Nonchemical influence of inspiratory pressure support on inspiratory activity in humans

BRIGITTE FAUROUX,1 DANIEL ISABEY,2 GILBERT DESMARAI,2 LAURENT BROCHARD,1 ALAIN HARF,1 AND FRÉDÉRIC LOFASO1

1Service de Physiologie, Explorations Fonctionnelles, Institut National de la Santé et de la Recherche Médicale U 492, Hôpital Henri Mondor, 94010 Créteil; and 2Ecole Supérieure d'Ingénieurs en Electrotechnique et Electronique, 93160 Noisy le Grand, France

Fauroux, Brigitte, Daniel Isabey, Gilbert Desmarais, Laurent Brochard, Alain Harf, and Frédéric Lofaso. Nonchemical influence of inspiratory pressure support on inspiratory activity in humans. J. Appl. Physiol. 85(6): 2169-2175, 1998.—To determine whether nonchemical inhibition of respiratory activity occurs during inspiratory pressure support (IPSV) ventilation, respiratory motor output (in 9 subjects), obtained by calculating transdiaphragmatic pressure-time products, and central respiratory output (in 5 subjects), obtained by integrating the electromyographic activity of the diaphragm (EMGdi) during mechanical inspiratory time, EMGdi per minute, and electrical inspiratory time, as determined from onset to peak EMGdi, were compared during spontaneous ventilation (control) and IPSV with (IPSV + CO2) and without (IPSV) correction of hypocapnia. Both IPS and IPS + CO2 induced significant decreases in transdiaphragmatic pressure-time products (46 ± 31 and 53 ± 23%, respectively), EMGdi during mechanical inspiratory time (49 ± 12 and 57 ± 14%, respectively), EMGdi per minute (65 ± 22 and 69 ± 15%, respectively), and electrical inspiratory time (73 ± 8 and 65 ± 6%, respectively). Because correction of hypocapnia failed to eliminate the marked inhibition of both respiratory and central motor output seen with IPS, we conclude that nonchemical inhibition of respiratory activity occurs during IPSV.

METHODS

INSPIRATORY PRESSURE support ventilation (IPSV) is a popular form of partial ventilation that can be used in spontaneously breathing patients in a variety of clinical situations, including weaning from mechanical ventilation (16) and noninvasive ventilatory support in acute (5) and chronic (30) respiratory failure. During IPSV, each spontaneous breath is assisted by a constant level of positive pressure applied throughout inspiration. As a result, when ineffective effort and double triggering are not observed, breathing frequency is determined by the patient, and tidal volume (VT) depends on the combined action of the pressure generated by the inspiratory muscles, the ventilator, and the impedance of the respiratory system (25).

IPSV has been shown to increase alveolar ventilation and to reduce inspiratory effort (2, 12, 17, 25). The mechanism of inspiratory muscle inhibition during IPSV is not clear. A reduction in arterial PCO2 (PaCO2) may be an important cause of respiratory muscle inhibition during IPSV. However, IPSV may also have a substantial inhibitory effect on respiratory activity even in the absence of PaCO2 changes. Two studies that compared inspiratory activity at the same end-tidal PCO2 (PETCO2) with and without IPSV found evidence of nonchemical inhibition of inspiratory activity during IPSV. Shams and Scheid (26) reported that anesthetized cats exhibited inhibition of inspiratory activity during IPSV, which persisted in part after correction of hypocapnia but was abolished when correction of hypocapnia was combined with vagotomy. However, these findings may not be generalizable to humans because vagal influences in humans are fairly weak. Scheid et al. (25) evaluated respiratory responses to inhaled CO2 in normal human subjects during IPSV and found that IPSV effectively increased ventilation and reduced inspiratory activity at any given PETCO2. However, they assessed respiratory center output on the basis of the occlusion pressure P0.1, which only reflects the initial part of the respiratory drive and is only minimally informative as to what happens later during inspiration.

