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New modalities for non-invasive ventilation

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ABSTRACT – There is now substantial evidence supporting the use of non-invasive ventilation in acute hypercpanic exacerbations of chronic respiratory failure, and early trials show nocturnal ventilatory support may benefit chronic heart failure patients with sleep disordered breathing. Attention is now being focused on innovative modes which adapt respiratory support to the user's ventilatory pattern, eg adaptive service ventilation and assured volume delivery 'intelligent' ventilation.

KEY WORDS: NIV, adaptive servo-ventilation, high intensity ventilation

Definitions and indications for non-invasive ventilation

In contrast to invasive ventilation, which is delivered by an endotracheal tube or tracheostomy, non-invasive ventilation is applied either by positive pressure through a mask or nasal and/or oral interface, or via negative pressure supplied round the chest wall with a shell or body-encompassing tank ventilator. Although negative-pressure ventilation has a long history, being used extensively during the poliomyelitis epidemics of the previous century, current delivery of non-invasive ventilation in acute and chronic circumstances is predominantly via positive-pressure systems.

The evidence base (Box 1) for non-invasive positive-pressure ventilation (NIV) is now extensive, particularly in acute ventilatory failure, where there is evidence from randomised controlled trials and meta-analysis[1] to support the first-line use of NIV in acute acidotic hypercapnic exacerbations of chronic obstructive pulmonary disease (COPD), and to wean patients with COPD off invasive ventilation. For chronic application, there are extensive case-series data on the use of NIV in chronic restrictive disorders (eg chest wall and neuromuscular disease),[2] with one randomised controlled trial (RCT) showing improved survival in patients with motor neurone disease of approximately 7 months,[3] and other cohort series showing a major increase in survival in patients with Duchenne muscular dystrophy treated with NIV.[4,5] All these clinical situations exemplify the pathophysiological vicious cycle of an overloaded respiratory system, leading first to nocturnal hypoventilation and then overt diurnal ventilatory failure. NIV is less successful in dealing with acute and chronic hypoxaemic respiratory failure because it does not address causes of hypoxaemia, such as ventilation–perfusion mismatch or diffusion difficulties, although NIV can offload the work of breathing (see, 'Palliation of breathlessness', below) and buy time for other therapies to take effect.

Early trials of NIV used volume pre-set ventilators, whereas over the past 20 years, pressure support bilevel ventilators have been used for most patients. However, there has been increasing interest in exploring whether improvements can be gained by modifying ventilator technology. Some of these developments and their implications for clinical practice are explored in this article.

Adaptive servo-ventilation in chronic heart failure

Approximately 1–2% of the population have heart failure, with the prevalence increasing as the population ages. Approximately 70% of those individuals have mild heart failure, New York Heart Association (NYHA) grade 2. Previously, it was felt that periodic breathing and/or a Cheyne Stokes pattern of waxing and waning ventilation was a characteristic of end-stage heart failure, NYHA grade 4. More recently, it has been shown that not only Cheyne Stokes respiration (CSR) is present in those with milder heart failure, but also that other forms of sleep-disordered breathing, such as obstructive sleep apnoea (OSA), are common. Either OSA or central sleep-disordered breathing (CSA) can occur in approximately half of patients with mild to severe chronic heart failure (CHF).[6] Moreover, these forms of sleep-disordered breathing can be associated with intermittent hypoxaemia and surges of catecholamines, which further compromise left ventricular function. This can be complicated by swings in

Box 1. Evidence base for non-invasive positive pressure ventilation.

Strong evidence (Level A)
- Acute exacerbations of COPD
- To facilitate weaning in COPD
- Acute cardiogenic pulmonary oedema
- Immunocompromised patients

Reasonable evidence (Level B)
- Postoperative respiratory failure
- Motor neurone disease
- Do not intubate patients
- Cystic fibrosis, obesity hypoventilation

Cohort series, case reports
- Restrictive disorders
- Upper airway obstruction
- Acute respiratory distress syndrome

COPD = chronic obstructive pulmonary disease.

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intrathoracic pressure caused by OSAs, which reduce pre-load, and high levels of oxidative stress.

