ORIGINAL ARTICLE

Effect of assist negative pressure ventilation by microprocessor based iron lung on breathing effort

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Background: The lack of patient triggering capability during negative pressure ventilation (NPV) may contribute to poor patient synchrony and induction of upper airway collapse. This study was undertaken to evaluate the performance of a microprocessor based iron lung capable of thermistor triggering.

Methods: The effects of NPV with thermistor triggering were studied in four normal subjects and six patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) by measuring: (1) the time delay (TDtr) between the onset of inspiratory airflow and the start of assisted breathing; (2) the pressure-time product of the diaphragm (PTPdi); and (3) non-triggering inspiratory efforts (NonTrEf). In patients the effects of negative extrathoracic end expiratory pressure (NEEP) added to NPV were also evaluated.

Results: With increasing trigger sensitivity the mean (SE) TDtr ranged from 0.29 (0.02) s to 0.21 (0.01) s (mean difference 0.08 s, 95% CI 0.05 to 0.12) in normal subjects and from 0.30 (0.02) s to 0.21 (0.01) s (mean difference 0.09 s, 95% CI 0.06 to 0.12) in patients with COPD; NonTrEf ranged from 8.2 (1.8)% to 1.2 (0.1)% of the total breaths in normal subjects and from 11.8 (2.2)% to 2.5 (0.4)% in patients with COPD. Compared with spontaneous breathing, PTPdi decreased significantly with NPV both in normal subjects and in patients with COPD. NEEP added to NPV resulted in a significant decrease in dynamic intrinsic PEEP, diaphragm effort exerted in the pre-trigger phase, and Non-TrEf.

Conclusions: Microprocessor based iron lung capable of thermistor triggering was able to perform assist NPV with acceptable TDtr, significant unloading of the diaphragm, and a low rate of NonTrEf. NEEP added to NPV improved the synchrony between the patient and the ventilator.

lthough clinical studies suggest that negative pressure ventilation (NPV) provided by iron lung can be as affective as invasive mechanical ventilation for the treatment of severe acute respiratory failure in patients with chronic obstructive pulmonary disease (COPD),¹² negative pressure ventilators are actually considered second line choice for noninvasive ventilatory assistance3 for several reasons, including the fact that, traditionally, NPV is a controlled mechanical ventilation-that is, the device provides a fixed number of breaths per minute irrespective of the patient's own breathing pattern. If the mechanical and spontaneous respiratory cycles are not matched, however, the patient "fights" the ventilator, resulting in discomfort and excessive respiratory muscle effort. Airway pressure or flow signals are generally used in positive pressure ventilators to detect inspiratory efforts of patients and to trigger the mechanical breath (assist and assist-control ventilation).4

Unlike positive pressure ventilation during NPV, the airway opening is free and, as a consequence, it is not possible to monitor continuously airway pressure and flow and to use these signals to trigger mechanical breath. The lack of patient triggering capability during NPV may contribute not only to poor patient synchrony, but also to induction of upper airway collapse⁵ due to the lack of coordinated activation between upper airway muscles and inspiratory muscles.⁶ We have recently shown that a prototype microprocessor based iron lung was able to improve the ventilatory pattern and arterial blood gas tensions and to unload inspiratory muscles in patients with an acute exacerbation of COPD.⁷

This study was undertaken to evaluate the performance of the thermistor triggering system used to deliver assist NPV with this new model of iron lung.

METHODS Subjects

Six men with COPD admitted to the Respiratory Intensive Care Unit (RICU) of the Careggi Hospital and treated with NPV for acute respiratory failure and four normal men were studied. Details of these subjects are given in table 1. The patients were recruited consecutively and studied during recovery from acute respiratory failure within 72 hours of admission to the RICU. The diagnosis of COPD was confirmed by clinical history and pulmonary function tests performed in a clinically stable condition before or after admission to hospital.

All subjects were informed of the nature and extent of the investigation and all gave consent to the procedures as approved by the Human Studies Committee of our institution.

