Homeward bound: a centenary of home mechanical ventilation

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Abstract

The evolution of home mechanical ventilation is an intertwined chronicle of negative and positive pressure modes, and their role in managing ventilatory failure in neuromuscular diseases, and other chronic disorders. The uptake of non-invasive positive pressure ventilation has produced widespread growth in home ventilation internationally, and fewer patients ventilated invasively. As with many applications of domiciliary medical technology, home ventilatory support has either led or run in parallel with acute hospital applications, and has been influenced by medical and societal shifts in the approach to chronic care, the creation of community support teams, a preference of recipients to be treated at home, and economic imperatives. This review summarises the trends and growing evidence base for ventilatory support outside hospital.

Introduction

The idea of assisting ventilation has evolved through four broad eras from the middle ages and renaissance to the present time : a) an understanding of cardiopulmonary anatomy and observation that positive pressure ventilation applied to the trachea could inflate the lungs[1;2], b) the development of manually applied bellows, later automated, applied via a mask to resuscitate those with acute respiratory failure due to fires, mining and drowning accidents, c) an exploration of negative pressure ventilatory support reaching its zenith in mass use of iron lungs in the poliomeyelitis epidemics of the 1950s, and d) a shift back to positive pressure ventilation delivered non-invasively, coupled with a greater understanding of sleep disordered breathing and respiratory muscle physiology, enhanced by technological advances in portable ventilator design and interface technology in the 1970s and 1980s.

Evolution

A century ago there was no acute ventilatory support available for the hundreds of thousands of victims of the 1918 Spanish Flu outbreak, and indeed it is arguable whether ventilatory support would have been lifesaving in the presence of overwhelming infection and intractable hypoxemia due to acute lung injury. In 1907 Heinrich Drager[3] had patented a portable time-cycled device powered by compressed oxygen which delivered positive pressure during inspiration and negative pressure during expiration via mask. These were manufactured in bulk and used to resuscitate victims of gas poisoning accidents or fires in the mining industry. This development had been preceded in the late 1800s by a creative burst of invention of negative pressure devices across Europe and the new world, typically consisting of a cabinet design encircling the individual's chest or lower body and powered by variety of mechanisms, sometimes manually by the patient![4] Negative pressure devices advanced significantly with the iron lung and motorised pump designed by Drinker and colleagues, who reported prolonged support of ventilation in The Lancet in 1931[5]. Iron lungs (or tank ventilators) reached their apogee with the devices developed by the manufacturer JH Emerson (Cambridge MA, USA), based on the design of Drinker and predecessors. Deployment of these tank ventilators in the polio epidemics of the 1950s in the USA and Europe, undoubtedly saved lives, despite their bulk and expense (Figure 1). The limitations of negative pressure ventilation were exposed by the huge polio outbreak in Denmark in 1952. Not only were there insufficient iron lungs but these failed to adequately ventilate those with bulbar polio, and the death rate rose to 80%, only to fall markedly with the introduction of tracheotomy and invasive ventilation[6]. It is notable that while tracheotomy ventilation proved the stimulus for the advance of invasive positive pressure ventilation and modern Intensive Care Units, some polio survivors were discharged home using more portable negative pressure devices such as the cuirass and negative pressure jackets - these constituted some of the earliest domiciliary non-invasive ventilator users[7].

Negative to positive pressure

Negative pressure devices including iron lungs saw a reawakening of interest in the 1970s and 1980s to treat a range of patient with chronic respiratory failure including those with chest wall disease and COPD, an application stimulated by an increased knowledge of respiratory muscle pathology[8;9] and ventilatory changes during sleep. Sullivan and colleagues reported home continuous positive airway pressure therapy (CPAP) use for obstructive sleep apnoea in 1981[10]. While early cohort studies in patients with chronic respiratory failure due to neuromuscular and chest wall disease used volume ventilators to augment minute ventilation as opposed to delivering fixed positive pressure, cross pollination from the development of continuous CPAP blowers and masks to treat obstructive sleep apnoea led to the increasing use of smaller bilevel pressure support devices. This meant that by the early 1990s non-invasive ventilatory support, whether in hospital or home was delivered largely via positive pressure devices. Reports and case series[11-13] patients on positive pressure non-invasive home ventilation began multiplying by the late 1980s and 1990s in neuromuscular, chest wall and obstructive lung disease patients, demonstrating improvements in life expectancy and quality of life in those with chest wall disease and non-progressive eg. (post poliomyelitis) or slowly progressive neuromuscular disorders. An illustrative timeline is given in Figure 2.

