ORIGINAL ARTICLES

Physiologic Effects of Noninvasive Ventilation in Patients With Chronic Obstructive Pulmonary Disease

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OBJECTIVE: Noninvasive mechanical ventilation has been of use in the treatment of some forms of chronic and acute respiratory failure. However, the benefits of its use in patients in the stable phase of severe chronic obstructive pulmonary disease (COPD) remain unclear. A combination of continuous positive airway pressure (CPAP) and pressure support ventilation (PSV) may improve respiratory mechanics and alveolar ventilation, and reduce inspiratory muscle effort. In this study, we analyzed the physiologic effects of differing levels of CPAP and CPAP plus PSV in patients with stable severe COPD.

PATIENTS AND METHODS: Work of breathing, breathing pattern, oxygen saturation measured by pulse oximetry, PaO_2, and $PaCO_2$ were analyzed in a group of 18 patients under the following conditions: *a)* baseline; *b)* CPAP, 3 cm H_20; *c)* CPAP, 6 cm H_20; *d)* CPAP 3 cm H_20 plus PSV 8 cm H_20; and *e)* CPAP 3 cm H_20 plus PSV 12 cm H_20.

RESULTS: CPAP at pressures of 3 and 6 cm H_20 was associated with an increase in tidal volume (V_T) from a mean (SD) baseline value of 0.52 (0.04) L to 0.62 (0.04) and 0.61 (0.03) L, respectively. Minute ventilation increased from 8.6 (0.5) L/min to 10.8 (0.6) and 10.9 (0.5) L/min, respectively. Mean inspiratory flow (V_T/Ti) increased from 0.35 (0.02) L/s to 0.44 (0.02) and 0.41 (0.02) L/s, respectively, and dynamic intrinsic positive end-expiratory pressure (PEEPi,dyn) was reduced from 1.63 (0.7) cm H_20 to 1.1 (0.06) and 0.37 (0.4) cm H_20, respectively. CPAP did not reduce the work of breathing. Association of CPAP at 3 cm H_20 with PSV of 8 or 12 cm H_20 increased V_T to 0.72 (0.07) and 0.87 (0.08) L, respectively, while minute ventilation increased to 12.9 (0.8) and 14.9 (1.1) L/s, respectively. Mean inspiratory flow also increased to 0.50 (0.03) and 0.57 (0.03) L/s, respectively. Work of breathing was reduced from 0.90 (0.01) J/L to 0.48 (0.06) and 0.30 (0.06) J/L, respectively, while PEEPi,dyn increased to 1.30 (0.02) and 2.42 (0.08) cm H_20, respectively. With combined CPAP of 3 cm H_20 and PSV of 12 cm H_20, $PaCO_2$ was reduced from a baseline value of 41.2 (1.5) mm Hg to 38.7 (1.9) mm Hg. All of the changes were statistically significant ($P<.05$).

CONCLUSIONS: CPAP of 3 cm H_20 in combination with PSV improved breathing pattern, increased alveolar ventilation, and reduced work of breathing. These results offer a rational basis for the use of noninvasive mechanical ventilation in the treatment of patients with stable severe COPD.

Key words: *Noninvasive ventilation. Pressure support ventilation. Chronic respiratory failure. Work of breathing. Pulmonary disease, chronic obstructive. COPD. Continuous positive airway pressure.*

Efectos fisiológicos de la ventilación no invasiva en pacientes con EPOC

OBJETIVO: La ventilación mecánica no invasiva ha sido útil en el tratamiento de algunas formas de insuficiencia respiratoria aguda y crónica. Sin embargo, sus posibles beneficios para pacientes con enfermedad pulmonar obstructiva crónica (EPOC) grave en fase estable continúan siendo objeto de controversia. La combinación de presión positiva continua de la vía aérea (CPAP) y presión de soporte (PS) puede mejorar la mecánica respiratoria, el trabajo muscular y la ventilación alveolar. Estudiamos los efectos fisiológicos de diferentes cifras de CPAP y CPAP + PS en pacientes con EPOC grave en fase estable.

PACIENTES Y MÉTODOS: En 18 pacientes se determinaron el trabajo respiratorio, el patrón respiratorio, la oximetría de pulso y los gases sanguíneos en las siguientes condiciones: *a)* basal; *b)* CPAP: 3 cmH_2O; *c)* CPAP: 6 cmH_2O; *d)* CPAP + PS: 3 y 8 cmH_2O, respectivamente, y *e)* CPAP + PS: 3 y 12 cmH_2O, respectivamente.