Measurements

Spirometric tests were performed according to the standard technique and functional residual capacity (FRC) was measured by helium dilution technique. Predicted values for lung function variables are those proposed by the European Respiratory Society.⁸ Arterial oxygen saturation (Sao₂) was monitored throughout the experiments by an oximeter (3900P Datex-Ohmeda, Louisville, CO, USA).

Airflow was measured with a no 2 Fleisch pneumotachograph connected to the face mask and a Validyne pressure transducer (Validyne Corporation, Northridge, CA, USA) and flow signal was integrated into volume. The breathing pattern and minute ventilation were determined from this signal.

Mouth pressure (Pm) and tank pressure (Ptank) were measured using differential pressure transducers (Validyne) through a side port of the face mask and the iron lung, respectively. Oesophageal (Poes) and gastric (Pga) pressures were measured with conventional balloon catheter systems

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	Age (years)	BMI	VC (% pred)	FEV_1 (% pred)	FEV ₁ /VC (%)	Pao ₂ /Fio ₂ *	Paco ₂ * (kPa)	pH*
Normal subjects	s							
1 .	40	24.7	109	108	80			
2	39	23.6	96	95	78			
3	35	21.8	103	103	83			
4	42	24.5	97	99	82			
COPD patients								
5 '	67	22.7	57	26	35	250	9.2	7.32
6	75	25.9	50	41	47	221	9.3	7.33
7	65	27.0	68	38	43	207	9.8	7.30
8	64	22.8	81	39	37	250	9.0	7.33
9	76	22.9	33	20	38	203	9.6	7.31
10	73	24.8	67	42	42	161	10.4	7.32

connected to Validyne differential pressure transducers, as previously described.⁹ One balloon positioned in the mid oesophagus and containing 0.5 ml of air measured Poes, while the other, positioned in the stomach 65–70 cm from the balloon tip to the nares and containing 2 ml of air, simultaneously measured Pga. Poes was used as an index of pleural pressure (Ppl) and Pga as an index of abdominal pressure. Transpulmonary (PL) and transdiaphragmatic (Pdi) pressures were obtained by electrical subtraction of Ppl from Pm, and of Ppl from Pga, respectively. Total lung resistance was measured during resting breathing using the isovolume method of Frank *et al*,¹⁰ and dynamic lung compliance (Cdyn) was determined by dividing VT by the difference in PL between points of zero flow.

Negative pressure ventilation was provided by a prototype model of an iron lung (Coppa, Biella, Italy) capable of thermistor triggering. Unlike old models of tank ventilators, this unit was controlled by a microprocessor, operated via a rotary pump, and was capable of providing control ventilation, assist/control ventilation, and continuous negative extratho-



Figure 1 Recordings of flow, transdiaphragmatic pressure (Pdi), and tank pressure (Ptank) in a patient with COPD receiving assist negative pressure ventilation. The continuous vertical line indicates the onset of inspiratory effort, the dashed vertical line indicates the start of inspiratory flow, and the dotted vertical line indicates the start of assisted breath. The partitioning of the pressure-time product of the diaphragm is shown: effort required to overcome PEEPi (PTPdiPEEPi), effort required to trigger the assisted breath (PTPdiTr), and effort exerted in the posttrigger phase. TDPEEPi and TDtr indicate the time delay between the onset of inspiratory effort and the start of inspiratory flow, and the time delay between the onset of inspiratory flow and the start of assisted breath, respectively.

racic pressure. The thermistor used to trigger the assisted breath was a thermally sensitive device of common use in sleep studies (Alice 4 Sleep Diagnostic System, Respironics Inc, Pittsburgh, PA, USA) and was activated by a change in temperature due to the onset of inspiratory airflow. A computer touch screen incorporated in the iron lung allowed the following settings: inspiratory negative pressure (up to $-80 \text{ cm H}_2\text{O}$), baseline pressure ($-30 \text{ to } +30 \text{ cm H}_2\text{O}$), inspiratory time (0.4-8.0 s), expiratory time (in control mode), trigger sensitivity (arbitrary scale, 1-10), backup control breathing rate (in assist/control mode).

