/4, with persistent hypercapnia 48 hours after cessation of acute NIV. Therapy

was established across four expert home ventilation centres, using high pressure ventilation: IPAP of 19.2 ± 3.4 cmH$_2$O and EPAP of 4.8 ± 1.0 cmH$_2$O, with a moderate back-up rate of 15 ± 3 breaths per minute.

The intervention reduced mean nocturnal partial pressure of transcutaneous CO$_2$ (tcCO$_2$) in the NIV arm compared to standard treatment [mean difference tcCO$_2$ -0.8 kPa (-0.4 to -1.3); P<0.001]. There was also a treatment effect on daytime pCO$_2$ favouring the NIV arm at 1-year [mean difference pCO$_2$ -0.5 kPa (-0.04 to -0.9); P<0.05]. However, there was also an improvement in daytime pCO$_2$ in the standard treatment arm, and the between-group effect was lost when the pCO$_2$ data were standardised to the condition state in which the measurement was taken, such as the addition of supplementary oxygen, at baseline and 1-year follow-up.

Patient characteristics, ventilator settings and adherence were similar to the study of Köhnlein *et al.* (11). However, no effect was noted on survival. Mortality at 1-year in both the control and intervention groups was similar to that in the control arm of the study of Köhnlein *et al.* (11). The reasons for this discordant result may be attributed to spontaneous resolution of respiratory failure that occurs with recovery from an acute exacerbation. As such, recruited patients may not have had significant chronic hypercapnic respiratory failure, that could be expected to be improved with NIV. Furthermore, the adverse influence on survival of the index exacerbation may have been dominant over any effect of NIV (16).

Two recent small single centre RCTs have provided further but conflicting data to the RESCUE study in the post-acute exacerbation setting. The two trials operated different designs with Cheung *et al.* (17) in Hong Kong, using a sham RCT. The study randomised 47 COPD patients (age 75.9 ± 5.8 years) to receive NIV (n=23) or continuous positive airway pressure (CPAP) (n=24), following acute admissions requiring NIV (having screened 235). Patients were enrolled 48 h after being weaned from NIV and although hypercapnia was not an entry requirement, had moderate hypercapnic respiratory failure (PaCO$_2$ 7.7 ± 1.0 kPa in the NIV and 7.3 ± 1.0 kPa in the CPAP groups). The primary end point was respiratory deterioration due to hypercapnic exacerbation, defined as the requirement for NIV in the sham CPAP arm, or escalation of NIV to greater than 12 h/day in the NIV arm. Relatively low ventilator pressures were used with a mean IPAP of 14.8 ± 1.1 cmH$_2$O, EPAP 5 cmH$_2$O but with high levels of adherence to NIV therapy (7–9 h/night). This trial showed a significant benefit of NIV with 38.5% of the

intervention group *vs.* 60.2% of the control group requiring admission and ventilatory support at 1 year [log-rank test, P=0.039; HR = 0.39 (0.16–0.98), P=0.047]. However, it must be noted that the trial did not achieve its planned sample size and did not find a difference in survival, all cause admissions, arterial blood gasses and adverse events, between groups.

Funk *et al.* (18) utilised a withdrawal open labelled RCT and randomized 26 patients to continuation (n=13) or withdrawal (n=13) of NIV 6 months after an acute hypercapnic exacerbation following which NIV was established. A large number of patients were screened in order to complete the trial (n=998). The primary outcome was respiratory deterioration requiring either re-initiation of NIV, extended NIV use, or invasive ventilation, depending on group allocation. Re-initiation of NIV could be due to deteriorating objective (respiratory failure) or subjective (patient or clinician determined clinical worsening). There was a significant benefit of NIV in terms of the primary outcome, although this was principally due to subjective rather than objective criteria for re-initiation of NIV and as such, subject to potential bias. Furthermore, there was no benefit in terms of all-cause re-admission or exacerbation frequency.

The reason for conflicting results from these two small studies compared to the much larger RESCUE study is largely attributable to study design, with the choice of primary outcome in the work by Funk *et al.* and Cheung *et al.* favouring a benefit from NIV. The more applicable primary outcome in the RESCUE study, that of respiratory admission free survival, and its large sample size, makes the data more generalizable. Currently, data therefore does not support the routine use of NIV in patients post-acute exacerbation of COPD. Further data is needed in light of the study by Köhnlein and co-workers to establish if those patients with moderate hypercapnia (PaCO$_2$ >7 kPa), following achieving a degree of clinical stability, will benefit. This group is being examined in a prospective randomised controlled study in the UK that has completed recruitment and is in the follow-up phase (HOT HMV UK; UKCRN 8059).