RESULTADOS: La CPAP de 3 y 6 cmH_2O se asoció con aumento del volumen corriente (Vc), que de un valor basal medio (± desviación estándar) de 0,52 ± 0,04 pasó a 0,62 ± 0,04 y 0,61 ± 0,03 l, respectivamente. La ventilación minuto aumentó de 8,6 ± 0,5 a 10,8 ± 0,6 y 10,9 ± 0,5 l/min, respectivamente. El flujo medio inspiratorio (Vc/Ti) pasó de 0,35 ± 0,02 a 0,44 ± 0,02 y 0,41 ± 0,02 ml/min, y la presión positiva al final de la inspiración intrínseca (PEEPi dinámica) disminuyó de 1,63 ± 0,7 a 1,1 ± 0,06 y 0,37 ± 0,4 cmH_2O, respectivamente. La CPAP no disminuyó el trabajo respiratorio. La asociación de CPAP de 3 cmH_2O con PS de 8 y 12 cmH_2O aumentó el Vc a 0,72 ± 0,07 y 0,87 ± 0,08 l, mientras la ventilación minuto aumentó a 12,9 ± 0,8 y 14,9 ± 1,1 l/min, respectivamente. El Vc/Ti también aumentó a 0,50 ± 0,03 y 0,57

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± 0,03 l/s, respectivamente. El trabajo respiratorio disminuyó desde 0,90 ± 0,01 a 0,48 ± 0,06 y 0,30 ± 0,06 J/l, mientras que la PEEPi dinámica aumentó a 1,30 ± 0,02 y 2,42 ± 0,08 cmH_2O, respectivamente. Con CPAP de 3 cmH_2O y PS de 12 cmH_2O la presión arterial de anhídrido carbónico disminuyó de un valor basal de 41,2 ± 1,5 a 38,7 ± 1,9 Torr. Todos estos cambios fueron estadísticamente significativos (p < 0,05).

CONCLUSIONES: El uso de CPAP de 3 cmH_2O con PS mejoró el patrón ventilatorio, aumentó la ventilación alveolar y disminuyó el trabajo respiratorio. Estos resultados ofrecen fundamentos para un uso racional de la ventilación mecánica no invasiva para el tratamiento de los pacientes con EPOC grave en fase estable.

Palabras clave: *Ventilación no invasiva. Presión de soporte. Insuficiencia respiratoria crónica. Trabajo respiratorio. EPOC. Presión positiva continua de la vía aérea.*

Introduction

Noninvasive mechanical ventilation has been of use in the treatment of some forms of chronic and acute respiratory failure, particularly in patients with chronic obstructive pulmonary disease (COPD).[1,2] However, the benefit of its use in patients in the stable phase of severe COPD remains unclear.[3-10] It has been proposed that there is a state of chronic respiratory muscle fatigue explained by excessive mechanical load due to high airflow resistance and pulmonary hyperinflation, which gives rise to an unfavorable force–length relationship and less efficient work of breathing.[1,4,11,12] Thus, noninvasive mechanical ventilation may be beneficial in a number of ways. Application of appropriate continuous positive airway pressure (CPAP) to counteract intrinsic positive end-expiratory pressure (PEEPi) could improve respiratory mechanics and reduce muscle work.[13,14] Also, increasing levels of pressure support reduce work of breathing and increase tidal volume (V_T) and minute ventilation (V_E).[1,4,8,15] A combination of CPAP and pressure support ventilation (PSV) could represent the most physiologically effective approach to noninvasive mechanical ventilation in patients in the stable phase of severe COPD. As yet, there is no formal consensus on the indication for prolonged noninvasive mechanical ventilation in those patients. There are 2 points on which insufficient information is available: firstly, the best technique or combination of techniques to be applied, and secondly, the most appropriate pressures for use in such patients.

The general aims of this study were to analyze the physiologic effects of noninvasive mechanical ventilation with nasal masks using CPAP and CPAP plus PSV in a population of patients with stable severe COPD.