Prevalence

A first international perspective on the extent of home ventilation was seen in the Eurovent study published in 2005[14]. The majority of patients receiving home mechanical ventilation in northern European centers and university practices had neuromuscular disease while in southern Europe a growing proportion of patients with lung and airways disease was reported. Prevalence rates ranged from 0.1 to 10 per 100,000 in Poland and Sweden respectively with only 13% receiving ventilation via tracheotomy. In Massachusetts a census of prolonged mechanical ventilation reported by King[15] showed prevalence increasing from 2.8 per 100,000 to 7.1 per 100 thousand from 1983 to 2006. But here practice differed from that in Europe with significant numbers of long term ventilated patients managed in hospitals or long term acute care facilities. Almost 10 years later in the USA Sunwoo et

al[16] detailed the changing landscape of adult home ventilation with non-invasive ventilation progressively replacing tracheotomy ventilation and widening indications despite the fact that guidelines were lacking apart from in some neuromuscular conditions such as amyotrophic lateral sclerosis (ALS)[17] and Duchenne muscular dystrophy[18].

Inherited muscular dystrophies, myopathies and spinal muscular atrophy

Duchenne muscular dystrophy (DMD) patients represent one of the first groups to receive home positive pressure ventilation, after use in polio patients, and one of its greatest success stories. Early application by Rideau[19] in France in the 1970s taken up by Bach, Hill, Sortor and others in the USA[20-22] and Robert[23], Leger[24], Brathwaite[25] and colleagues in Europe showed that mask NIV was feasible in a range of chronic neuromuscular and chest wall disorders, and could also be used to wean invasively ventilated patients onto NIV to enable discharge from ICU[26]. Early case series showed marked improvement in survival (although no advantage to treatment prior to the development of symptoms[27]), with more recent results showing DMD patients living into middle age. For NIV combined with cough assist devices there is also evidence of significant reduction in pulmonary morbidity and hospital admissions[28]. Few randomised trials have been carried out in these patient groups, but where these exist evidence strongly supports use of ventilatory support[29]. A notable feature of the dissemination of mechanical ventilation into the home has been the stark differences in practice with tracheotomy ventilation being rare in the UK and USA and more common in Scandinavia, France, Japan and the Gulf States, for example. Increasing numbers of children with neuromuscular and other disorders requiring NIV in childhood are now successfully treated and transitioning to adult care[30;31].

Similar improvements in outcome have been seen in other relatively slowly progressive disorders such as congenital muscular dystrophies, spinal muscular atrophy type II and myopathies[31]. Mouthpiece ventilation is an option during the day for some neuromuscular patients[32]. In type I SMA with onset after 3 months NIV may prolong survival or can be used to palliate symptoms[33;34].

Amyotrophic lateral sclerosis (ALS):

Ventilatory support in ALS is one of the few neuromuscular conditions subject to a randomised controlled evaluation. In a Cochrane review of mechanical ventilation for ALS in 2013[35] the authors identified only two randomised trials of non-invasive ventilation, including 54 patients in total and complete data in only one trial[36]. This showed an increase in average survival from 171 to 219 days, and in those with mild to moderate bulbar weakness the survival increase was 205 days, and quality of life was maintained. In those patients with severe bulbar weakness, survival was not increased but symptoms improved.