Synthesis of existing clinical trials suggests domiciliary NIV is unlikely to be beneficial if PaCO$_2$ is <7 kPa during the stable state and patients should therefore be reassessed following an acute exacerbation for the persistence of hypercapnia after a period of recovery. Effective NIV should be confirmed by overnight monitoring of tcCO$_2$ and ventilator settings adjusted, to achieve a greater than 20% reduction in PaCO$_2$ during spontaneous breathing during

the initiation phase. The four largest RCTs investigating the effects of HMV in hypercapnic COPD are summarised in *Table 1* (6,7,10,11).

Novel modes of ventilation

Novel NIV modes have been introduced previously, but have not frequently made the transition to be incorporated into clinical practice (19,20). More recently hybrid pressure support (PS) volume targeted modes have been introduced, with some evidence of enhanced overnight control of ventilation, but at the expense of detriment to sleep quality (21,22). Subsequent trials have failed to demonstrate clinically meaningful differences between these hybrid modes and standard fixed bi-level ventilation when titration methods have been standardized and have suggested no significant impact on objective sleep quality (23,24). Further developments in ventilator technology have incorporated control of back-up rate and automatic titration of EPAP to optimize upper airway patency and maintain minute ventilation.

Intelligent volume-assured pressure support (iVAPS) is a hybrid mode of NIV, providing continual automatic adjustment of PS to achieve a set target volume, with the addition of a monitored back-up rate design to maximise patient triggered breaths. In a randomised non-inferiority trial, Kelly and colleagues (25) investigated iVAPS as an alternative mode to standard PS, in 18 patients with chronic obstructive or restrictive lung disease being established on HMV. iVAPS achieved similar control of sleep disordered breathing, with no significant difference in objective sleep parameters. Interestingly, the iVAPS mode delivered a lower median PS [8 (inter-quartile range 6–10) *vs.* 10 (inter-quartile range 9–11) cmH_2O; P=0.001] with an associated increase in adherence [median 5:40 (4:42–6:49) *vs.* 4:20 (2:27–6:17) h:min/night; P=0.004]. In addition to enhanced adherence patients had a preference for treatment with the iVAPS mode, however this is confounded by the open label nature of the trial design. Further work with this mode has demonstrated equivalent control of overnight ventilation compared with high intensity NIV but again with improvements in subjective sleep quality (26).

In addition to the breath-by-breath adaptation of PS to achieve target volumes and manipulation of back-up rates to ensure minimum ventilation, a novel NIV mode has been introduced that assesses upper airway patency, in order to ensure overnight titration of EPAP termed average-volume assured pressure support-auto-titrating EPAP (AVAPS-AE).

This mode has been evaluated in 10 patients established on domiciliary NIV for COPD-obstructive sleep apnoea (OSA) overlap syndrome in a non-randomized, open label study (27). Similar to other work described above, the novel mode showed clinical equivalence compared to standard fixed level PS in terms of control of sleep disordered breathing and objective sleep quality. As with other novel modes AVAPS-AE was associated with lower mean delivered PS (AVAPS-AE 15±3 cmH_2O, fixed level PS 18±7 cmH_2O, P=0.155), which translated to improved subjective sleep quality [sleep comfort visual analogue scale mean change 12 mm (95% CI 3–21 mm); P=0.013] and enhanced ventilator adherence (AVAPS-AE 8:27±1:31 h:min *vs.* fixed level PS 6:21±2:02 h:min; P=0.035). *Table 2* summarizes four of these novel mode studies.

Pulmonary rehabilitation (PR) & home mechanical ventilation (HMV)

The significant benefits of PR in patients with COPD are well established (28,29), however the role of NIV and PR remains unclear (30). Márquez-Martín *et al.* (31) compared the combined use of exercise training and NIV, with the two interventions separately. Forty-five patients with severe COPD (GOLD 4) and hypercapnic respiratory failure (PaO_2 <60 mmHg, $PaCO_2$ >45 mmHg), clinically stable for three months, were recruited over a 4-year period and randomized into three groups for an intervention of 12 weeks. Forty-three completed the study and 27 were on long-term oxygen therapy (LTOT). Median IPAP was 16 cmH_2O and EPAP was 4 cmH_2O. Exercise capacity improved in the rehabilitation and the combined group, but not in the ventilation alone group. In the 6MWT, the group receiving both NIV and training had a median improvement of 83 m *vs.* 40 m in the group receiving ventilation alone and 42 m in the group that underwent training alone. Though the differences were not statistically significant difference, potentially due to sample size, they do concur with two previous studies suggesting an additive effect of NIV and PR (32,33).