Patients and Methods

Patients

The study was undertaken in the Department of Pathophysiology and the Respiratory Function Laboratory of the Intensive Care Department, Hospital de Clínicas, Montevideo, Uruguay. Informed consent was provided in all cases and the study protocol was approved by the Institutional Review Board. Eighteen patients with severe COPD (mean [SD] forced expiratory volume in 1 second [FEV_1], 38.8% [12.1%]) in the stable phase of the disease were assessed. Diagnosis of COPD was obtained according to the criteria of the American Thoracic Society.[16,17] The demographic, anthropometric, and functional characteristics of the patients are shown in Table 1.

Parameters Measured

All patients were studied in a seated or semireclining position. Noninvasive mechanical ventilation was provided with a BiPAP ventilator (Respironics, Murrysville, Pennsylvania, USA). In all cases, normal treatment was continued for each patient. Airflow (L/s) was measured with a Fleisch pneumotachograph (model 21071B, Hewlett Packard, Palo Alto, California, USA) connected to a flow transducer (model 47304A, Hewlett Packard). The volume was determined by integration of the flow signal (Respiratory Integrator, model 8815A, Hewlett Packard). Airway pressure (cm H_2O) was obtained with a differential pressure transducer. The pressure transducer and pneumotachograph were introduced into the circuit between the nasal mask and the expiratory valve. In this way, airflow could be measured along with inspiratory and expiratory tidal volume. This setup allowed confirmation that the circuit did not contain significant leaks. Changes in pleural pressure were estimated by measurement of esophageal pressure (cm H_2O). This was measured by inserting a balloon catheter in the middle third of the esophagus and connecting it to a differential pressure transducer (Microswitch, Freeport, Illinois, USA), according to the technique described by Baydur et al[18] (described in more detail below). All signals were digitized with an analog-to-digital converter connected to a computer at a sampling rate of 100 Hz. Analysis of respiratory pattern and mechanics was performed with a signal analysis program designed in our laboratory (Monse 90, Montevideo, Uruguay). V_E (L/min), V_T (L), inspiratory time (T_I, seconds), expiratory time (T_E, seconds), total length of respiratory cycle (T_{TOT}, seconds), breathing rate (cycles/min), mean inspiratory flow (V_T/T_I, mL/s), duty cycle (T_I/T_{TOT}), dynamic PEEPi (PEEPi,dyn, cm H_2O), and work of breathing (J/L) were obtained using the mean of at least 10 successive respiratory cycles from recordings of airway pressure, airflow, volume, and esophageal pressure. PEEPi,dyn was measured as the

TABLE 1
Demographic, Anthropometric, and Functional Characteristics of the Patients Studied*

Age, y	65.6 (5.8)
Sex, women/men	2/16
BMI, kg/m^2	25.4 (7.41)
pH	7.39 (0.03)
$PaCO_2$, mm Hg	42.4 (6.3)
PaO_2, mm Hg	71.9 11.8)
HCO_3^-, mEq/L	25.1 (1.9)
FEV_1, %	38.8 (12.1)
VC, %	80 (14.9)
FEV_1/FVC, %	40.7 (12,3)
FRC, %	154 (42.2)
RV, %	188 (64.7)
TLC, %	112 (21.9)

*Data are shown as means (SD), except where otherwise indicated.
TLC indicates total lung capacity; VC, vital capacity; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; HCO_3^-, plasma bicarbonate; BMI, body mass index; RV, residual volume.

reduction in esophageal pressure, in cm H_2O, from the beginning of inspiratory muscle work until the onset of inspiratory flow.[19] Mechanical work of breathing was calculated using the Campbell diagram,[20] taking chest wall compliance as equivalent to 5% of the theoretical vital capacity for each patient. This method allowed analysis of mechanical work of breathing with its 2 main components: elastic work of breathing (J/L) and resistive work of breathing (J/L).

Study Protocol

The clinical study was prospective. Measurements were performed with the patients in a seated or semireclining position with a fraction of inspired oxygen of 0.21. Following topical anesthesia (10% lidocaine gel) an esophageal balloon catheter was introduced nasally and passed down to the stomach. The balloon was inflated with 0.5 mL of air and it was confirmed that positive deflections were present in the pressure recordings coinciding with respiratory effort. Then, with the balloon deflated, the catheter was withdrawn approximately 10 cm to situate it in the middle third of the esophagus, at which point it was reinflated with the same volume of air. Under those conditions, the optimal position was determined using the occlusion test.[18]

Airflow, volume, airway pressure, and esophageal pressure were recorded after a 30-minute period in each of the following conditions: *a)* baseline; *b)* CPAP 3 cm H_20; *c)* CPAP 6 cm H_20; *d)* CPAP 3 cm H_20 plus PSV 8 cm H_20; and *e)* CPAP 3 cm H_20 plus PSV 12 cm H_20.

