Physiological effects and optimisation of nasal assist-control ventilation for patients with chronic obstructive pulmonary disease in respiratory failure

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Abstract
Background – A study was undertaken to investigate the effects of non-invasive assist-control ventilation (ACV) by nasal mask on respiratory physiological parameters and comfort in acute on chronic respiratory failure (ACRF).

Methods – Fifteen patients with chronic obstructive pulmonary disease (COPD) were prospectively and randomly assigned to two non-invasive ventilation (NIV) sequences in spontaneous breathing (SB) and ACV mode. ACV settings were always optimised and therefore subsequently adjusted according to patient’s tolerance and air leaks.

Results – ACV significantly decreased all the total inspiratory work of breathing (WOBinsp) parameters, pressure time product, and oesophageal pressure variation in comparison with SB mode. The ACV mode also resulted in a significant reduction in surface diaphragmatic electromyographic activity to 36% of the control values and significantly improved the breathing pattern. SB did not change the arterial blood gas tensions from baseline values whereas ACV significantly improved both the PaO₂ from a mean (SD) of 8.45 (2.95) kPa to 13.31 (2.15) kPa, PaCO₂ from 9.52 (1.61) kPa to 7.39 (1.39) kPa, and the pH from 7.32 (0.03) to 7.40 (0.07). The respiratory comfort was significantly lower with ACV than with SB.

Conclusions – This study shows that the clinical benefit of non-invasive ACV in the management of ACRF in patients with COPD results in a reduced inspiratory muscle activity providing an improvement in breathing pattern and gas exchange. Despite respiratory discomfort, the muscle rest provided appears sufficient when ACV settings are optimised.

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Keywords: non-invasive ventilation, assist-control mode, work of breathing, breathing pattern, respiratory comfort, acute on chronic respiratory failure, chronic obstructive pulmonary disease.

The clinical effectiveness of non-invasive ventilation (NIV) is now well established in the treatment of patients with chronic obstructive pulmonary disease (COPD) with acute on chronic respiratory failure (ACRF). In these patients NIV could avoid the need for intubation in 50–70% of cases, thus reducing significantly the morbidity and duration of hospital stay. Administered via nasal or face mask, NIV can use assist-control (ACV) or pressure support ventilation (PSV). During ACV mode the ventilator delivers a positive pressure breath at a preset tidal volume in response to the patient’s inspiratory effort or at a preset rate if no patient effort occurs within the preselected time period. The PSV mode is a pressure targeted mode in which each breath is patient triggered and supported. A preset positive airway pressure is maintained constant throughout the patient’s spontaneous inspiratory effort, allowing patients to control their inspiratory flow, inspiratory time, and tidal volume. This is believed to increase patient-ventilator synchrony and comfort. However, there are potentially important physiological differences between these two NIV modes, especially in patients with COPD – for example, PSV may compensate for mask air leaks better than ACV but may deliver volumes less reliably, particularly in the presence of variable respiratory mechanics or unstable ventilatory drive. In addition, the PSV mode is not always available with the ventilators used. According to various authors and despite some contradictory results, ACV and PSV may provide similar results regarding success or failure in terms of the need for intubation. However, there have been few studies on the physiological mechanisms which could explain this clinical benefit. The physiological rationale for the usefulness of NIV in ACRF has been essentially studied with PSV or pressure-controlled ventilation very similar to PSV, and rarely with ACV mode. The physiological effects of NIV in patients with stable severe chronic respiratory failure have also been reported more with PSV than with the ACV mode. The physiological mechanism possibly responsible for the clinical benefit of NIV with ACV mode in ACRF has thus not been well studied and documented.