Patient-ventilator asynchrony (PVA)

Despite clinical benefits, a significant proportion of patients are unable to adhere to their HMV prescription (34). PVA describes the poor interaction between patient and ventilator. Ramsay and colleagues (35) using parasternal electromyography during HMV set-up, found PVA is

Table 1 Recent RCTs of HMV in patients with COPD

Study	Population	Inclusion	Numbers		Age (years)		PaCO$_2$ (kPa)		NIV setting	Primary outcome	Mortality (1 year)	
			NIV	Control	NIV	Control	NIV	Control			NIV	Control
Struik (10) 2014	Netherlands, recruited from 47 hospitals to 3 HMV centres, RCT; recruited 2007–2012	GOLD ≥3, >48 h off ventilatory support (invasive or NIV) for ARF & prolonged daytime PaCO$_2$ >6.0 kPa off O$_2$	101	102	64±9	64±8	7.8±1.2	7.7±1.3	IPAP 19.2±3.4, EPAP 4.8±1.0, back-up 15±3 breaths/minute, 68% on O$_2$, 6.3±2.4 h/night	Time to event-readmission for respiratory cause or death: NIV 65% vs. control 64%	30%	29%
Köhnlein (11) 2014	Germany, Austria 36 centres, open-label RCT; recruited 2004–2011	GOLD 4, stable (no exacerbation 4/52 run-in), baseline PaCO$_2$ ≥7 kPa & pH >7.35	102	93	64±8	62±9	7.8±0.8	7.7±0.7	IPAP 21.6±4.7, EPAP 4.8±1.6. Backup 16.1±3.6 breaths/minute. To reduce baseline PaCO$_2$ by ≥20%, or achieve PaCO$_2$ <6.5 kPa. 5.9±3.1 h/day	1-year survival: 11.8% vs. 33% (log rank P=0.0004; HR 0.24, 95% CI 0.11–0.49)	12%	33%
McEvoy (6) 2009	Australia, four teaching centres, open label RCT; recruited 1998–2003	GOLD ≥3, NIV + LTOT vs. LTOT; age <80, stable, PaCO$_2$ >46 mmHg ≥2 previous 6 months; on LTOT 3/12	72	72	67 (95% CI 65–69)	69 (95% CI 67–71)	7.0 (95% CI 6.8–7.2)	7.3 (95% CI 7.0–7.5)	IPAP 12.9 (95% CI 12.5–13.4), EPAP 5.1 (95% CI 4.8–5.3); 4.5±3.2 h/night	Adjusted survival favoured NIV-intention to treat HR 0.63 (95% CI 0.40–0.99); P=0.045; per protocol analyses HR 0.57 (95% CI 0.33–0.96); P=0.036. Unadjusted survival HR 0.82 (95% CI 0.53–1.25)	17%	22%
Clini (7) 2002	Italian (20 centres) & French (1), open label RCT, 2-year follow-up; recruited 1996–2000	Severe COPD*, pCO$_2$ >6.6 kPa, stable (pH >7.35, no exacerbations within 4 weeks); NIV + LTOT vs. LTOT; 1 month run-in then randomisation; 32 excluded (6 bronchial reversibility; 26 improvement in pCO$_2$ >10% from baseline)	43	47	64±7	66±14	7.2±0.6	7.4±0.6	IPAP 14±3, EPAP 2±1; 9±2 h/day	Change daytime PaCO$_2$ on O$_2$: difference between groups widened from 0.13 kPa to 0.66 kPa; at 2 years mean PaCO$_2$ 7.23 & 7.89 kPa in NIV & control groups respectively; P=0.002, treatment effect 4.270 (95% CI 1.58–9.96)	18%**	17%**

Mean ± SD unless denoted. *, ATS Guidelines 1995; **, 2-year follow-up. RCT, randomised controlled trial; HMV, home mechanical ventilation; NIV, non-invasive ventilation; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease Classification; ARF, acute respiratory failure; IPAP, inspiratory positive airway pressure (cmH$_2$O); EPAP, expiratory positive airway pressure (cmH$_2$O); HR, hazard ratio; CI, confidence interval; LTOT, long-term oxygen therapy; SD, standard deviation; ATS, American Thoracic Society.

