Target volume settings for home mechanical ventilation: great progress or just a gadget?

Wolfram Windisch, Jan Hendrik Storre

Home mechanical ventilation (HMV) is a well-established treatment option for patients with chronic hypercapnic respiratory failure, whereby non-invasive positive pressure ventilation (NPPV) serves as the predominant means of HMV delivery. In general, there are two physiologically-different modes of NPPV deliveries, volume-preset NPPV and pressure-preset NPPV. During volume-preset NPPV a fixed inspiratory volume (V_{insp}) is set at the ventilator, while the inspiratory positive airway pressure (IPAP) varies depending on airway resistance. Conversely, V_{insp} varies during pressure-preset NPPV, while IPAP remains fixed. The advantage of volume-preset NPPV is that V_{insp} and hence tidal volume, are relatively stable; however, this can lead to a breath-by-breath variation in IPAP levels that can become a burden for the patient, and the leakages that regularly occur during NPPV are not compensated for. In contrast, the V_{insp} that is delivered during pressure-preset NPPV may be unstable due to increased airway resistance; however, given that the variation in IPAP is lower, this is often better tolerated by the patient. In addition, leak compensation is provided by pressure-preset NPPV, as shown by in vitro and in vivo studies. In addition, ventilators providing pressure-preset NPPV are cheaper. Thus, pressure-preset NPPV has become the predominant means of delivering HMV. Nevertheless, randomised controlled trials have shown that volume- and pressure-preset NPPV generally have comparable effects on improvements in blood gases, sleep quality and health-related quality of life (HRQL), although pressure-preset NPPV is reportedly better tolerated due to fewer gastrointestinal side effects. However, clinicians should always weigh the advantages and disadvantages of the two different approaches on an individual patient basis.

Recently, the so-called hybrid modes have been developed to overcome the disadvantages of volume- and pressure-preset NPPV, respectively. These modes seek to combine the advantages of the two classical modes, that is, the stability of V_{insp} and the avoidance of cumbersome variations in breath-by-breath IPAP levels. This is achieved by setting a so-called ‘target volume’. Here, pressure-preset NPPV is primarily used, but instead of a fixed IPAP, a pressure range with minimal and maximal IPAP values is set at the ventilator. In response to the automatic calculations and adjustments made by the ventilator, IPAP can undergo a smooth transition within a preset range in order to reach the target volume.

The most extensively studied hybrid mode is the Average Volume Assured Pressure Support (AVAPS) mode. An initial randomised-controlled cross-over trial suggested that the addition of AVAPS to pressure-preset NPPV resulted in better control of nocturnal ventilation compared with pure pressure-preset NPPV in patients with obesity hypoventilation syndrome (OHS). However, both HRQL, as assessed by the Severe Respiratory Insufficiency (SRI) questionnaire, and sleep quality, as measured by polysomnography, showed similar improvements under each of the two modes. Subsequent trials that primarily included OHS and chronic obstructive pulmonary disease (COPD) patients showed an overall comparable outcome, although nocturnal hyperventilation was better controlled in some trials (table 1). However, in one study polysomnographic sleep quality was shown to be reduced during AVAPS compared with pure pressure-preset NPPV, probably as a result of considerably high target volume settings (table 1). However, observational periods were rather short in the previous trials, and in some cases patients were already familiar with pressure-preset NPPV prior to randomisation, thus indicating a selection bias. Therefore, the evidence for target volume setting remains inconclusive, and it is yet to be established whether these hybrid modes of ventilation have benefits that are clear and consistent enough to warrant official recommendations.

Murphy and colleagues randomly allocated 50 NPPV-naive patients with severe OHS (body mass index $50\pm7$ kg/m$^2$) either to pure pressure-preset NPPV using pressure support ventilation or to AVAPS mode, with 46 patients completing the trial. After 3 months of treatment, daytime arterial partial pressure of carbon dioxide (primary outcome) improved comparably in both groups by a mean 0.6 kPa. In addition, improvements in HRQL—again measured with the highly specific SRI—also showed a similar improvement in both groups, while both treatment strategies resulted in equivalent degrees of weight loss (table 1); therefore, AVAPS was not advantageous. This study significantly adds to the current body of knowledge about target volume setting used for HMV for the following reasons.

First, it is the largest randomised controlled trial investigating HMV with target volume settings, and second, the observational period is the longest implemented to date (table 1). Third, and most importantly, ventilator settings were individually adjusted according to a predefined protocol that included a nocturnal assessment period aimed at achieving optimal control of nocturnal ventilation. This protocol was a unique aspect of the study and held true for both modes, rather than just for the AVAPS settings. Therefore, patients could be discharged after optimal treatment had been established, with or without AVAPS. As a consequence, target volume settings did not provide any additional benefits compared with pressure-preset NPPV.

In reality, clinicians are regularly confronted with new technical developments for HMV, whereby new modes and features are increasingly provided without any evidence of benefits or even without clear recommendations on how to adjust the settings. Target volume serves as an excellent example: despite the lack of evidence for any actual benefits, many new-generation ventilators provide target volume modes. Confusingly, the nomenclature and algorithms used for IPAP adaptation vary considerably among different types of ventilators and

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manufacturers. In addition, real target volume settings also show considerable variation among different studies (table 1); this is most likely due to the lack in the availability of recommendations for its use. Indeed, the inappropriate use of these settings can even be harmful. Of note, Murphy and colleagues established that a target volume of 10 ml/kg ideal body weight was the most appropriate for AVAPS in their cohort.