All signals were received at 100 Hz using an analogue/ digital data acquisition system and were stored in a personal computer for subsequent analysis.

Protocol

Pulmonary function tests were performed when patients were clinically stable before or after hospital admission. The subjects were studied in the supine position enclosed in the tank ventilator with an airtight facial mask (Gibeck Respiration AB, Upplands-Vasby, Sweden). The cushion of the mask was inflated to fit the facial contour and to avoid any possible air leakage. The thermistor triggering was placed at the free way line of the pneumotachograph connected to the face mask. According to standard clinical practice in our unit, the level of intermittent negative pressure (ranging from -15 to -25 cm H₂O) in the patients had previously been titrated by the attending physician to minimise or abolish clinical signs of respiratory distress such as accessory muscle use and to obtain a respiratory rate between 15 and 30 cycles/min; in normal subjects the intermittent negative pressure level was set according to subjective compliance (ranging from -7 to -10 cm H₂O). The backup frequency was set at 6 cycles/min such that every breath was subject initiated. Oxygen was administered to patients through a side port in the face mask and was maintained constant throughout the study.

Once each subject was well acquainted with the experimental setting, data were recorded during a 10 minute period under control conditions—that is, while breathing spontaneously through the face mask with the iron lung switched off. Three trials were then performed in each subject in random order: (1) NPV with trigger sensitivity set at 50% of maximum sensitivity (NPVtr50); (2) NPV with trigger sensitivity set at 75% of maximum (NPVtr75); and (3) NPV with trigger sensitivity set at 100% of maximum (NPVtr100). In patients three further trials were performed after the application of -5 cm H₂O negative extrathoracic end expiratory pressure (NEEP) during NPV: (1) NPV-NEEPtr50; (2) NPV-NEEPtr75; and (3) NPV-NEEPtr100. Between each experimental condition the patients returned to spontaneous breathing for 15 minutes to allow the physiological variables to recover their

	Normal subjects			Patients with COPD		
	NPVtr50	NPVtr75	NPVtr100	NPVtr50	NPVtr75	NPVtr100
TDtr (s)	0.29 (0.02)	0.25 (0.01)	0.21 (0.01)	0.30 (0.02)	0.25 (0.01)	0.21 (0.01)
NonTrEf (%)	8.2 (1.8)	3.4 (0.9)	1.2 (0.1)	11.8 (2.2)	6.2 (1.1)	2.5 (0.4)
Autocycling (%)	0.0 (0.0)	0.8 (0.5)	2.6 (0.7)	0.0 (0.0)	1.0 (0.5)	2.7 (0.7)

 Table 2
 Time delay, non-triggering inspiratory efforts, and autocycling episodes at each sensitivity setting during NPV in normal subjects and patients with COPD

TDtr=time delay between the onset of inspiratory flow and the start of assisted breathing; NonTrEf=non-triggering inspiratory effort (% of total breaths); Autocycling=ventilator autocycling episode (% of total breaths); tr50, tr75, tr100=trigger sensitivity set at 50%, 75%, and 100% of maximum sensitivity.

baseline values. Data were recorded during a 5 minute period after a 15 minute period in each experimental condition when a stable breathing pattern was observed.

Data analysis

At each sensitivity setting tested, triggering performance was assessed by measuring (1) the time delay (TDtr) between the onset of inspiratory flow and the start of assisted breathing; (2) the pressure-time product per breath of the diaphragm (PTPdi) obtained by measuring the area under the Pdi signal from the onset of its positive deflection to its return to baseline; (3) non-triggering inspiratory effort (NontrEf) defined as an inspiratory attempt (decrease in Ppl >1 cm H₂O with simultaneous change in flow) that failed to start an assisted breath; and (4) ventilator autocycling episode defined as an assisted breath in the absence of inspiratory effort.