We conducted a study in healthy humans during IPSV in which 1) the PETCO2 level was controlled by addition of CO2 to the inspired air and 2) respiratory motor output was evaluated by recording esophageal (Pes) and transdiaphragmatic pressures (Pdi) and central respiratory output by recording the electrical activity of the diaphragm. Our objective was to determine the relative contributions of reduced PETCO2 and mechanical unloading to inspiratory activity inhibition during IPSV. Specifically, we compared the parameters of inspiratory activity during spontaneous ventilation and IPSV before and after returning PETCO2 to its spontaneous level by adding CO2 to the inspired air during IPSV.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
INSPIRATORY ACTIVITY DURING PRESSURE SUPPORT

During pressure support (IPS), whereas during the other it contained CO2 in the inhaled gas was air during one period and 21% O2 and the remainder N2 (IPS-CO2) in the concentration needed to obtain a PETCO2 level identical to, or no more than, 1 Torr above the level noted during the control 1 period. Air and the CO2-corrected mixture were tested in random order.

Data Analysis

The variables were analyzed, after stabilization, between minutes 10 and 12 of each period.

The following variables were read by breath: mechanical inspiratory time (mTI), as the onset of the inspiratory flow to the onset of the expiratory flow; mechanical expiratory time (mTE), as the remainder of the total breath duration; VT from the calibrated integrated flow signal; and PETCO2, as the peak of the airway CO2 record. From these, the following parameters were calculated by breath: total inspiratory time, Ttot (mTI + mTE), respiratory rate [RR = 1/(mTI + mTE)], and total ventilation [minute ventilation (VE) = VT · RR].

Intrinsic positive end-expiratory pressure (PEEPi) was measured as the amplitude of the negative deflection of Pes between the onset of inspiratory effort and the onset of inspiratory flow. Respiratory motor output was evaluated on the basis of the transdiaphragmatic pressure-time product (PTPdi).

We computed PTPdi as the area subtended by transdiaphragmatic pressure (Pdi; Pdi = gastric pressure – Pes) above the end-expiratory baseline over inspiratory time (16). PTPdi was multiplied by the respiratory frequency and expressed in centimeters of water per second per minute.

In addition, the positive deflection of Pdi (ΔPdi) was measured at 250 (ΔPdi250) and 500 ms (ΔPdi500) after the onset of inspiratory activity, detected by the onset of esophageal negative deflection.

Central respiratory output was evaluated from EMGdi. The EMGdi signal was band-pass filtered between 20 Hz and 1 kHz. The artifacts caused by the electrocardiogram were manually gated off. In addition, the signal was rectified and was processed in two different ways according to Lopez et al. (19), involving 1) integration to obtain the total electrical activity per breath (integrated EMGdi) and 2) averaging over 200-ms intervals to obtain a moving-time average signal.

Because the EMGdi signal continued into expiration during control periods and because end inspiration may be passive during IPSV (2), integrated activity per breath was determined not only during mTI but also during Ttot. These parameters are referred to as respiratory-integrated EMG (EMGdi,mTI) and total integrated EMGdi (EMGdi,Ttot). In addition, because respiratory frequency might change across periods and because we wished to quantify diaphragm electrical activity independently from Ttot, integrated EMG activity was also expressed per minute (EMGdi,min). Furthermore, the peak inspiratory amplitude of the moving-time average signal (EMGdi,peak) and the electrical inspiratory time (eTI), as determined from onset to peak EMGdi, were also measured.

EMGdi parameters were expressed as percentages of the mean of the two control periods.

Individual mean values were calculated for each variable in a given session by averaging the breath-by-breath variables during the last 2 min of the recordings for each period.

Possible changes in end-expiratory volume associated with IPSV were analyzed by using inductive plethysmography when control 1 was abruptly replaced by an IPSV period (IPS or IPS-CO2) and when an IPSV period was abruptly replaced by control 2.
INSPIRATORY ACTIVITY DURING PRESSURE SUPPORT

Statistical Analysis

Results are presented as means ± SD. For all data, except the EMG data, statistical differences among the four periods were tested by using analysis of variance for repeated measurements. In addition, analysis of variance takes into account the order in which subjects received IPS and IPS + CO2. When appropriate (F-test with P < 0.05), pairwise comparisons were performed by using Fisher’s least statistical difference test.