Table 2 Novel ventilator mode studies

Study	Intervention & duration	Design	Population	Primary outcome	Comments
Jaye, 2009, UK single-centre, randomized cross-over trial, NCT00252252 (24)	AutoVPAP vs. standard PS NIV. 2/12 duration	2-, 1-month intervention periods	Neuromuscular disease or chest wall disease & nocturnal hypoventilation, nocturnal $TcCO_2$ >6.5 kPa. All on NIV for >6/12 & all stable >3/12. 41 fulfilled inclusion criteria. 25 were recruited & n=20 completed study. Age: 42±17.6; $PaCO_2$: 5.8±1.0 kPa	Mean overnight oxygen saturation (SpO_2)—no significant difference	Mean & maximum overnight $TcCO_2$ higher on AutoVPAP vs. standard NIV 7.2 (6.7–7.7) vs. 6.7 (6.1–7.0) kPa (P<0.001) & 8.1±0.82 vs. 7.3±0.65 (P<0.001), respectively. Decrease stage 1 sleep 16%±9% vs. 19%±10% on AutoVPAP
Kelly, 2014, UK single-centre, randomized cross-over trial, NCT00901485 (25)	iVAPS or standard PS NIV. 2/12 duration	2-, 1-month intervention periods. PSG with $TcCO_2$ monitoring performed at baseline & 1 month	COPD or restrictive lung disease & newly diagnosed nocturnal hypoventilation (daytime $PaCO_2$ >6.0 kPa, or overnight sleep study mean $TcCO_2$ >6.0 kPa or peaks of $TcCO_2$ >6.5 kPa); n=69 assessed; 23 randomized to PS (n=12) or iVAPS (n=11). n=18 completed the intervention. Age 54 (41–61)*, BMI: 33 (24–41); $PaCO_2$ 6.4 (5.9–6.6) kPa	Mean overnight oxygen saturation (SpO_2)—no difference between groups	iVAPS delivered lower PS [8.3 (5.6–10.4) vs. 10.0 (9.0–11.4) cmH_2O; P=0.001] for same ventilatory outcome (overnight: SpO_2 96% (95–98%) vs. 96% (93–97%); P=0.13 & $TcCO_2$ 6.5 (5.8–6.8) vs. 6.2 (5.8–6.9); P=0.54]*. No difference for spirometry, respiratory muscle strength, sleep quality, arousals or O_2 desaturation index. Adherence greater with iVAPS [5:40 (4:42–6:49) vs. 4:20 (2:27–6:17)* h:min/night; P=0.004]
Ekkernkamp 2014, randomized, open-label, cross-over (26)	iVAPS & HI-NIV. 12/52 duration	Patients set-up and monitored during 2 days in-patient stay followed by 6/52 of intervention; assessed by blood gases and compliance and then commenced second modality	COPD already on HI-NIV for >2/12, pH >7.34 (n=14). n=1 dropped out (new cancer). Age: 64.3±7.5; BMI: 31.1±10.1; $PaCO_2$: 42.9±6.5. HI-NIV: IPAP 25.5±3.8, EPAP 5.8±2.1, RR 12±2.6 breaths/min. iVAPS: alveolar target volume (L/min) 11.5±3.1, minimum PS 14.7±4.1, maximum 24.7±4.1	Time spent in N3/4 sleep—no significant difference	Significant decrease $TcCO_2$ during iVAPS (P=0.003). No difference in PSG measures of sleep quality. Improved subjective sleep quality using visual analogue scale (P=0.04) with iVAPS. Blood gases and compliance did not differ
Murphy, 2015, two UK centres, sequential treatment, NCT01601977 (27)	Auto-titrating vs. standard PS NIV. 8/52 duration	Initiated standard NIV with 14-day home actigraphy prior to PSG. Commenced auto-titrating NIV with repeat PSG. Single night oximetry capnography day 28. End study assessments day 56 (repeat PSG). Auto-titrating target volume 10 mL/kg IBW to deliver PS 4–26 cmH_2O, EPAP 4–14 cmH_2O; back-up 10–20 breaths/min	COPD-OSA overlap hypercapnic respiratory failure, already established on standard NIV for >6/12 (n=10). Exclusions: ENT surgery <90 days or untreated non-respiratory sleep disorder. Age: 63±8; BMI: 33±8; $PaCO_2$ 7.0±2.0 kPa	Difference in mean $TcCO_2$—no significant difference	No change in objective sleep quality (PSG or actigraphy). Improvement in subjective sleep comfort-visual analogue scale (P=0.027). Adherence increased (P=0.010) with an increase by day 14 (126 min 95% CI 9–243 min; P=0.035). No change in daytime gas exchange

Mean ± SD unless denoted. *, median (interquartile range). AutoVPAP, autotitrating bi-level ventilator; PS, pressure support; NIV, non-invasive ventilation; $TcCO_2$, transcutaneous CO_2; iVAPS, Intelligent volume-assured pressure support; PSG, Polysomnography; COPD, chronic obstructive pulmonary disease; BMI, body mass index; HI-NIV, high intensity NIV; IPAP, inspiratory positive airway pressure (cmH_2O); EPAP, expiratory positive airway pressure (cmH_2O); RR, respiratory rate; IBW, ideal body weight; OSA, obstructive sleep apnoea; ENT, Ear nose and throat; SD, standard deviation.

frequent and, in contrast to other studies (36,37), not associated with an adverse impact on nocturnal gas exchange. The significance of this high observed level of PVA is unclear, with further data pending on the relationship between ventilator comfort and adherence (http://www.clinicaltrials.gov, NCT01371149).