Using methodology adapted from that of Sassoon *et al*,¹¹ PTPdi was partitioned into three different components (fig 1): (1) effort required to overcome dynamic intrinsic positive end expiratory alveolar pressure (PTPdiPEEPi); (2) effort required to trigger the assisted breath (PTPdiTr); and (3) effort exerted in the post-trigger phase (PTPdiPost). Dynamic PEEPi was calculated as the amount of negative deflection in Ppl preceding the start of inspiratory flow from which the expiratory rise in Pga, if any, was subtracted.¹²⁻¹⁴ The time delay between the onset of inspiratory effort and the start of inspiratory flow (TDPEEPi) was also calculated (fig 1). The total time delay between the onset of inspiratory effort and the start of assisted breathing (TDPEEPi+tr) was calculated as TDPEEPi + TDtr.

Mean values of variables at each level of trigger sensitivity were compared with analysis of variance for repeated measures or the Scheffe test of multiple comparisons where appropriate. A p value of ≤ 0.05 was considered statistically significant. Results are presented as mean (SE) and as the mean difference with 95% confidence interval (95% CI).

RESULTS

No significant difference in the pattern of breathing between each trial of NPV was observed in either normal subjects or patients with COPD. As shown in table 2, TDtr decreased significantly with increasing trigger sensitivity both in normal subjects and in COPD patients (p<0.001 for both); the mean difference (95% CI) between NPVtr50 and NPVtr100 was 0.08 s (0.05 to 0.12) in normal subjects and 0.09 s (0.06 to 0.12) in patients with COPD. Furthermore, for a given trigger sensitivity, TDtr was similar in the two groups of subjects. Non-triggering inspiratory efforts decreased and autocycling episodes increased with increasing trigger sensitivity in both groups (p<0.01 for both; table 2). For any given level of trigger sensitivity, autocycling episodes were similar in the two groups, whereas non-triggering inspiratory efforts were more frequent in patients with COPD than in normal subjects (p<0.05). The combination of NEEP and NPV resulted in a significant decrease in non-triggering inspiratory efforts in patients with COPD at any given level of trigger sensitivity (8.5 (1.5)%, 4.2 (0.8)%, and 1.6 (0.4)% at 50%, 75%, and 100% of maximum trigger sensitivity, respectively, p < 0.01).

PTPdi was markedly reduced during each trial of NPV compared with spontaneous breathing both in normal subjects and in COPD patients (p<0.001; fig 2), and increasing trigger sensitivity caused a progressive decrease in PTPdi in both groups of subjects. The mean difference (95% CI) between spontaneous breathing and NPVtr100 was 10.9 cm H₂O.s (9.4 to 12.3) in normal subjects and 12.2 (8.3 to 16.1) in patients with COPD.

During spontaneous breathing all patients had dynamic PEEPi (4.3 (0.6) cm H_2O) that did not change significantly during trials of NPV (table 3). The combination of NEEP with NPV caused a significant reduction in dynamic PEEPi at any given level of trigger sensitivity (p<0.001; table 3); this reduction was associated with a significant shortening in both TDPEEPi and TdPEEPi+tr at any given level of trigger sensitivity



Figure 2 Pressure-time product per breath of the diaphragm (PTPdi) in (A) normal subjects and (B) patients with an acute exacerbation of COPD during spontaneous breathing (SB) and during negative pressure ventilation with trigger sensitivity set at 50% (Tr50), 75% (Tr75), and 100% (Tr100) of maximum trigger sensitivity.

Table 3 Dynamic is a cute exacerbat	ntrinsic PEEP and partit ion of COPD during NF	tioning of diaphragm effort in patients PV	
	Partitioni	ng of diaphragm effort	