Concerning the EMG data, statistical differences among the four periods were tested by using the nonparametric Friedman test. The 5% level was chosen as significant. When a significant difference was observed, bilateral comparisons were performed by using the Wilcoxon signed-rank test.

RESULTS

Figure 1 shows examples of recordings during control, IPS, and IPS + CO2 periods.

Analysis of variance for repeated measurements did not detect any order effect.

No changes in end-expiratory volume were observed when control 1 was abruptly replaced by an IPS period (IPS or IPS + CO2), or when an IPS period was abruptly replaced by control 2. In addition, PEEP was consistently <1 cmH2O, suggesting that all subjects were near the functional residual capacity in all the conditions.

The ventilatory pattern, and PETCO2, PTPdi, ΔPdi250, and ΔPdi500 values observed in each condition are given in Table 1.

PTPdi individual data are shown in Fig. 2.

No differences were found between the two control periods.

IPS induced a significant increase in Vt with no effect on RR (Table 1). Consequently, IPS induced a significant increase in VE and a significant decrease in PETCO2 (Table 1).

Decreases in PTPdi, ΔPdi250, and ΔPdi500 were also seen during IPS (Fig. 2, Table 1).

During IPSV, returning PETCO2 to normal (IPS + CO2) was associated with small but significant increases in the mTtot/Ttot ratio, a slight, nonsignificant increase in RR, and a significant increase in VE (with no effect on Vt) (Table 1). The small VE increase was associated with small, insignificant increases in PTPdi, ΔPdi250, and ΔPdi500 (Table 1, Fig. 2). However, these parameters remained lower during IPS + CO2 than during the control periods, although PETCO2 values were identical (Table 1, Fig. 2).

Table 1. Values of breathing pattern with 4 conditions evaluated

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>IPS</th>
<th>IPS + CO2</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT, ml</td>
<td>597 ± 143</td>
<td>1,103 ± 485*</td>
<td>1,037 ± 265†</td>
<td>631 ± 253</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>13 ± 3.1</td>
<td>12.9 ± 5.7</td>
<td>15.1 ± 4.6</td>
<td>13.7 ± 2.5</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>7.6 ± 1.3</td>
<td>12.3 ± 2.7*‡</td>
<td>14.7 ± 2.1†</td>
<td>8.2 ± 3.2</td>
</tr>
<tr>
<td>mTt/Ttot, %</td>
<td>36 ± 5</td>
<td>25 ± 8*‡</td>
<td>29 ± 5†</td>
<td>36 ± 5</td>
</tr>
<tr>
<td>Vt/Tt, l/s</td>
<td>0.35 ± 0.05</td>
<td>0.88 ± 0.23*</td>
<td>0.87 ± 0.18</td>
<td>0.39 ± 0.19</td>
</tr>
<tr>
<td>PETCO2, Torr</td>
<td>40.2 ± 2.6</td>
<td>30.0 ± 2.9*‡</td>
<td>41.1 ± 2.6</td>
<td>40.1 ± 3.54</td>
</tr>
<tr>
<td>PTPdi, cmH2O·s⁻¹·min⁻¹</td>
<td>253 ± 137</td>
<td>103 ± 73*</td>
<td>131 ± 99</td>
<td>220 ± 64</td>
</tr>
<tr>
<td>ΔPdi250, cmH2O</td>
<td>1.9 ± 0.8</td>
<td>0.8 ± 0.5*</td>
<td>0.9 ± 0.7†</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>ΔPdi500, cmH2O</td>
<td>4.1 ± 1.3</td>
<td>2.1 ± 1.5*</td>
<td>2.8 ± 1.9†</td>
<td>4.1 ± 0.8</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 9 subjects. VT, tidal volume; VE, minute ventilation; mTt/Ttot, mechanical inspiratory time-to-total cycle time ratio; PETCO2, end-tidal CO2 pressure; PTPdi, transdiaphragmatic pressure-time product; ΔPdi250, positive deflection of transdiaphragmatic pressure at 250 ms after onset of inspiratory activity; ΔPdi500, positive deflection of transdiaphragmatic pressure at 500 ms after onset of inspiratory activity. *P < 0.05, IPS vs. control 1 and control 2. †P < 0.05, IPS + CO2 vs. control 1 and control 2. ‡P < 0.05, IPS vs. IPS + CO2.
The main results regarding EMGdi are shown in Fig. 3. We found no differences between IPS and IPS+CO₂. In contrast, all expressions of the integral of EMGdi and eTI during IPS+CO₂ remained lower than during the control periods, despite identical PETCO₂ values (Fig. 3). EMGdi_peak was reduced during IPS and during IPS+CO₂ compared with the control periods (73 ± 8% and 65 ± 6%, respectively), but these differences did not reach statistical significance.