Cazzolli and Oppenheimer[37] report that in patients electively started on NIV 100% users felt glad they chose NIV, but in 50 tracheotomy ventilated patients, many had undergone tracheotomy as a result of emergency care and fewer were satisfied with their quality of life. Failure to be involved in decision-making about institution of tracheotomy ventilation has been found to have an adverse impact on quality of life in other studies. There are still considerable national differences in care provided for ALS patients. The American Academy of Neurology Practice Parameters[17] on drug, nutritional and respiratory therapies in ALS recommend NIV to lengthen survival and slow decline of FVC (level of evidence B) and to improved quality of life (level of evidence C). National Institute for Clinical Evidence (NICE) guidelines[38;39] in the UK recommend referral for assessment for NIV if daytime arterial oxygen saturation is 93% or less, forced vital capacity less than 70% predicted, maximum inspiratory pressure is less negative than -60cmH20, or if marked symptoms of sleep disordered breathing or orthopnea are present. The initiation of NIV is recommended in the presence of daytime hypercapnia, symptomatic sleep disordered breathing and deteriorating pulmonary function. Serial measurement of respiratory muscle strength is an accurate predictor of survival[40]. It is not clear whether earlier initiation of NIV offers any survival advantage.

The addition of cough assistance techniques is particularly advantageous in ALS and may prolong duration of effective non-invasive approaches when combined with percutaneous feeding. Effective respiratory therapy to clear secretions and breath stacking with a lung volume recruitment bag should first be explored but in those with cough peak flow less than 270l/min clearance of secretion is likely to be impaired during a chest infection and cough peak flow loss than 160l/min suggest severe reduction in cough adequacy. Here use of cough insufflation-exsufflation devices can significantly improve cough peak flow. Current scientific evidence does not support the widespread use of mechanical insufflation-exsufflation in neuromuscular disorders due to a lack of randomised, controlled trials[41], but these devices are employed clinically on a pragmatic basis and recommended as good practice by guidelines[38;42]. As with initiating NIV, setting up insufflation-exsufflation pressure may be more challenging in bulbar ALS patients. Andersen et al[43] recently compared upper airway responses in ALS patients with no bulbar disease, to those with spastic pseudobulbar and hypotonic bulbar features. The response of the larynx, aryepiglottic folds and hypopharynx may vary considerably in these groups, suggesting careful titration of settings starting with low IPAP values in bulbar group. In this study optimisation of settings was achieved using direct transnasal laryngoscopy but knowledge of these variables may be helpful in the absence of such interventions, especially as Farrero et al[44] have shown that with careful titration, NIV use in bulbar ALS patients may be successful in over 50% of cases. In those in whom NIV cannot be initiated palliative care approaches are key.

NIV in COPD

In chronic obstructive pulmonary disease (COPD) respiratory failure was recognised almost as soon as it became possible to measure carbon dioxide[45;46], a facility which came after the recognition of the principle of both positive and negative pressure ventilation[47]. One of the first recorded use of mechanical ventilation in COPD was the acute application of a negative pressure device reported in

1951[48] and it is unsurprising therefore that the first use of chronic home ventilation in COPD also used a negative pressure approach[49].

Following pioneering work by Braun[50], Rochester[9], Lisboa[51] Cropp and Dimarco[52], Zibrak[53]and others on assessing the impact of negative pressure ventilation on respiratory muscle function, Shapiro and co-workers[49] randomised 184 COPD patients to receive active or sham negative pressure ventilation. The study concept would now be considered outdated since the stated aim was to rest the respiratory muscles in order to relieve fatigue which was thought to be present and thus improve their function. In fact subsequent studies showed that low frequency fatigue of the respiratory muscles is in fact more difficult to elicit in COPD patients than normal subjects[54-56], as might be expected given both the presence of diaphragm shortening[57] and the switch to fatigue resistant type I fibres which was also subsequently demonstrated[58;59]. Given this subsequent knowledge it is perhaps unsurprising that no differences were found between treatment and sham groups, especially given other issues which were high levels of inadequate or non-adherence coupled with the fact that the mean PaCO2 at entry was only 44 mmHg (6.4 kPa).