Although continuous positive airway pressure therapy (CPAP) can address obstructive events, there have been no rigorous long-term trials of CPAP in patients with heart failure and OSA, and a randomised controlled trial of CPAP[7] in CSA did not show favourable effects, other than in a *post-hoc* analysis, where benefit was seen in those patients in whom CPAP suppressed apnoea and hypopnoeas.[8] The mode of adaptive servo-ventilation (ASV) has been developed to deal primarily with central sleep apnoea and/or CSR, but also incorporates positive pressure during expiration so that obstructive episodes can also be obviated. As shown in Fig 1, ASV aims to smooth out the waxing–waning pattern of CSR by increasing inspiratory positive airway pressure support when ventilatory effort falls and reducing it again to a pre-set minimum level as ventilatory effort increases. An early study of ASV[9] showed similar short-term effects to CPAP therapy, but over 6 months apnoeas and hyponoeas were suppressed better by ASV.

Further trials have suggested that ASV could improve cardiac function.[10] At present, ASV is being explored in two large randomised controlled trials: Serve-HF, which is exploring the role of ASV in patients with CHF with predominant CSA; and Advent-HF, which is recruiting patients with heart failure and OSA and CSA. The results of these trials will determine whether non-invasive ventilation in ASV mode is a useful complement to standard drug therapy in patients with heart failure.

High intensity NIV in patients with COPD

Although there is no doubt that NIV is gold-standard therapy in acute hypercapnic exacerbations of COPD, results from trials of domiciliary NIV in COPD have been more mixed. In 2010, McEvoy[11] showed a survival advantage to NIV combined with long-term oxygen therapy (LTOT), over LTOT alone, but did not find improvements in quality-of-life scores. It has been suggested that frequent hypercapnic exacerbators benefit most from long-term NIV and the results of further trials are due. However, it remains true that some of the discordant results might be because of variations in the way that NIV is applied. There is a persuasive argument that targeting CO_2 control rather than simply reducing respiratory muscle effort might yield better longer term outcomes.[12] Indeed, research suggests that the predominant mechanism of action of NIV is via an improvement in control of breathing.[13] This is probably enhanced by a reduction in CO_2 that decreases cerebral bicarbonate levels, thereby increasing chemosensitivity to CO_2.[13]

The concept of 'high-intensity' NIV was developed to explore whether using an approach with a high inspiratory positive airway pressure level together with a high back-up rate, such that the patient's breathing is controlled, is likely to be more successful than using lower inspiratory pressures. In a randomised crossover trial[14] of high-intensity (mean inspiratory positive airway pressure 28.6 +/– 1.6 cm H_2O in controlled mode) versus low-intensity (mean inspiratory pressure 14.6 +/-0.8 cm H_2O) NIV in patients with stable hypercapnic COPD, nocturnal PCO_2 fell in favour of high-intensity therapy, and duration of use at night was longer than in the low-intensity limb. Additionally, only high-intensity NIV resulted in a decrease in exercise-induced breathlessness and daytime $PaCO_2$ and improvement in spirometry and severe respiratory insufficiency quality-of-life score. Contrary to expectation, there was no increase in barotrauma and/or pneumothorax in the high-intensity group and sleep quality was not impaired.[15]

Initiation of these high pressures does seem to be more time consuming and it is notable that a longer inpatient admission was required to acclimatise patients. Perhaps what is most noticeable from this work is the relatively low pressures in the comparison limb. A more pragmatic approach might be to set inspiratory pressure at least high enough to control nocturnal hypoventilation. Whether controlled mode is required over and above the patient triggering each breath with adequate back-up rate (spontaneous timed mode) is difficult to determine from these studies. It is possible that spontaneous timed mode (with inspiratory pressure support) is sufficient.

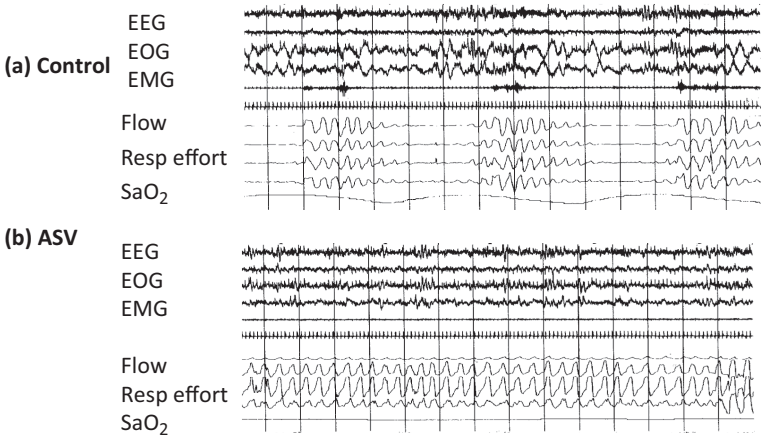

Fig 1. Sleep study data in a patient with chronic heart failure. (a) Patient breathing spontaneously during sleep exhibiting waxing and waning pattern of Cheyne–Stokes respiration with respiratory effort interspersed with central apnoeas. (b) Same patient as in (a) using adaptive servo-ventlation, which has eliminated Cheyne–Stokes respiration and dips in SaO_2. EEG = electroencephalogram; EMG = electromyogram; EOG = electrooculogram; SaO_2 = arterial oxygen saturation.