The objective of this study was therefore to investigate the effects of non-invasive ACV via a nasal mask on the physiological respiratory parameters – that is, respiratory muscle function, gas exchange and breathing pattern – as well as on respiratory comfort in an homogeneous population of COPD patients with ACRF.
Nasal assist-control ventilation in COPD

Methods
The study was conducted in a medical intensive care unit and approved by the ethical committee of the Charles Nicolle University Hospital. All patients gave their written informed consent. Patients enrolled in the study had known COPD or a high probability of the disease on the basis of the clinical history, physical examination, chest radiography, and/or previous pulmonary function test data. Additional criteria for enrollment included hypercapnic acute respiratory failure requiring NIV according to the following criteria: 2–4 tachypnoea (>25/min) or bradypnoea (<12/min), PaO₂ ≤ 8 kPa (60 mm Hg) in ambient air, PaCO₂ ≥ 6.5 kPa (49 mm Hg) in ambient air or worsening with a low nasal oxygen flow (<3 l/min), respiratory acidosis (pH ≤ 7.35), a normal level of consciousness or moderate signs of respiratory encephalopathy (drowsiness, confusion, flapping tremor). Patients were included if they showed at least three of these criteria and if they tolerated NIV during the first few hours after admission. Patients with ACRF requiring immediate endotracheal intubation or any contraindication to the insertion of an oesophageal tube were not included.

Figure 1 Representative polygraphic recordings (10 mm/s) of respiratory mechanic parameters (V, VT, Paw), oesophageal pressure (Poes), diaphragmatic electromyographic activity (raw and integrated EMGdi), and end tidal carbon dioxide fraction (FETO2) during non-invasive ventilation with spontaneous breathing (SB) and assist-control ventilation (ACV) in patient 4. Note the increase in VT and Paw, and the decrease in Poes and EMGdi between SB and ACV.

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STUDY PROTOCOL
The study was conducted during the 48 hours following admission for ACRF. Each patient was investigated fasting, in a semirecumbent position in bed, and in quiet conditions. Throughout the study patients were asked to close their mouth firmly in order to limit the deleterious effect of air leaks. All patients were randomly submitted to two consecutive NIV sequences via the same ventilator and nasal mask for a minimal duration of 30 minutes. One sequence in spontaneous breathing (SB) and one in assist-control ventilation (ACV) in patient 4. Note the increase in VT and Paw, and the decrease in Poes and EMGdi between SB and ACV.

MEASUREMENTS
All patients were ventilated using the same ventilator (Evita 2, Dräger Medical Inc, Lübeck, Germany) and were connected to the ventilator via a tightly fitting nasal mask (Respironics, Murrysville, Pennsylvania, USA). The humidifier of the ventilator circuit was disconnected during the trial to decrease the workload necessary to overcome the circuit resistances. The following general data were recorded for all patients: past history, current diseases and treatment, arterial blood gas tensions on admission, and simplified acute physiological score (SAPS). Each patient was investigated using the same apparatus and polygraphic recorder (fig 1). Instantaneous flow rate was measured using a pneumotachograph (Fleisch No 1, Zurich, Switzerland) connected to a differential pressure transducer (Validyne MP45, Validyne Cor., Northridge, California, USA). The pneumotachograph was connected between the nasal mask and the Y-piece of the ventilator circuit. Corresponding volume variations (VT) were obtained by electrical integration of instantaneous flow rates. Minute ventilation (V̇E) was defined as the product of VT and RR. Airway pressure (Paw) was measured at the nasal mask by a differential
pressure transducer (Validyne MP45, Validyne Corporation, Northridge, California, USA). Oesophageal pressure (Poes), reflecting intrapleural pressure, was measured using the method described by Milic-Emili et al.\textsuperscript{21,22} via a latex balloon placed in the middle third of the oesophagus and connected to a differential pressure transducer (Validyne MP45). The proper position of the balloon was confirmed by an occlusion test.\textsuperscript{21} Variations in Poes (ΔPoes), considered to be a parameter of inspiratory effort, were measured as the difference between minimum and maximum Poes.\textsuperscript{13} Dynamic intrinsic positive end-expiratory pressure (PEEPi,dyn), reflecting the end of the expiratory pressure gradient between the alveoli and the nasal mask, was measured on the Poes curve as the difference between point 0 and the Poes point corresponding to cancellation of insufflation flow,\textsuperscript{21} averaged from 10 representative cycles. Total inspiratory work of breathing (WOBinsp) was determined using Campbell's diagram method\textsuperscript{20} by integration of the area plotted between the pressure-volume (Poes-Vt) and the chest wall compliance (Cw) curves.\textsuperscript{26,27} Since it is impossible to measure Cw without complete relaxation, we assumed, as others have,\textsuperscript{26,20} that it was equal to 4% of the theoretical vital capacity.\textsuperscript{29} WOBinsp was calculated from the mean of five cycles and expressed in joules (J). WOBinsp thus enabled calculation of WOBinsp in relation to Vt (WOBinsp/Vt in J/l) or to RR (WOBinsp/RR in J/min). Pressure time product (PTP), a better indicator of the energy expenditure of respiratory muscles,\textsuperscript{11,32} was obtained from the product of Ti and the area under the Poes curve corresponding to Ti. In addition to ΔPoes, WOBinsp and PTP, respiratory muscle activity was evaluated by the diaphragmographic electromyogram (EMGdi) activity amplitude with bipolar skin surface electrodes.\textsuperscript{13} The EMGdi signal obtained (raw EMGdi) was then amplified (Universal amplifier 13-4615-58, Gould Electronics Inc, Cleveland, Ohio, USA) and filtered (30–300 Hz), rectified and electronically integrated every 100 ms (integrated EMGdi) to obtain a moving time average which was then analysed using the method of Lopata et al.\textsuperscript{34} The diaphragmatic activity was evaluated by the maximum or peak amplitude of the integrated EMGdi signal (pEMGdi). This quantitative value, averaged from 10 cycles, was also expressed as a percentage of the control value obtained in SB.