DISCUSSION

Breathing is a complex motor activity originating in a central neural drive located in the medulla and pons. This central neural drive is controlled via reflexes involving specialized organs that sense body fluid composition changes reflecting O₂ demands and CO₂ production. The sensory organs involved in these homeostatic reflexes are peripheral arterial chemoreceptors and central chemoreceptors. However, reflexes initiated by chemoreceptors, i.e., the chemical control of breathing, are not the only mechanisms responsible for the control of breathing. Respiratory control is also influenced by other regions of the brain and by peripheral afferent information from receptors in the airways and respiratory muscles. The resulting pattern of control is efficient and responsive to change. It has been suggested that the peripheral nonchemical receptors sense changes in mechanical conditions of ventilatory loading and adjust the breathing pattern to economize work of breathing (7). In humans, studies of ventilatory loading have found evidence of nonchemical control of respiratory activity (7). A nonchemical influence on inspiratory activity has also been observed during ventilatory unloading by volume-controlled mechanical ventilation (1). As a result of this nonchemical influence, the thoracic displacement induced by volume-controlled mechanical ventilation (CMV) may exert an inhibitory influence on inspiratory activity (1).

Over the last few years, partial ventilatory support techniques such as IPSV and proportional assist ventilation (PAV) have generated considerable interest as an alternative to volume CMV. Partial ventilatory support techniques decrease inspiratory activity, although it is the patient’s inspiratory effort that triggers the ventilator-assisted breath. However, the mechanisms by which partial ventilatory assistance reduces inspiratory neuromuscular output have recently been questioned, and evidence has been found suggesting that nonchemical
inhibition of inspiratory activity may exist during IPSV (26).

Shams and Scheid (26) found that anesthetized cats receiving IPSV exhibited a decrease in respiratory drive as assessed by EMGdi and demonstrated that this decrease was due not only to the induction of hypocapnia but also to influences from vagal afferents. When hypocapnia was corrected by CO₂ inhalation, the amplitude of the iEMG remained reduced during IPSV in comparison with normal breathing. However, these results may not be generalizable to humans because vagal influences in humans are fairly weak. In a study of intensive-care-unit patients, Bonmarchand et al. (4) found that improvement in the shape of the pressure increase during IPSV was associated with a decrease in diaphragmatic activity, although 

\[ \text{Paco}_2 \]

remained unchanged. This finding suggests that nonchemical inhibition of inspiratory activity exists during IPSV and is influenced by the shape of the pressure increase. However, this study was performed in patients with acute respiratory failure, and its results may not apply to patients with chronic respiratory failure or to healthy subjects. Scheid et al. (25) evaluated respiratory responses to inhaled CO₂ in normal human subjects during IPSV and found that IPSV effectively increased ventilation and reduced inspiratory activity at any given PETCO₂. However, they assessed respiratory center output on the basis of the occlusion pressure \( P_{0.1} \), which reflects the initial part of the respiratory drive and is only minimally informative as to what happens later during inspiration. Morrell et al. (20) observed that during non-rapid-eye-movement sleep IPSV caused a decrease in EMGdi, in the absence of any changes in VT, PETCO₂, or respiratory frequency. However, they found no consistent effects on EMGdi in awake subjects. The discrepancies between the findings of Morrell et al. and Scheid et al. may be ascribable to differences in the IPSV devices used. For example, we recently demonstrated (16) that the device used by Morrell et al. was less efficient in reducing inspiratory activity than the one used by Scheid et al.