Intelligent ventilation modes

Several new approaches have been introduced over the past few years to try to combine bilevel pressure support with the delivery of an assured minute or tidal volume. The underlying goal of these modes is to better adapt to the patient's own ventilatory pattern and needs, which vary during different stages of sleep and with different activities during the day. Some devices also have an 'intelligent' back-up rate and a 'learn' mode, in which the ventilator adapts to the patient's respiratory effort and pattern (Fig 2).

Average volume-assured pressure support (AVAPS) was the first of these modes. An early randomised crossover trial of AVAPS vs standard pressure support in

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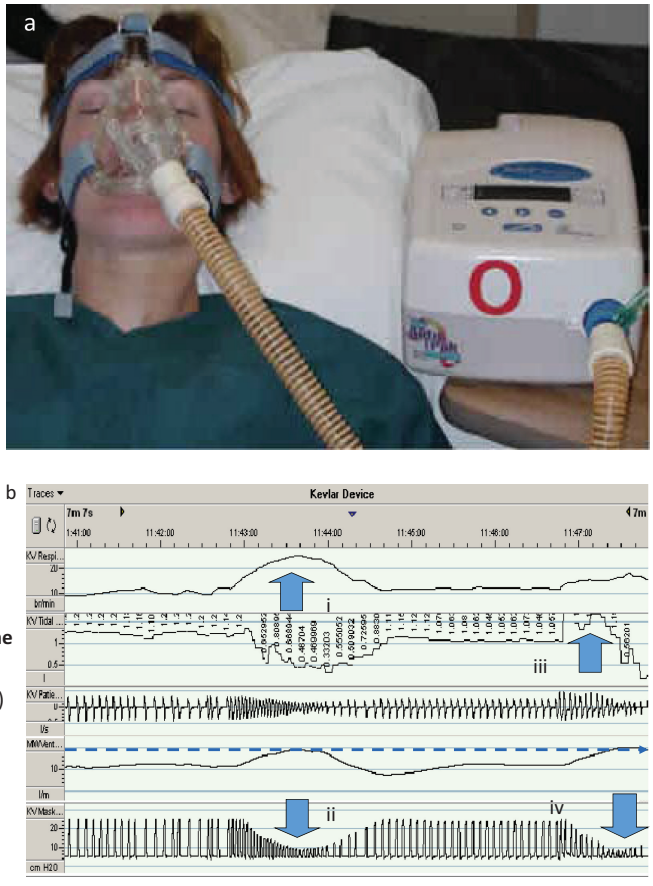

Fig 2. Respiratory pattern during intelligent ventilation. (i) Patient begins taking rapid breaths and minute ventilation increases. (ii) Ventilator reponds by decreasing inspiratory pressure support to maintain overall ventilation. (iii) Patient again takes rapid breaths. (iv) Ventilator responds within a few breaths by decreasing pressure support to main constant ventilation. Reproduced with permission from J Kelly.

patients with obesity hypoventilation showed a small improvement in nocturnal PCO_2 but no long-term quality-of-life improvement.[16] In very obese patients, Murphy *et al*[17] confirmed there was no long-term advantage in AVAPS over optimally titrated bilevel pressure support, and results in patients with COPD are equivocal. The intelligent volume assist pressure support (iVAPS) ventilator targets tidal volume rather than minute ventilation and has been shown to produce equivalent control of nocturnal hypoventilation to a group expertly set-up on NIV.[18] Also in a group with predominantly restrictive disorders newly starting NIV, iVAPS resulted in improved adherence overnight and a reduction in stage 1 sleep,[18] suggesting sleep initiation when starting NIV was improved. These results suggest that intelligent ventilation has a role in certain subgroups, but has not been demonstrated to be superior to conventional pressure-support NIV in all patient groups.