All signals (Vt, Vr, Paw, Poes, FETCO\textsubscript{2}, and EMGdi) were simultaneously displayed and recorded using a polygraphic recorder (ES 2000 V12, Gould Electronics Inc, Cleveland, Ohio, USA) (fig 1). Polygraphic recordings of 10–15 respiratory cycles with a paper speed of 10 and 50 mm/s were used to measure Vt, inspiratory (Ti) and expiratory (Te) times, total cycle duration (Ttot), RR, mean inspiratory flow (Vt/Ti), relative inspiratory time (Ti/Ttot), and FETCO\textsubscript{2} for each cycle. They were then averaged from the entire tracing. A digitisation table (Hewlett Packard 9874 A) and a personal computer (Hewlett Packard 9835 A) were used for measurements and calculations on each entire recording.

The respiratory comfort (level of dyspnoea, well being) was assessed in the last minutes of each ventilation sequence on a 100 mm visual analogue scale (VAS). The patient’s status was located between a value of 0 (“I don’t feel at all comfortable”) and 100 (“I feel very comfortable”) and converted into a numerical value for statistical analysis. Preference for each of the two modes was also noted.

**Results**

The main clinical and respiratory characteristics of the 15 patients with COPD are shown in table 1. All showed evidence of severe hypercapnic ACRF requiring NIV. These ACRF episodes were related to bronchial infection in 14 cases and to pneumonia in one case (patient 3). Table 1 also shows the main ventilatory settings used in ACV mode during the trial after optimisation. No evidence was found for any carry-over (interaction) or period effects so all the results presented are for the non-parametric treatment effects.

In comparison with SB, all the WOBinsp parameters (WOBinsp/cycle, WOBinsp/Vt, WOBinsp/RR), and PTP were significantly decreased with ACV (p <0.001; table 2) and all patients demonstrated a decrease in their individual values. The pEMGdi was also sig-
significantly reduced (p = 0.004) with a decrease of 36% with ACV in comparison with control values in SB mode. The mean Paw was significantly higher with ACV (p < 0.001). PEEP, dyn did not change between the two NIV sequences while APoes was significantly decreased with ACV (p < 0.001).