Breathing pattern was recorded under baseline conditions by connecting the pneumotachograph and the airway pressure transducer to a mouthpiece, using a nose clip to prevent air leakage through the nostrils. When the patient received noninvasive mechanical ventilation, those recording devices were inserted between the nasal mask and the expiratory valve of the equipment. In each of those conditions, arterial oxygen saturation was monitored continuously by pulse oximetry (SpO_2). Samples of arterial blood were also obtained from the radial or pedal artery for blood gas analysis under 3 different conditions: baseline, CPAP 6 cm H_2O, and CPAP 3 cm H_2O plus PSV 12 cm H_2O.

Statistical Analysis

Data are shown as means (SD). Differences between treatments were assessed by analysis of variance (ANOVA) for repeated samples. Differences between groups of paired data were assessed by Student *t* test with Bonferroni correction, using the data obtained by ANOVA. A value of *P* less than .05 was considered statistically significant.

Results

Noninvasive mechanical ventilation by nasal mask at the levels of CPAP and PSV used were well tolerated in all cases. The protocol did not have to be suspended at any point for discomfort, lack of adaptation, dyspnea, air leaks, or any other complication arising from use of the technique. The main results of the study are shown in Table 2. V_E displayed a significant increase over baseline values with application of both levels of CPAP and both combinations of CPAP and PSV ($P<.05$). This was accompanied by a significant increase in V_T over baseline ($P<.05$) without any notable change in breathing rate or duty cycle. In parallel, a significant increase was observed in mean inspiratory flow in all 4 of the conditions analyzed ($P<.05$) (Figure 1). Significant reductions in elastic work, resistive work, and total work of breathing were only observed with combined CPAP and PSV ($P<.05$) (Figure 2). PEEPi,dyn at baseline was 1.63 (0.7) cm H_2O; a significant reduction in that value was observed with CPAP at both of the pressures used and with the addition of PSV at 8 cm H_2O ($P<.05$), while application of PSV at 12 cm H_2O caused an increase in PEEPi,dyn compared with baseline ($P<.05$). SpO_2 and PaO_2 did not display statistically significant changes under any of the conditions analyzed. There was a significant decrease in $PaCO_2$ from baseline levels with CPAP 3 cm H_2O plus PSV 12 cm H_2O ($P<.05$).

TABLE 2
Respiratory Parameters Under the Conditions Analyzed*

	Baseline	CPAP 3 cm H_2O	CPAP 6 cm H_2O	CPAP 3 cm H_2O Plus PSV 8 cm H_2O	CPAP 3 cm H_2O Plus PSV 12 cm H_2O
V_E, L/min	8.60 (0.5)	10.8 (0.6)†	10.9 (0.50)†	12.9 (0.8)†	14.9 (1.1)†
V_T, L/min	0.52 (0.04)	0.62 (0.04)†	0.61 (0.03)†	0.72 (0.07)†	0.87 (0.08)†
BR, cycles/min	17.7 (1.1)	17.8 (0.90)	18.4 (0.9)	18.7 (0.9)	18.0 (0.9)
V_T/T_I, L/s	0.35 (0.02)	0.44 (0.02)†	0.41 (0.02)†	0.50 (0.03)†	0.57 (0.03)
T_I/T_{TOT}	0.41 (0.04)	0.42 (0.04)	0.45 (0.10)	0.43 (0.04)	0.44 (0.06)
EWB, J/L	0.25 (0.10)	0.26 (0.16)	0.24 (0.08)	0.15 (0.12)†	0.09 (0.05)†
RWB, J/L	0.63 (0.26)	0.57 (0.17)	0.55 (0.18)	0.36 (0.19)†	0.24 (0.17)†
TWB, J/L	0.90 (0.01)	0.78 (0.05)	0.76 (0.04)	0.48 (0.06)†	0.30 (0.06)†
PEEPi,dyn, cm H_2O	1.63 (0.7)	1.10 (0.06)†	0.37 (0.4)†	1.30 (0.02)†	2.42 (0.08)†
SaO_2, %	94.3 (0.7)	94.7 (0.6)	93.6 (0.9)	95.3 (0.7)	94.4 (0.9)
PaO_2, mm Hg	71.3 (2.5)		70.4 (2.1)		72.8 (3.0)
$PaCO_2$, mm Hg	41.2 (1.5)		41.3 (1.9)		38.7 (1.9)†