Large trials powered for mortality or combined morbidity and mortality outcomes in which positive pressure have been employed are summarised in table 1. The most notable trends in the evolution of NIV seem to have been the following; first more recent studies have used higher levels of inspiratory pressure support which intuitively might permit more efficient CO2 clearance and better oxygenation; thus, simply put, earlier studies may have failed by delivering suboptimal ventilation. This trend may continue in the future with the use of ventilators with more sophisticated modes designed to deliver a preset volume within physician prescribed pressure limits; such devices have been evaluated in acute COPD[60], obesity[61] and mixed patient populations[62] with inconsistent results thus far. A second reason why positive studies have more recently emerged likely reflects the use of

strategies designed specifically to target hypercapnia rather than more general ambition such as respiratory muscle rest or relief of dyspnoea; this philosophy blends with the previous point and reflects diminishing concern regarding potentially harmful effects of high airway pressure which, while demonstrated after invasive mechanical ventilation have never been shown to be an issue in NIV. Lastly investigators have become more sophisticated in recognising that the point of greatest need and therefore likely most easily demonstrable benefit is after acute exacerbation of COPD. As well as accounting for over 50% of the lifetime costs of acute care, in-patient admission is both distressing and dangerous for patients with a typical 7% inpatient mortality and 30% 3 month readmission rate.

A range of factors may explain the divergence in results from Konlein et al[63] showing improved survival in hypercapnic COPD patients treated with home NIV, and those by Struik at al[64] in which no difference was found in outcome in patients randomised to home NIV after an exacerbation. Differences in COPD phenotype and selection - the Kohlein et al patients had chronic stable hypercapnia and there was high mortality in control group, while the post exacerbation patients in Struik et al study may still have had potential for recovery, therefore making initiation of NIV on discharge after a hypercapnic exacerbation seem premature. The Murphy et al [65]study includes patients who remained hypercapnic two weeks after an exacerbation rather than on discharge. Hence it seems that patients most likely to benefit from NIV are those who require NIV for an in-patient hypercapnic COPD exacerbation and who remain hypercapnic while convalescent[65]. Going forward it is well established that physical frailty is a good marker of the likelihood of readmission[66;67], and it may be that patient selection for future trial could also profit by including a measure of physical function and/or combining NIV with a rehabilitation program[68].

NIV in Bronchiectasis

Adoption of ventilatory support was extended to patients with bronchiectasis from experience in patients with other causes of respiratory failure, notably COPD. There are many pathophysiological similarities between COPD and bronchiectasis and NIV offers the potential benefit of augmenting airway clearance. However, early observational studies in mixed cohorts of patients with chronic respiratory failure identified patients with bronchiectasis doing less well compared to other groups discussed below.

In 1994, Leger et al[11] described 25 patients with bronchiectasis where the three year drop out was 48%, they identified no change in hospital stay in the year following NIV introduction. In 1995, of a further cohort of 13 patients with bronchiectasis[69] only 20% continued NIV at two years – markedly reduced compared to patients with neuromuscular disorders (Figure 3). In 1997, Benhamou et al[70] reported a case-control study of 14 patients with bronchiectasis using NIV and LTOT or controls using LTOT only, described benefits of reduction in days in hospital with NIV but no change in PaO2 or mortality. Interestingly, in this study, volume ventilation was used and generally well tolerated. In 2004, Dupont et al[71], described 48 patients with bronchiectasis following their first ICU admission with respiratory failure. 54% required intubation, 27% used NIV. The one year mortality in this group of patients was 40%. Poor prognostic factors included age and intubation. NIV did not worsen survival but only 10 patients continued NIV in the longer term. More recently, a 2009 series of 35 patients from Saudi Arabia with more severe bronchiectasis presenting to the ICU with respiratory failure were reported[72]. 31% required intubation and 57% were managed with NIV. The ICU mortality was 34% and 4 year mortality 60%. This study highlighted premorbid activity in addition to age, premorbid condition and ICU interventions including intubation as major determinants of mortality[72].

Unlike data in stable hypercapnic COPD, the literature of NIV in bronchiectasis consists only of small, observational studies with no randomised controlled trials. Moving forward, there are opportunities

for RCTs early in the course of disease perhaps targeting development of overnight hypercapnia to define when respiratory support may be most useful.