NIV to palliate breathlessness in end-stage malignancy

In a recent trial, Nava and colleagues[19] explored the tolerability of NIV in patients with solid tumours complicated by acute respiratory failure (ARF) in a randomised comparison to high-flow oxygen therapy with the key aim of reducing breathlessness. Life expectancy in these patients was estimated to be less than 6 months. Morphine was used in both groups and the primary outcomes were a reduction in breathlessness and dose of morphine used at 48 h. Importantly, patients with end-stage solid tumours and ARF resulting from an acute exacerbation of COPD or heart failure were excluded from this trial because it was felt there was sufficient evidence already to support the use of NIV in these situations.

The results showed that breathlessness decreased more in the NIV group and morphine requirements were decreased compared with those receiving oxygen therapy. Patients were stratified by PCO_2 level on entry to trial and it is notable that improvements in breathlessness and the reduced need for morphine occurred predominantly in the patients with hypercapnia ($PaCO_2$ >6.0 kPa).[19] Of the patients, 11% were not able to tolerate NIV in the run-in period, whereas all were able to tolerate high-flow oxygen therapy. Adverse effects were generally minor.

Therefore, these results are helpful but it is vital to set goals when the aim of NIV is to palliate symptoms rather than act as life support, such that if these objectives are not achieved, NIV can be rapidly withdrawn and will not to add to the patient's burdens.[20] In contrast to gradual changes in arterial blood gas tensions, breathlessness should be relieved rapidly after starting NIV (if the ventilator settings are correct) and so the efficacy of therapy can be judged by the patient and team within minutes or hours. In addition to reducing breathlessness, NIV might enable the more effective use of morphine or other sedative analgesia without causing excessive sleepiness or progressive CO_2 retention.

Challenges to implementing NIV

Despite extensive evidence supporting the use of NIV across a broad range of clinical conditions (Box 1), several surveys across both the USA and Europe have found wide variation in utilisation rates, from 0% to over 50%,[21–24] with only 10–30% of patients with COPD or CHF receiving NIV for ARF. This compares to literature that suggests usage rates for NIV in ARF resulting from COPD and CHF should be approximately 70% and 20%, respectively.[25,26] The main reasons given for lower utilisation rates in these surveys were a lack of clinician knowledge and training.

Clinical experience with NIV also seems to be a decisive factor in the success of its use. A systematic review of the predictors of NIV failure[27] found that patient tolerance of, and compliance with, NIV therapy is closely related to clinician expertise. Girou and colleagues,[25] in a study of French intensive care units, demonstrated a significant fall in mortality and in the incidence of nosocomial pneumonia as the rate of NIV utilisation increased,

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changes that the authors attributed to a 'learning effect'. In addition, Carlucci *et al*[28] demonstrated that increasing clinical experience with the use of NIV meant that more severely ill patients could be treated while maintaining a constant NIV success rate. Finally, Lopez-Campos *et al*[29] found a significantly higher failure rate (67% vs 11%) for those patients receiving NIV on internal medicine wards compared with a respiratory ward. The only difference between respiratory ward care and care on other wards was the level of staff experience in NIV.

Taken together, these studies suggest that improving the education and training of clinicians in NIV should be a key part of any measures designed to increase NIV utilisation rates and enhance the success of NIV therapy. Delivering effective training for NIV is challenging. Conferences and lectures often have little effect,[30] whereas practical hands-on experience is more consistently successful. A combination of didactic sessions focussing on evidence-based practice and patient selection, alongside practical hands-on sessions covering technical aspects of NIV, including NIV physiology and rationale, practical tips for initiating NIV, interface selection, circuit set-up, selection and titration of settings, and troubleshooting is suggested.[31] Sessions should also cover recognition and management of NIV failure.

Medical simulation is ideally suited to this type of training and has previously been shown to be effective in training nursing staff in the practical use of NIV. The use of simulation enables clinicians to develop clinical skills while protecting patients from unnecessary risk because the 'learning curve' of practical training occurs away from the patient's bedside.[32] Recent radical changes in patterns of healthcare mean that trainees are exposed to fewer patients, shorter training opportunities and fragmentation of the traditional clinical team structure, meaning that traditional models of training in clinical practice are becoming increasingly unsustainable. Simulation-based medical education is able to bridge the skills gap that is emerging.

As an example, at the Royal Brompton Hospital, London, a computer-based simulator training programme for NIV has been developed in association with ResMed (Bella Vista, Australia) and the European Respiratory Society (ERS). The programme provides the full spectrum of teaching described above and uniquely enables the trainee to select and adjust ventilator settings and view physiologically accurate patient responses to therapy. Thus, this type of approach should provide a safe and effective environment for clinicians to develop their knowledge and skills in NIV, with the aim of translating these skills into increased uptake of NIV and improved clinical practice and outcomes.

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