*Data are shown as means (SD).
CPAP indicates continuous positive airway pressure; PSV, pressure support ventilation; V_E, minute ventilation; V_T, tidal volume; BR, breathing rate; V_T/T_I, mean inspiratory flow; T_I/T_{TOT}, duty cycle; EWB, elastic work of breathing; RWB, resistive work of breathing; TWB, total work of breathing; PEEPi,dyn, dynamic intrinsic positive end-expiratory pressure; SaO_2, arterial oxygen saturation.
†$P<.05$ compared with baseline.

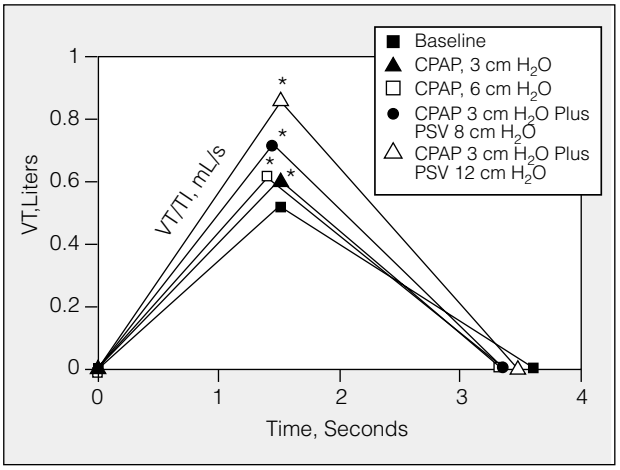

Figure 1. Schematic representation of the respiratory cycle over time under the conditions studied. Provision of continuous positive airway pressure (CPAP) plus pressure support ventilation (PSV) led to a significant increase in tidal volume (V_T) and mean inspiratory flow (V_T/T_I) compared with baseline (*P*<.05). No significant changes were observed in the length of the respiratory cycle. **P*<.05.

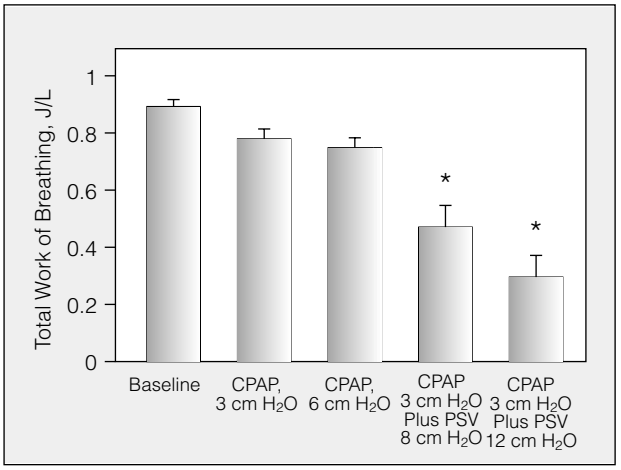

Figure 2. Work of breathing under the conditions analyzed. Bars show mean values; whiskers indicate SD. Provision of increasing levels of pressure support ventilation (PSV) led to a significant reduction in work of breathing (*P*<.05). CPAP indicates continuous positive airway pressure. **P*<.05.