NIV in Cystic fibrosis (CF)

Historically, ICU admission has been avoided in patients with CF and respiratory failure because of poor outcomes[73]; the development of effective lung transplantation has challenged this view. There are now data that demonstrating where sudden decline with a potentially reversible cause such as a pneumothorax or major haemoptysis, survival following ICU admission can be excellent[74-76]. Invasive ventilation for worsening respiratory failure caused by respiratory infection where there is no possibility of transplantation continues to have a poor prognosis with survival of just 10-30%[73].

In CF, unlike bronchiectasis, there have been a number of small, studies demonstrating NIV improves airway clearance; a facet of ventilatory support which can be very useful. In 2013, a meta-analysis[77] identified 15 studies but only seven of which met inclusion criteria, a total of 106 patients. Of these 7 trials, 6 were single intervention studies and 1 examined nocturnal NIV over a 6 week period (8 patients). All were cross over studies. There were four trials (79 patients) using NIV against another specified method of chest physiotherapy. The authors concluded sessions of airway clearance using NIV may be easier, were preferred by the patient and may improve some parameters of lung function. There was no change in sputum expectoration. The authors also reviewed three trials (27 patients) which examined overnight NIV and found, when used with oxygen, NIV may improve overnight gas-exchange and exercise tolerance[78]. Longer RCTs looking at effects of NIV on airway clearance and exercise are required.

NIV has advantages over invasive ventilation as it allows cough and clearance of secretions and can avoid ICU admission. A retrospective analysis[79] of 113 patients with end-stage CF, using volume preset ventilation, has been reported. The authors divided patients in into three groups: A Awaiting

lung transplantation, B Patients not yet on the transplant list and C patients who were not for transplantation. The mean duration of NIV support for groups A, B and C was 61 (1–600) days, 53 (1–279) days and 45 (0–379) days, respectively. In this study of end-stage patients, they reported NIV with additional entrained oxygen improved hypoxia but not hypercapnia and survival of transplanted patients in group A was comparable to milder patients not on NIV[79]. The widespread use of NIV in end-stage CF both as a bridge to transplantation and in palliation, where NIV can be delivered at home, allows a degree of autonomy for patients to make informed choices about where and how supportive care is delivered.

NIV in obesity hypoventilation

The association between sleepiness and obesity has been recognised in the literature since at least the early 19th century. Famously, the English satirist and polymath Charles Dickens created the character Joe who appears in the Pickwick Papers. "A wonderful fat boy - habited as a serving boy standing upright on the mat, eyes closed as if asleep". (Charles Dickens 1837). This excellent and very funny book was widely read at the time. Osler was clearly a fan and referenced Dickens' astute observations in his 1903 medical textbook[80]. Medical journals however lagged someway behind. The syndrome of alveolar hypoventilation was described in the 1950's by Auchincloss et al[81] and Burwell et al[82]. Since the first accounts of the effectiveness of respiratory support there has been an almost exponential rise in provision of various forms of home respiratory support. Changing population demographics with an epidemic of emerging obesity particularly in the developing world[83], are likely to change future delivery of home ventilation and the proportion of patients with OHS using NIV are likely to rise. In many societies, middle age obesity is now the new norm and the emergence of the super-obese pose significant and unique problems for healthcare delivery.

The use of NIV in this population has increased dramatically over the past 15 years though the evidence base for the shift in respiratory support from CPAP is somewhat lacking. There is good

evidence that PAP improves outcomes in OHS but randomised controlled trials comparing CPAP and NIV have been either too short or small to demonstrate significant differences in mortality to date[84;85]. Until those data become available an individualised, patient-centred approach in provision of respiratory support, with a switch from CPAP to NIV in those patients who require high CPAP pressure, are in respiratory failure or have residual OHS despite CPAP, seems sensible[86-88].

PAP is only one aspect of supporting the obese patient, optimal lifestyle advice must be delivered in the context of an integrated bariatric service with surgical interventions available.