New modes and features like target volume have already been successfully applied for COPD, chronic obstructive pulmonary disease; ESS, Epworth Sleepiness Score; IBW, ideal body weight; OHS, obesity hypoventilation syndrome; PaCO₂, arterial partial pressure of carbon dioxide; PtcCO₂, transcutaneous partial pressure of carbon dioxide; RCT, randomised controlled trial; VT, tidal volume.

Table 1 Clinical studies on target volume during pressure-preset ventilation

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Cohort</th>
<th>Target volume setting</th>
<th>Main target volume outcomes*</th>
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| Storre et al7 † | 2006 | 6-week cross-over RCT (n=10)    | OHS†       | 7 ml/kg IBW (n=5), 10 ml/kg IBW (n=5)                       | ▶ Greater reduction in nocturnal PtcCO₂  
▶ Comparable effect on polysomnography  
▶ Comparable effect on quality of life                                                |
| Janssens et al8 † | 2009 | 1-day cross-over RCT (n=12)     | OHS†       | 7.5±0.8 ml/kg body weight                                   | ▶ Greater reduction in nocturnal PtcCO₂  
▶ Worse polysomnography                                                                 |
| Ambrogio et al11 † | 2009 | 1-day cross-over RCT (n=28)     | Mixed‡     | 8 ml/kg IBW or 110% of baseline VT                          | ▶ Comparable effect on polysomnography  
▶ Greater nocturnal minute volume                                                      |
| Crisiselli et al12 † | 2009 | 5-day cross-over RCT (n=9)      | COPD‡      | 8 ml/kg IBW                                                  | ▶ Comparable improvements in morning PaCO₂  
▶ Subjective improvement in sleep efficiency                                           |
| Oscroft et al13 † | 2010 | 8-week cross-over RCT (n=24)    | COPD‡      | 11.0±3.9 l/min (minute volume)                              | ▶ Comparable effects on:  
– Daytime blood gases  
– Lung function and exercise capacity  
– Quality of life  
– Nocturnal PtcCO₂                                                                 |
| Murphy et al14 † | 2012 | 3-month RCT (n=46)              | OHS‡       | Individual adjustments aimed at achieving control of nocturnal hypoventilation while abolishing obstructive events | ▶ Comparable effects on:  
– Daytime PaCO₂ improvements  
– Quality of life  
– Weight loss  
– Comparable improvements in ESS                                                     |

*Compared with conventional pressure-preset non-invasive positive pressure ventilation (NPPV).
†Mode for target volume: average volume assured pressure support.
‡Patients naive to any form of NPPV.
§Mode for target volume: intelligent volume assured pressure support.
¶Patients already established on pressure-preset NPPV.

COPD, chronic obstructive pulmonary disease; ESS, Epworth Sleepiness Score; IBW, ideal body weight; OHS, obesity hypoventilation syndrome; PaCO₂, arterial partial pressure of carbon dioxide; PtcCO₂, transcutaneous partial pressure of carbon dioxide; RCT, randomised controlled trial; VT, tidal volume.
Stability of inflammatory phenotypes in asthma

Ruth H Green, Ian Pavord

While asthma has long been recognised as a heterogeneous disease, recent interest has concentrated on the identification of phenotypes based on the pattern of inflammation in the airways. The application of induced sputum as a non-invasive ‘inflammometer’ has facilitated this process, resulting in the recognition of apparently distinct ‘eosinophilic’ and ‘non-eosinophilic’ phenotypes. The characterisation of patients in this way appears attractive since the response to treatment, particularly with inhaled corticosteroids, has been shown to differ according to the pattern and extent of inflammation. This has contributed to the concept of a ‘holy grail’ of individualised therapy based on phenotypic expression and a flurry of studies aiming to further explain and refine the phenotypic diversity seen in both adults and children with asthma. A number of questions remain, however, and one important one raised by Fleming et al is whether there are differences in the nature and significance of airway inflammation between adults and children with asthma.

Adult studies using induced sputum have consistently identified distinct eosinophilic and non-eosinophilic asthma subgroups. While the use of inhaled corticosteroids, which effectively suppress sputum eosinophilia, is a significant confounder, normal sputum eosinophil counts have been reported in up to 25% of adult patients with untreated symptomatic asthma1 and for over 50% of adult patients treated with high doses of inhaled corticosteroids.2 Simpson and colleagues have suggested that airway inflammation in adult asthma could be further categorised into four inflammatory subtypes, namely, neutrophilic asthma (neutrophils >61%), eosinophilic asthma (eosinophils >3%), mixed granulocytic asthma (neutrophils and eosinophils both increased) and paucigranulocytic asthma where neutrophils and eosinophils are both within the normal range.4 In populations of patients with stable adult asthma, the majority treated with inhaled corticosteroids, paucigranulocytic asthma appeared to be the most common inflammatory phenotype followed by neutrophilic inflammation.5 6 Non-eosinophilic asthma has also been reported in children with asthma.7 8 Paucigranulocytic asthma was the predominant finding in children with stable asthma, but in contrast with adults eosinophilic inflammation was more likely and neutrophilic inflammation uncommon.8 In adults studied during the stable phase, clinical features are similar across the inflammatory phenotypes although sputum eosinophilia appears to predict a greater likelihood of asthma exacerbation9 and non-eosinophilic patients may be more likely to be female subjects and non-atopic than the remaining group.10 Findings in children differ in that the presence of eosinophilic inflammation appears to predict more severe persistent asthma with impaired lung function and increased AHR.11 12 Differences in inflammatory phenotypes have also been reported between adults and children presenting with an acute severe

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