Discussion

Noninvasive mechanical ventilation using a nasal mask was well tolerated, as no air leaks, discomfort, or patient–ventilator asynchrony were observed.[21] It has been reported that CPAP improves gas exchange during acute exacerbations of COPD, while this remains to be demonstrated conclusively outside of periods of exacerbation.[14,22] However, CPAP may also provide benefits by counteracting PEEPi and reducing work of breathing and the energy requirements for initiating respiration.[19,22,23] O'Donoghue et al[24] studied the effects of CPAP on lung volumes in stable COPD and showed that values of CPAP close to 10 cm H_2O reduced PEEPi and muscle work, with a significant increase in lung volume. In our study, CPAP at 3 and 6 cm H_2O counteracted PEEPi,dyn without significant alteration in work of breathing. However, we can not draw any conclusions regarding its effects on lung volumes and this failure represents a methodological limitation of the study. As mentioned, work of breathing was calculated based on the areas under the curves for esophageal pressure and volume.[25] Since there may be an isometric contraction at the beginning of inspiration to counteract PEEPi, work of breathing may therefore be underestimated in such a calculation. Consistent with previous reports, all of the patients included in our study had relatively low PEEPi,dyn, around 2 to 3 cm H_2O.[24,26] Although CPAP of 3 to 6 cm H_2O led to a significant increase in V_E, V_T, and V_T/T_I, no significant changes were observed in breathing rate or the distribution of times in the respiratory cycle. Various factors should be taken into consideration in interpreting the changes in $PaCO_2$. Firstly, the circuit used did not contain a valve to prevent rebreathing. Consequently, the lack of reduction in $PaCO_2$ in parallel with increased V_E and V_T could be due, at least in part, to rebreathing of exhaled breath.[27,28] It can be concluded that CPAP applied at these pressures, despite causing a reduction in PEEPi,dyn, did not contribute to reducing work of breathing or to improving gas exchange.

The assistance provided by PSV for work of breathing is particularly important for patients with COPD. When the respiratory muscles are permanently subjected to unfavorable mechanical conditions, they enter a state of chronic fatigue that compromises their functional reserve.[11] In exacerbations of chronic respiratory failure, noninvasive mechanical ventilation reduces hypercapnia, raises arterial pH, and reduces the requirement for tracheal intubation and invasive mechanical ventilation, and also reduces mortality and length of hospital stay.[1,29,30] PSV also reduces electromyographic activity and diaphragmatic effort both in the stable phase and in exacerbations of the disease.[8,12,15] However, the benefit of noninvasive mechanical ventilation in patients with stable severe COPD remains unclear.[3-9,17,31] The greatest benefit could probably be obtained in the most severe disease, particularly in the presence of hypercapnia. The reduction in $PaCO_2$ obtained with noninvasive mechanical ventilation has been attributed to an improvement in alveolar ventilation and a possible recovery from respiratory muscle fatigue as a result of reduced muscle work.[4-6] In this study, PSV 12 cm H_2O was associated with an increase in V_T, V_E, and V_T/T_I, reduced $PaCO_2$, and a reduction in work of breathing. It can be inferred, then, that the reduction in $PaCO_2$ was the result of improved alveolar ventilation and a reduction in the metabolic production of carbon dioxide. As mentioned, the absence of a valve to prevent rebreathing may have led to partial rebreathing of exhaled breath, and that could have limited the effects of improving breathing pattern. Thus, inclusion of a valve in the circuit might lead to greater reduction of $PaCO_2$.

PSV at 12 cm H_2O led to a slight but significant increase in PEEPi,dyn. The can be attributed to the increased airflow and tidal volume generated by the technique.[4,5] Nevertheless, a reduction in elastic work of breathing was also seen. Given that no changes in oxygenation of arterial blood were observed, the reduction in $PaCO_2$ can be attributed to increased alveolar ventilation. This would be consistent with the findings of Díaz et al,[32] who found no changes in the ventilation–perfusion ratio under these conditions.

Some limitations derived from the design of the protocol are worthy of special consideration. The short period during which each of the ventilation profiles was applied may suggest that a study performed over a longer period would improve the results obtained. The effect of noninvasive mechanical ventilation on alveolar ventilation could have been improved with a valve included in the circuit to prevent rebreathing. The data-collection system required a pneumotachograph and connections for the measurement of pressures and airflow. The increase in dead space that could have been introduced as a consequence should be taken into account when interpreting the results.

In summary, we have shown that noninvasive mechanical ventilation is well tolerated in patients with stable severe COPD and, in physiologic terms, is beneficial when an appropriate combination of CPAP and PSV is applied. This allows improvement of breathing pattern and alveolar ventilation, leading to a reduction in work of breathing. Discussion of the possible benefits of noninvasive mechanical ventilation for the long-term treatment of this type of patient should be based on knowledge of the physiologic effects of the technique.

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