Obesity hypoventilation syndrome (OHS)

OHS is defined as the presence of obesity [body mass index (BMI) >30 kg/m^2] and unexplained arterial hypercapnia, in the presence of sleep disordered breathing, usually OSA (38). There are a wide range of clinical phenotypes that meet the definition of OHS which can be categorized by the type of sleep disordered breathing present (39). Unfortunately, much of the data currently available groups all of these phenotypes together and therefore fail to assess whether response to treatment differs (summary of recent trials provided in *Table 3*). There are uncontrolled and small RCT data to support the use of CPAP (43), fixed level NIV (41,44) and volume assured NIV (23), in the treatment of OHS, with the only direct comparison on these therapies showing equivalence (40).

Masa *et al.* (42) performed a three-limb multi-centre RCT in which 221 patients with OHS and severe OSA were randomised to lifestyle modification alone, or PAP therapy (CPAP or NIV) combined with lifestyle modification, to assess clinical efficacy, as measured by improvement in daytime hypercapnia following 2 months of treatment. CPAP was titrated using overnight polysomnography and NIV initiated with volume targeting hybrid PS mode, with a moderate backup rate. EPAP was titrated using overnight polysomnography. All treatment arms showed improvement in hypercapnia, with the magnitude of improvement greatest for patients randomized to NIV. The magnitude of improvement in PaCO$_2$ in the NIV arm was significantly better than for lifestyle modification alone. However, NIV was not significantly superior to CPAP. The study was not powered to detect small differences in change in PaCO$_2$ and the patients were only modestly hypercapnic (PaCO$_2$ 50–51 mmHg) at baseline. Both PAP arms produced improvements in subjective sleep quality and health related QOL that was not found with lifestyle advice alone. NIV therapy was, in addition, associated with statistically significant improvements in lung function and exercise capacity not found with either CPAP or life style modification [ratio of forced expiratory volume in one second (FEV$_1$) improved 4.8%±13%; P<0.01 and 6MWT

increased by 32±58 m; P<0.001]. The study represents the largest RCT performed in OHS and as such greatly informs the management of patients. Whilst the data must only be applied to those patients with significant OSA, as patients with 'lone OHS' were excluded, this represents the phenoytype of the majority of patients encountered (45). Furthermore, the suggestion of superiority of NIV in terms of both weight loss and exercise capacity requires more detailed analysis. Previous data using volume targeted NIV in OHS indicated a reduction in weight following treatment associated with increased daytime physical activity (23) and is in contrast to the weight gain associated with CPAP therapy in eucapnic OSA (46). Whilst the data does not yet indicate a clear physiological or clinical superiority, multi-dimensional therapy, targeting weight loss, as well as the control of sleep disordered breathing, are essential (47). This study is the first phase of the Pickwick project, a larger study of 36 months duration that has hospitalization as the primary outcome with the original control group being re-randomized to NIV or CPAP at the end of the initial 3 months phase. The future outcomes of this trial will be greatly anticipated.

Amyotrophic lateral sclerosis (ALS) [motor neuron disease (MND)]

The landmark trial demonstrating benefit of NIV in ALS has established the therapy as gold standard in patients who develop respiratory insufficiency in the absence of significant bulbar involvement (48). Due to the poor tolerance of NIV in some patients, leading to treatment failure, there has been interest in alternative methods of managing respiratory failure in ALS. Diaphragm pacing has shown potential benefit in pilot work, necessitating further investigation (49).

The Diaphragm pacing in ALS (DiPALS) study assessed the potential benefit of diaphragm pacing in patients with ALS. Patients were randomized to standard care (NIV alone) or the addition of diaphragm pacing at the point of clinically significant respiratory insufficiency (50). The trial was powered to recruit 108 patients (randomized 1:1) assuming a 25% absolute survival benefit at 12 months in favour of diaphragm pacing. The trial was terminated early at the recommendation of the independent Data Monitoring and Ethics Committee (DMEC) with 37 patients randomised in each group. At study completion in December 2014 median survival in the pacing group was 11.0 *vs.* 22.5 months in the NIV only arm; adjusted HR 2.27 (1.22–4.25); P=0.009.