Palliative NIV

In many situations home ventilation is instituted with the aim of improving life expectancy as well as quality of life. Application with the sole intention to reduce dyspnoea or symptoms of sleep disordered breathing and enable optimal use of opiates is just as valid[89]. Home NIV can therefore be use as a palliative tool in patients with ALS/MND and has also been shown to reduce dyspnoea and opiate requirements in patients with endstage cancer and respiratory failure[90]

Interfaces

As well as progress with ventilators an important step towards making NIV easier to use has been the development of the interface which connects the patient to the ventilator. In one of the first studies undertaken in patients with a COPD exacerbation by Brochard et al[91] a face mask had to be developed for use by the investigators (Figure 4); in contrast a range of masks is now available (some, but not an exclusive selection shown in Figure 5). Most typically a patient will opt for one covering either the nose alone or nose and mouth but bigger devices are available which can be worn like a helmet (used for acute NIV), as well as smaller ones which use nasal cushions to insert into the nose or, as function purely as an oral interface retained by teeth and gums. Smaller

interfaces suitable for paediatric use have been a welcome advance, although the problem of young patients developing mid facial hypoplasia from long term use of facial masks has not been completely solved. Materials have also progressed so that normally a silicone cushion is used which is less irritant to the skin. The interested reader is referred to Pisani and co-workers[92] for a more detailed consideration of masks currently available, and potential complications and contraindications.

Global home ventilation in 2017 and beyond

International comparisons of the organisation of home ventilation are difficult as inevitably linked to reimbursement for healthcare and overall financial provision. Undoubtedly however, the ability to provide ventilatory support in the home has reduced hospital and ICU stays, the move from invasive ventilation via tracheotomy to a combination of non-invasive techniques and cough assist devices has simplified care, and quality of life for many patients with chronic respiratory failure has improved in the last century. As described in the sections above, manufacturers have assisted with the development of more portable, responsive ventilators which attempt to minimise asynchrony, longer battery life and more ergonomic interfaces. 3D printing is likely to advance the ability to personalise fit and individualise interfaces.

Downloadable data from ventilators has been available for some while, which can facilitate expert care in the home. Telemonitoring is posited as crucial to the future of home ventilation. Routine telemonitoring of CPAP now occurs in some countries with daily transmission of data on leak, respiratory events and adherence . Trials of early generation telemonitoring systems in ventilatory support patients have produced mixed results[93;94]. However the utility of remote monitoring is likely to improve if telemonitoring options can focus on specific problem solving – adapting the new user to the device, optimising settings in the home and reducing hospital attendances for patients in remote environments or for whom mobility/travel are problematical.

While RCTs have not been possible in some areas of rare neuromuscular disease, effective RCTs establishing the appropriate place for long term use of NIV COPD[63-65;95], and the Serve-HF trial[96] showing adaptive servo ventilation does not produce beneficial effects in chronic systolic heart failure patients with central sleep apnea have been influential landmarks in the field, while at the same time increasing our understanding of the underlying pathophysiology. Research priorities now include ascertaining the role of long term NIV in different COPD phenotypes and its impact on quality of life, unravelling the effects of NIV on respiratory and cardiovascular consequences of obesity hypoventilation syndromes, understanding long term outcome of NIV in paediatric ventilatory disorders, determining the role of palliative NIV, and optimal use of cough assist devices, amongst others.

The use of physiological concepts to develop new modes such as proportional assist ventilation96 and volume assured pressure support ventilation has in many ways been a stimulus the better understanding ventilator patient interaction and pathophysiology , rather than in changing outcomes. As efforts continue to produce more intelligent ventilators and assistive technology in the home we should bear in mind that intelligent operators are required too, and that training of physicians, allied health team members and carers to select patients, optimise ventilatory control and investigate further indications for NIV are just as crucial.