The effects of NIV on breathing pattern are shown in table 3. Ve was significantly increased with ACV (p = 0.02) compared with SB. This improvement in Ve was achieved by a significant increase in VT (p < 0.001) while a parallel decrease in RR was observed (p = 0.01). This last finding during ACV was related to an increase in Ttot (p = 0.028) due to a significant increase in Ti (p = 0.002) and a decrease in Tt (p = 0.01). ACV also significantly affected Ti/Ttot (p < 0.001) and increased Ve/VTot (p < 0.001) in comparison with SB.

A comparison of arterial blood gas tensions on admission with those obtained with ACV revealed a significant increase in PaO2 (mean (SD) 8.45 (2.93) vs 13.31 (2.15); p < 0.001) with a parallel improvement in PacO2 (9.52 (1.61) vs 7.39 (1.39); p = 0.001) and pH (7.32 (0.03) vs 7.40 (0.07); p = 0.009). No change was found between arterial blood gas tensions on admission and those obtained with SB mode. During the trial oxygenation parameters were also significantly improved between SB and ACV although FiO2 did not change between the two sequences. Among the alveolar ventilation parameters baseline pH, PacO2, and PETCO2 were significantly improved with ACV (p < 0.001; table 4).

The mean (SD) VAS rating for respiratory comfort was 57.23 (30.12) mm during ACV, significantly smaller than that during SB mode at 77.46 (14.66) mm with a mean difference of 24 mm (95% CI –10 to 80 mm, p = 0.05), indicating that ACV was less acceptable to the patients.

None of the 15 patients with COPD finally required intubation. All were subsequently successfully managed with daily NIV using ACV in 10 cases and PSV in five who profited more by this last mode in the long term.

Discussion

This study provides a better understanding of the physiological mechanisms underlying the clinical benefits which may be expected from NIV with ACV mode in the treatment of acute illness.
exacerbations of COPD. It shows that, during NIV, ACV acts by reducing total WOBinsp while at the same time improving breathing pattern and gas exchange. Despite optimised settings adapted to the clinical tolerance of patients, these beneficial physiological effects are achieved at the expense of respiratory discomfort which is experienced by all patients in comparison with the SB mode.

The conditions of this study involved the usual emergency situation in which such patients are admitted. We used initial ACV settings as previously reported but it proved necessary in most patients to change these settings subsequently for reasons of tolerance or air leaks around the nasal mask. We found that a lower than recommended mean inhaled Vt of 9 ml/kg provided a significant, and probably sufficient, reduction in WOBinsp with improved breathing pattern. This optimisation was nevertheless subject to interindividual variations which had to be taken into account when interpreting our results and setting ventilators. It is thus probable that settings suggested up to now – which can be obtained only at the price of an increased Paw (that is, by increasing Vt with ACV) – would have led to a greater decrease in WOBinsp but at the expense of more patient discomfort. It is essential to take this fact into account when choosing initial settings from NIV. Furthermore, our settings did not cause any significant variation in PEEPdyn which may contribute, particularly in COPD, to an additional imposed workload via dynamic hyperinflation as has sometimes been observed with non-invasive PSV. The optimised settings presented in this study could constitute baseline settings for future use of non-invasive ACV.

We used several parameters to evaluate inspiratory muscle function, and more especially that of the diaphragm. To the best of our knowledge, calculation of WOBinsp with NIV is reported here for the first time. During ACV we did not calculate the work performed by the patient as the difference between ventilator work during assisted and controlled mechanical ventilation was not calculated but a significant reduction was found in transdiaphragmatic pressure (Pdi), PTP and electrical activity of the diaphragm, and Apoes in patients with chronic obstructive or restrictive respiratory disease. Similar results with PSV using a mask have also been reported in patients with stable COPD. To the best of our knowledge, no previous study has specifically evaluated the physiological effects of ACV during NIV in a large population of COPD patients with ACRF. Carney et al first reported on improved muscle activity. However, they used a pressure control mode and only investigated two patients with COPD in ACRF of a study population of 12 subjects.