Table 3 Summary of recent trials in obesity hypoventilation syndrome

Study	Intervention & duration	Population	Primary outcome	Comments
Piper, 2008, Australia single-centre RCT, ACTRN12050000096651 (40)	CPAP vs. NIV. Duration: 3/12	Inclusion: BMI >30 kg/m², awake PaCO₂ >45 mmHg; absent significant respiratory, neuromuscular or other disorder; FEV₁/FVC ≥70%; no major psychiatric illness; not already on positive pressure therapy. Exclusions: persisting nocturnal hypoxaemia (SpO₂ <80% for >10 min), acute rise in TcCO₂ during REM sleep ≥10 mmHg or increase in afternoon to morning PaCO₂ ≥10 mmHg in those patients with awake PaCO₂ >55 mmHg despite optimal CPAP. 85 screened. 40 excluded (most commonly ARF) or declined. 9/45 available met a priori criteria for initial CPAP failure & commenced NIV on clinical grounds. Remaining 36 randomized to CPAP (n=18) or NIV (n=18). IPAP 16±2 & EPAP 10±2. Age: NIV 47±13, CPAP 52±17; BMI: NIV 54±9, CPAP 52±7; PaCO₂: NIV 49 (47–57), CPAP 52 (49–55)*	Change daytime pCO₂—no significant difference between groups	PaCO₂ improved in both (CPAP Δ 6±8 mmHg; NIV Δ7±7 mmHg); no between-group difference (P=0.7). No difference in compliance (5.8±2.4 h/night CPAP vs. 6.1±2.1 NIV). Subjective improvement in daytime sleepiness in both. Subjective sleep quality & psychomotor vigilance performance better with NIV.
Murphy, 2012, two UK centres single (subject) blind RCT, ISRCTN63940700 (23)	AVAPS vs. standard PS. Duration: 3/12	Inclusion: BMI >40 kg/m²; daytime PaCO₂ >6 kPa & pH >7.34; absence of another identifiable cause of hypoventilation; FEV₁/FVC >0.70; FVC <70%. 62 screened, 50 recruited; n=2 drop-outs from each group; n=23 in both completed. Standard PS: IPAP 25±6.3 cmH₂O. AVAPS Vte 657±96 mL. Small difference in EPAP— 10±2 cmH₂O & 9±1 cmH₂O in fixed-level PS & AVAPS groups, respectively (P=0.03). Backup rate 14±1 breaths/minute both. Overall Age: 55±11; BMI: 50 (±7) kg/m²; PaCO₂: AVAPS 7.0±0.7, PS 6.8±0.8 kPa	Change daytime pCO₂—no significant difference between groups	PaCO₂ improvement in both (AVAPS Δ0.6 kPa, 95% CI 0.2–1.1, P<0.01 vs. PS Δ0.6 kPa, 95% CI 0.1–1.1, P=0.02); no between-group difference (Δ0.1 kPa, 95% CI 0.7–0.6, P=0.87). No significant differences in daytime gas exchange, anthropometric measures, spirometry, HRQL or daytime somnolence. Both groups demonstrated significant improvement in BMI
Borel, 2012, US, RCT, NCT00603096 (41)	NIV vs. control. Duration: 1/12	BMI >30, PaCO₂ >45 mmHg, no COPD or neuromuscular disease. 143 screened; excluded 101 (PaCO₂ <45 mmHg); n=37 randomized NIV (n=19) or lifestyle (n=18); 1 withdrawal in each. Age: NIV 58±11 vs. 54±6 (P<0.05); BMI: NIV 39.6±6.3 vs. 39.6±4.5; PaCO₂: NIV 48±4.5 vs. 45±3 mmHg (P<0.05). Mean IPAP 18±3 & EPAP 11±2 cmH₂O; mean back-up rate breathing frequency 13±2 cycles/min	Change daytime pCO₂—significantly increased reduction in NIV group	ΔPaCO₂ =−3.5 mmHg 95% CI, −6.2 to −0.8. Mean nocturnal SpO₂ increased (Δ =5.1%, 95% CI 2.9–7.2); increase in REM sleep proportion (Δ =10%, 95% CI 3.4–17.1)
Masa, 2015, Spanish, Multi-centre RCT, NCT01405976 (42)	NIV, CPAP or control. Duration: 2/12	BMI >30, PaCO₂ >45 mmHg, pH >7.35 & no clinical worsening during 2/12; excluded: COPD, neuromuscular, chest wall, metabolic disease, severe OSA (AHI >30), narcolepsy or restless leg syndrome. Control received lifestyle modification (as did other groups). 351 selected; 49 excluded (n=9 incapacity to complete questionnaires, n=11 severe chronic illness, n=1 severe nasal obstruction, n=28 no consent; n=81 non-severe OSA. Remaining 221 randomized to NIV (n=71) CPAP (n=80) or control (n=70). Completed: NIV (n=64), CPAP (n=69), control (n=67). NIV: EPAP 4–8 cmH₂O, & IPAP 18–22 cmH₂O, respiratory rate 12–15 breaths/min. Age: NIV 64±11, CPAP 57±13, control 60±13; BMI: NIV 43±6.7, CPAP 45±7.6, control 44±7; PaCO₂: NIV 51±4.3, CPAP 50±4.5, control 51±4.2 mmHg	Change daytime pCO₂—all groups significantly improved; between group differences only significant between NIV & control	NIV −5.5 (±7), CPAP −3.7 (±6.6), control −3.2 (±6) mmHg. Spirometry & 6-MWD test results improved significantly only in NIV group in intragroup comparisons. Nocturnal oxygenation & sleep quality improved significantly with CPAP & NIV vs. control group; no significant differences between CPAP & NIV groups