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	PEEPi (cm H ₂ O)	PTPdipeepi (cm H ₂ O.s)	PTPdiTr (cm H ₂ O.s)	PTPdiPost (cm H ₂ O.s)			
NPVtr50	3.9 (0.6)	2.1 (0.4)	1.4 (0.2)	7.5 (1.6)			
NPVtr75	3.6 (0.5)	1.7 (0.3)	1.0 (0.1)	6.1 (1.2)			
NPVtr100	3.7 (0.4)	1.8 (0.3)	0.8 (0.1)	5.4 (1.1)			
NPV-NEEPtr50	1.8 (0.4)	0.9 (0.3)	1.0 (0.1)	7.0 (1.5)			
NPV-NEEPtr75	1.8 (0.3)	1.0 (0.3)	0.8 (0.1)	5.9 (1.0)			
NPV-NEEPtr100	1.9 (0.4)	0.7 (0.3)	0.6 (0.1)	5.8 (0.9)			
Values are mean (SE). NPV=negative pressure ventilation; NEEP=negative extrathoracic end expiratory pressure; tr50, tr75, tr100=trigger sensitivity set at 50%, 75%, and 100% of maximum trigger sensitivity; PTPdi=pressure/time product of the diaphragm; PEEPi=dynamic intrinsic positive end expiratory alveolar pressure; Tr=trigger phase; Post=post-trigger phase.							

(p<0.005, and p<0.01, respectively; fig 3). The partitioning of diaphragm effort is shown in table 3. During NPV increasing trigger sensitivity caused a significant reduction in both PTP-diTr (mean difference between NPVtr50 and NPVtr100 0.6 cm H₂O.s, 95% CI 0.3 to 0.9, p=0.001) and PTPdiPost (mean difference between NPVtr50 and NPVtr100 2.1 cm H₂O.s, 95% CI 0.8 to 3.4, p< 0.01), whereas PTPdiPEEPi did not change significantly. The addition of NEEP to NPV resulted in a significant decrease in PTPdiPEEPi (p<0.001) and PTPdiTr (p<0.01) at any given level of trigger sensitivity.

DISCUSSION

The present study provides evidence that, using a microprocessor based iron lung capable of thermistor triggering, it was possible: (1) to provide NPV in assist mode with a time delay of the trigger of about 0.2 s at the maximum sensitivity and a low rate of non-triggering inspiratory efforts; (2) to decrease markedly the pressure-time product of the diaphragm compared with spontaneous breathing both in normal subjects and in patients with an acute exacerbation of COPD; (3) to reduce the total time delay between the onset of inspiratory effort and the start of assisted breathing and nontriggering inspiratory efforts with the combination of NEEP and NPV.

Negative pressure ventilation is traditionally delivered in control mode15 and it has been reported that control NPV provided by iron lung is successful in patients with COPD and severe hypercapnic encephalopathy.1 In patients with preserved neural drive, however, controlled mechanical ventilation may cause asynchrony with the ventilator resulting in discomfort, excessive inspiratory muscle effort, and gas exchange deterioration.16 To overcome this limitation some negative pressure ventilators have incorporated patient triggered modes using pressure changes sensed via nasal prongs.¹⁵ Aaron and coworkers¹⁷ have recently evaluated the effectiveness of these pressure triggers in normal subjects. They found them to be slow (time delay 0.48-0.39 s) and insensitive to the inspiratory effort of subjects (non-triggering inspiratory effort ranging from 6% to 90% of total breaths), allowing a slight reduction in diaphragm effort. In the present study we used a microprocessor based iron lung capable of thermistor triggering and found that, in normal subjects, the time delay ranged from 0.29 s to 0.21 s with increasing trigger sensitivity, non-triggering inspiratory efforts ranged from 8.2% to 1.2%, and the PTPdi was reduced to 18% of the control value. In patients the time delay of triggering was similar, non-triggering inspiratory effort ranged from 11.8% to 2.5%, and the PTPdi was reduced to 38% of the control value. Although the time delay of the thermistor trigger we studied



Figure 3 Time delay between the onset of inspiratory effort and the start of inspiratory flow (TDPEEPI), time delay between the onset of inspiratory flow and the start of assisted breath (TDtr), and total time delay between the onset of inspiratory effort and the start of assisted breath (TDrEPI+tr) in patients with an acute exacerbation of COPD during negative pressure ventilation (NPV, black bars) and during the combination of negative extrathoracic end expiratory pressure (NEEP) with NPV (white bars). Values are mean (SE). Tr50, Tr75, and Tr100 indicate trigger sensitivity set at 50%, 75%, and 100% of maximum trigger sensitivity, respectively. *p<0.01, NPV versus NEEP + NPV.