Our results demonstrate a significant reduction in muscle activity indices when using NIV with the ACV mode compared with the SB mode, with Apoes, WOBinsp/Vt, WOBinsp/RR, and PTP being influenced the most. The baseline total workload was changed from a value that was close to the diaphragmatic fatigue threshold of 1.40 J/l to a normal value of 0.30–0.65 J/l. This difference in total WOBinsp between the SB and ACV modes could be due in part to the workload necessary to overcome the circuit and demand valve resistances. Nevertheless, as explained below, most of the cycles were also triggered during ACV in our patients. Interestingly, the WOB of the patients with the ACV mode was less than that reported in other studies with invasive endotracheal ventilation. The size of the endotracheal tubes can greatly influence the muscular effort required, and air leaks during NIV due to a poorly fitting mask or unsuitable settings also increase respiratory workload. Despite these possible limitations we found that non-invasive ACV can, like endotracheal ventilation, achieve one of the goals of assisted ventilation which is to provide muscle rest. Complete muscle rest could not be achieved during the trial because a certain degree of muscle activity persists with ACV, although this activity is close to normal. This is because we used a patient triggered mode of ventilation (ACV) to assist our patients. Even with endotracheal ventilation, ACV may allow considerable respiratory effort to persist which can be similar to the effort needed with SB.

The interpretation of WOBinsp may be difficult with NIV so we combined measurement of the EMGdi. It has been shown that during NIV the surface EMGdi activity was well correlated with that of EMGdi assessed by invasive oesophageal electrodes. The results paralleled that a lower mean in-dibi of 9 ml/kg provided a significant, and probably sufficient, reduction in WOBinsp with improved breathing pattern. This optimisation was nevertheless subject to interindividual variations which had to be taken into account when interpreting our results and setting ventilators. It is thus probable that settings suggested up to now – which can be obtained only at the price of an increased Paw (that is, by increasing Vt with ACV) – would have led to a greater decrease in WOBinsp but at the expense of more patient discomfort. It is essential to take this fact into account when choosing initial settings from NIV. Furthermore, our settings did not cause any significant variation in PEEPdyn which may contribute, particularly in COPD, to an additional imposed workload via dynamic hyperinflation as has sometimes been observed with non-invasive PSV. The optimised settings presented in this study could constitute baseline settings for future use of non-invasive ACV.

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NIV\textsuperscript{44} and this supports the view that NIV is of most benefit to patients with acute hypercapnic respiratory failure.\textsuperscript{44} The respiratory comfort of our patients was an essential factor for the acceptance and subsequent results of the NIV technique. The physiological effects of NIV could certainly be improved if it was not necessary to take into account this criterion. Despite the fact that we optimised the settings for ACV, all our patients preferred SB and PSV to the ACV mode in terms of respiratory comfort. A recent study to assess non-invasive ACV and PSV modes in 29 patients\textsuperscript{9} found that PSV was also better accepted and had fewer side effects than ACV. The anomaly that, despite adequate respiratory muscle rest with the ACV mode our patients experienced discomfort, could be related to the increase in Paw or the loss of control of breathing by ACV compared with the SB mode. Although we failed to demonstrate any correlation between Paw and VA explanations probably account for the fact that PSV is better tolerated than ACV but without any difference in clinical results.\textsuperscript{9}

In conclusion, we have shown that the use of non-invasive ACV in patients with COPD with ACRF results in a substantial decrease in the workload of the respiratory muscles with improvements in breathing pattern and gas exchange. These physiological effects are maximised if the ventilator settings are optimally adjusted according to the patient’s tolerance and the presence of air leaks. The main disadvantage of the ACV mode in the short term appears to be a feeling of respiratory discomfort experienced by the patients so physicians must optimise the ACV settings to improve the success of the technique. If respiratory comfort is the limiting factor then PSV may be preferable to ACV, although the ACV mode might be more physiologically appropriate during the early phase of ACRF in some patients with COPD who have unrestricted inspiratory effort, unstable ventilatory drive, and variable respiratory mechanics.

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