Mean ± SD unless denoted. *, median (interquartile range). RCT, randomized controlled trial; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; BMI, body mass index; FEV₁, ratio of forced expiratory volume in one second; FVC, forced vital capacity; TcCO₂, transcutaneous CO₂; ARF, acute respiratory failure; IPAP, inspiratory positive airway pressure (cmH₂O); EPAP, expiratory positive airway pressure (cmH₂O); Δ, change; AVAPS, average-volume-assured pressure support; PS, pressure support; Vte, tidal volume; HRQL, health related quality of life; COPD, chronic obstructive pulmonary disease; AHI, Apnoea-hypopnoea index; OSA, obstructive sleep apnoea; 6-MWD, 6-minute walk distance; SD, standard deviation.

Twenty-eight (76%) patients died in the pacing group and 19 (51%) patients died in the NIV alone group, with 162 adverse events (5.9 events per person-year) in the pacing group, of which 46 events were serious, compared with 81 events (2.5 events per person-year) in the NIV alone group, of which 31 events were serious. The pacing group were older (60±10 *vs.* 54±12) but otherwise baseline differences were similar and minimization was employed to balance for differences in age, sex, forced vital capacity (FVC), and bulbar function. It is not yet clear whether the excess deaths related to the effects of the surgery or the pacing itself, however, the trial illustrated the necessity for good quality evidence prior to the introduction of novel medical devices.

Two further studies, one in the US and one from France investigating application of diaphragm pacing are still pending (ClinicalTrials.gov, numbers NCT01938495 and NCT01583088), though the later study has suspended recruitment and in light of the DiPALS results careful consideration will be needed prior to any future work in this area.

Heart failure (HF)

SERVE-HF an international, multicentre RCT (51) investigated the impact on mortality and morbidity of treating predominantly central sleep apnoea (CSA) in a symptomatic HF population [New York Heart Association classification (NYHA) ≥II] with impaired left ventricular ejection fraction (LVEF ≤45%) with adaptive servo-ventilation (ASV, n=666) or control (n=659). The incidence of the primary end point (time to all-cause mortality or unplanned hospitalization for worsening HF) did not differ significantly between the ASV group and the control group [54.1% and 50.8%, respectively; HR 1.13 (0.97–1.31); P=0.10]. However, all-cause mortality and cardiovascular mortality were significantly higher in the ASV group [HR for death from any cause 1.28 (1.06–1.55); P=0.01; and HR for cardiovascular death 1.34 (1.09–1.65); P=0.006]. The company (Resmed) currently advises that ASV is contraindicated in patients with symptomatic, chronic HF (NYHA ≥II, with LVEF ≤45%) and moderate to severe predominant CSA.

The cause(s) of the increase in cardiovascular mortality in the ASV group is of great interest. It has previously been argued that CSA with Cheyne-Stokes pattern of respiration (CSA-CSR) is a compensatory response to severe HF, and in itself may not be injurious (52). Indeed, potential beneficial

effects of CSA-CSR include augmentation of stroke volume, increased lung volume with intrinsic positive end-expiratory pressure (PEEP) and cyclic respiratory muscle rest (52). Abolishment of this adaptation could thus be deleterious. A second explanation is that reduction in stroke volume, that occurs in HF patients with low pulmonary-capillary wedge pressures from application of NIV or CPAP (53-55), has significant consequences in this high risk group. In contrast, deployment of CPAP in patients with acute HF +/– high wedge pressures does not appear to impair cardiac performance (54-56).