was longer than those of the most recent flow and pressure triggering systems of positive pressure ventilators,¹⁸ the findings of our study suggest that the microprocessor based iron lung we used represents a major improvement, allowing use of assist NPV with an acceptable patient/ventilator interaction. In this short term physiological study, subjects wore a face mask and the thermistor trigger was placed at the free way line of the pneumotachograph connected to the face mask. This experimental set up was well tolerated by all subjects and it was necessary to measure airflow and to compute the time delay of trigger, dynamic PEEPi, and the partitioning of PTPdi (see Methods). Further long term studies with the thermistor placed directly in front of the nares and mouth, as during sleep studies, are necessary to assess the performance of this technology in a clinical setting.

In patients with an acute exacerbation of COPD, PEEPi associated with dynamic hyperinflation is frequently observed^{19 20} and acts as an inspiratory threshold load which must be fully counterbalanced by the inspiratory muscles before triggering the ventilator.²¹ As a result, the inspiratory effort exerted in the pre-trigger phase and the time delay between the onset of the inspiratory effort and the start of assisted breathing are increased, causing patient discomfort and patient/ventilator asynchrony.²² Nava and coworkers²³ have recently shown in a group of patients with COPD that, during face mask pressure support ventilation (Bird 8400 STi ventilator) with pressure triggering set at -1 cm H₂O, the TDPEEPi+tr averaged 0.21 s and the effort required to overcome dynamic PEEPi was about 17% of the pressure-time product of the inspiratory muscles. Furthermore, Leung and coworkers²⁴ reported that, in 11 patients (eight with COPD) treated with different assisted modes of invasive mechanical ventilation (Puritan Bennett 7200a ventilator) and pressure triggering set at $-1 \text{ cm H}_2\text{O}$, the TDPEEPi+tr averaged 0.39 s and non-triggering inspiratory effort occurred with all modes. In line with these findings, we found that, in patients with COPD, during NPV at maximum trigger sensitivity the TDPEEPi+tr was 0.34 (0.02) s, the PTPdiPEEPi was 22.5% of total PTPdi, and non-triggering inspiratory efforts were more frequent than in normal subjects.

The application of an external PEEP less than static PEEPi during positive pressure ventilation may reduce diaphragm effort and non-triggering inspiratory efforts, improving patient/ventilator interaction.^{25 26} In patients with PEEPi associated with dynamic hyperinflation, the physiological effect on inspiratory muscle function of the application of NEEP during NPV should be similar to that of external PEEP during positive pressure ventilation. In the present study we found that, in patients with COPD with acute respiratory failure, low values of NEEP added to NPV counterbalanced PEEPi and significantly reduced both TDPEEPi+tr and the diaphragm effort exerted in the pre-trigger phase (PTPdiPEEPi and PTPdiTr). As a consequence, patient/ventilator interaction was improved, as shown by the reduction in non-triggering inspiratory efforts. Because it is very difficult to obtain reliable measurements of static PEEPi in conscious patients with an acute exacerbation of COPD and because the relationship between static PEEPi and dynamic PEEPi, even corrected for abdominal muscle contraction, is affected by several factors,^{13 27} we did not titrate NEEP on the basis of the individual values of dynamic PEEPi. As suggested for the use of external PEEP during positive pressure ventilation,²⁸ a low value of NEEP was used in all the studied patients to minimise the risk of pulmonary hyperinflation.

In conclusion, we have shown that a microprocessor based iron lung capable of thermistor triggering was able to perform assist NPV with a marked reduction in diaphragm effort and a low rate of non-triggering inspiratory effort both in normal subjects and in patients with an acute exacerbation of COPD. It also appears that NEEP added to NPV improves the patient/ ventilator interaction, reducing the diaphragm effort in the pre-trigger phase and non-triggering inspiratory efforts. Further studies are needed to evaluate the role of assist NPV in a clinical setting.

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