Table 1

Study	N=	Design	Main inclusion/exclusion criteria	Mean $PaCO_2$	Mean pressures used	Notes	Outcome
Strumpf 1991[97]	19	Randomised cross-over over 3 month	No AECOPD previous 4 weeks, FEV1 <1 litre No OSA	46 mmHg	IPAP 15 cm H_2O	Only 7 of 23 enrolled completed both arms of the study	No change CO2 or other outcome measure
Meecham-Jones 1995[98]	18	Randomised cross-over 3 month trial	No AECOPD previous 4 weeks, $PaCO_2$ >45 mmHg, LTOT No OSA	56 mmHg	IPAP 17 cm H_2O EPAP 1.9 cmH_2O	14 completers Median 6.9 hr/d use	Improved ABG, no change 6MW
Gay 1996[99]	13	NIV vs control	No AECOPD $PaCO_2$ >45 mmHg,	51.6 mmHg	IPAP 12 cm H_2O EPAP 2 cmH_2O	13 randomised from 35 recruited, 3 of 7 in NIV group did not complete	NIV of no benefit
Lin 1996[100]	12	Randomised cross-over	No AECOPD previous 4 weeks, Patients had to be able to tolerate 2 weeks NIV before entry $PaCO_2$ >43 mmHg No OSA	50.5 mmHg	IPAP 14 cm H_2O EPAP 2 cmH_2O	2 weeks of therapy	No benefit
Clini 2002[101]	90	Prospective RCT. Inclusion criteria to be met 4 weeks after enrolment	No AECOPD previous 4 weeks. PaCO2>50 mmHg. LTOT>6 months MRC>1 FEV1<1.5l	54 mmHg in NIV group, 55.5 mmHg in LTOT group	IPAP 14 cm H_2O EPAP 2 cmH_2O	2 year follow up	Improved dyspnoea and HRQL but no effect on survival or admission
McEvoy 2009[95]	144	Prospective RCT.	No AECOPD previous 4 weeks. PaCO2>46	54.4 mmHg in LTOT	IPAP 12.9 cm H_2O	Powered for a 2 year study	Improved unadjusted but not adjusted

			mmHg. LTOT>3 months FEV1<1.5l/50 % pred	group 52.6 mmHg in LTOT + NIV	EPAP 5.1 cmH_2O		survival Worse general health and vigour
Kohnlein 2014[63]	195	Prospective RCT	No AECOPD previous 4 weeks $PaCO_2$>52.5mmHg GOLD IV COPD (I.e. FEV1 <30% predicted)	58.5 mmHg in NIV group and 57.7 mmHg in Control group.	IPAP 21.6 cm H_2O EPAP 4.8 cmH_2O	1 year survival	1 year survival advantage for NIV NIV titrated to reduce CO2 LTOT usage approx. 63% of participants Rate of emergency admissions unexpectedly low in both groups
Struik 2014[64]	201	Prospective RCT	GOLD III/IV Prior admission requiring NIV Convalescent $PaCO_2$>45 mmHg	59.2 mmHg in NIV group and 57.7 mmHg in Control group.	IPAP 19.2 cm H_2O EPAP 4.8 cmH_2O	1 year survival	Patients had had prior ventilatory support No benefit NIV 65% readmission rate
Murphy 2016[65]	116		CO_2 >52.5 mmHg within 2-4 weeks of exacerbation OSA excluded	59.2 mmHg	IPAP 24 cm H_2O EPAP 4 cmH_2O	1 year admission free survival	NIV titrated to target hypercapnia Mortality unchanged but reduced readmission rates at 1 and 12 months

Legends to Table and Figures

Table 1 Comparison of randomised controlled trials of home positive pressure ventilation in COPD

Figure 1 Iron lung

Figure 2 Timeline of development of home ventilation in last century

Figure 3 Probability of continuing NIV in neuromuscular disease, chest wall disorders, COPD and bronchiectaisis[69]

Figure 4 Early non-invasive ventilation masks used by Brochard et al[102]

Figure 5 Range of recent non-invasive ventilation interfaces:

Top row left to right: Fitlife paediatric total mask (Respironics), Airfit F20 (ResMed)

Middle row left to right: Simplus FF (Fisher & Paykel), Amara (Respirionics), JoyceOne (Lowenstein Medical)

Bottom row left to right: Airfit P10 Nasal plugs (ResMed), Amara View (Respironics), Mirage FX (Resmed)

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