ADaptive-servo VENTilation for treatment of OSA and CSA in Heart Failure (ADVENT-HF) (NCT01128816), a multi-centre, multi-national RCT aiming to randomize 860 patients with CSA and symptomatic systolic HF (American Heart Association B–D, LVEF <45%) had recruited 301 patients by March 2015. A DMEC review instigated following the publication of the SERVE-HF data did not recommend trial cessation and recruitment is ongoing.

In Japan a multicentre, open-label blinded-endpoint RCT—Study of the Effects of Adaptive Servo-ventilation Therapy on Cardiac Function and Remodelling in Patients with Chronic HF (SAVIOR-C)—recruited 213 outpatients with mild to severe HF (LVEF <40% and NYHA ≥II) assigned to ASV and medical therapy or medical therapy alone for 24 weeks (57). The primary outcome of LVEF did not differ between the two groups (both groups improved significantly), though NYHA class and Activities of daily living (ADL) improved significantly in the ASV group compared to the control arm.

Interstitial lung disease (ILD)

There have been few studies of ILD and HMV. PR in ILD is safe and improves functional exercise capacity, dyspnoea and QOL (58). Dreher and colleagues investigated the effects of PR in hypercapnic ILD patients (59). Those with hypercapnia received NIV (n=29); the remaining ILD patients served as a comparison group (n=319). PR improved the 6MWT distance achieved by 64.4±67.1 m *vs.* baseline (P<0.0001) in NIV patients and by 43.2±55.1 m (P<0.0001) in the control group [difference 21.1 (0.5–41.8) m; P=0.045]. PR improved the SF-36 mental component score *vs.* baseline in both groups. The results must be viewed in the context of the study design that compared hypercapnic ILD patients treated with NIV prior to PR, to eucapnic patients receiving PR alone. However, hypercapnia is acknowledged to be a

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poor prognostic feature in ILD and thus the significant physiological and clinical improvements would lead to a recommendation for initiating NIV in this group prior to attempting PR in order to maximize benefits.

The elderly

Three retrospective studies of patients commenced on HMV aged ≥75 have previously reported encouraging results; subsequent admissions to hospital were reduced in two studies (60,61) and the other study found no statistically significant differences between those aged ≥75 and the younger age groups in blood gas parameters, adherence and adverse events (62). In support of these findings Comer *et al.* (63) reported their experience of 256 patients set-up with HMV, including 103 aged ≥75. They found HMV in the elderly group was well tolerated and indeed found gas exchange to be improved compared to the younger groups.

Health care costs

The cost of maintaining ventilator dependent patients in an institutional setting is substantial, with cost benefits as well as patient preference for the home care setting (64). Care must be taken when evaluating HMV patients during acute admission as early tracheostomy and transfer to long term acute care facilities is incentivised in certain health care systems but will lead to high numbers of tracheostomy ventilated patients with the associated high long term morbidity and cost to the health care system (65). Thought should be given to the aggressive management of such patients with 24 h NIV and mechanical insufflation-exsufflation, which has excellent outcomes in maintaining neuromuscular patients during acute exacerbations, without the need for tracheostomy (66).

In addition to long term costs of care, a focus has been made on cost saving by utilizing out-patient setup of NIV in stable patients. This has been driven not just by cost pressures, but also the benefit of maintaining dependent patients within their established care environments. A recent RCT from Hazenberg *et al.* (67) investigated initial set-up of HMV at home (n=38) or in hospital (n=39), in patients diagnosed with chronic respiratory failure due to a neuromuscular or thoracic cage disease. Primary outcome was $PaCO_2$, while QOL and costs were secondary outcomes. At 6 months there was no significant difference between the two groups in improvements in $PaCO_2$ or QOL. However, cost savings in the home group were €3000 per patient,

suggesting equivalent physiological and clinical efficacy, but with enhanced cost-effectiveness. It must be remembered when extrapolating these data that the study was conducted in established ventilation centres, with significant experience in HMV in neuromuscular disease (NMD). Further data is pending on whether such benefits are experienced in other less dependent patients with chronic respiratory failure who are able to be setup in a daycase outpatient setting with the assistance of novel automated ventilator technology (http://www.isrctn.com, 51420481) (68).

Conclusions and future directions

Although many benefits of HMV have been established by either randomized controlled data or consensus opinion for certain disorders, such as NMD and obesity, it remains unclear what the optimum ventilator setup strategy should be, whether polysomnography is required, or if outpatient setup is clinically safe and efficacious. Furthermore, it is unclear what if any importance should be given to patient ventilator asynchrony and novel modes of ventilation, or what measures are most appropriate to assess efficacy of HMV. In other diagnostic groups, such as COPD the data is more equivocal and large-scale studies are still need to delineate the phenotypes of patients who may benefit from HMV.

Acknowledgements

None.

Footnote

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