To further explore in humans and during wakefulness the existence of nonchemical inhibition of ventilatory activity, we conducted a study in healthy volunteers receiving IPSV, in whom 1) the PETCO₂ level was controlled by adding CO₂ to the inspired circuit and 2) both the work performed by the diaphragm and the electrical activity of the diaphragm were evaluated.

The reason for the reduction in PTPdi, \( \Delta P_{d250} \), and \( \Delta P_{d500} \) during IPS and IPS + CO₂ compared with the control conditions is unclear because these indexes reflect not only neural drive but also a number of other factors, including velocity reflected by VT-to-mTi ratio and lung volume changes modified by IPSV. Therefore, we also recorded EMGdi, which provides a more direct assessment of central respiratory output. Because EMGdi is affected by changes in lung volume (8), the recording of EMGdi may not be representative of the central respiratory output. We did not observe changes in end-expiratory volume when control was abruptly replaced by an IPSV period and when the IPSV period was replaced by control. However, an absence of any change in end-expiratory lung volume during transition does not necessarily mean that this parameter remained constant throughout. We therefore studied PEEPi, which remained under 1 cmH₂O during all trials, suggesting that end-expiratory lung volume remained in the vicinity of the functional residual capacity in all conditions. In addition, Gandevia and McKenzie (8) demonstrated that inspiratory output, represented by EMGdi, is overestimated when lung volume is increased, whereas we observed a decrease in EMGdi despite an increase in VT during IPSV. We can therefore assume that the decrease in EMGdi during IPSV cannot be explained by a change in lung volume. Moreover, before starting this study, we tested various conditions of diaphragmatic activity recording, including anchoring of the EMG catheter with an inflated gastric balloon as a means of stabilizing the physical relationship between the electrodes and diaphragm (unpublished observations). We drew conclusions similar to those of Onal et al. (21), who found that changes in electrode position had minimal effects on EMG quantification and that stabilization of the catheter did not improve the reproducibility of EMG data. On the basis of these considerations, we believe that EMG data obtained under the conditions used in our study provide reasonably reliable data on the central neuromuscular output to the diaphragm.

Another key issue is the accuracy of PETCO₂ to track arterial CO₂, especially during mechanical ventilation. Unfortunately, we did not measure the changes in arterial-end-tidal CO₂ difference in the different experimental conditions. However, Simon et al. (29) have previously demonstrated no change in arterial-end-tidal CO₂ difference when spontaneous eupnea was compared with a situation of mechanical hyperventilation (with VT similar to those observed in our study) and isocapnic condition induced, as in our study, by adding CO₂ to the inspiratory circuit. Therefore, we believe that PETCO₂ yields a valid estimate of arterial CO₂ in our study.

Although our subjects had neither previous knowledge of the issue under investigation nor previous experience with respiratory experimentation, we cannot exclude a voluntary response effect. For example, as in other studies (2, 12, 17, 25), the absence of respiratory rate reduction during IPS in the face of major hypocapnia may be ascribable to a voluntary response. However, when we corrected the hypocapnia by adding CO₂ to the inspiratory circuit, we found that the level of respiratory activity still remained lower than during the control periods. This result is in keeping with a study by Morrell et al. (20), in which IPS during non-rapid-eye-movement sleep caused a decrease in EMGdi in the absence of changes in VT, PETCO₂, or respiratory frequency, suggesting that, during IPSV, nonchemical influences on breathing may be initiated during sleep, i.e., in the absence of voluntary responses. Our study suggests that these nonchemical influences may persist during wakefulness, bearing out the hypoth-
However, our analysis compared minutes 10 of the change in PETCO2. Direct comparison of our study to decrease in respiratory motor output was due only to los et al. (10). They demonstrated that during PAV the ventilatory response in the hypercapnic range (see Fig. 1).

A random order. Conceivably, when IPS + CO2 follows a trial of IPS, the hypocapnia during the previous IPS session may continue to influence respiratory motor output for some time during the IPS + CO2 session. However, our analysis compared minutes 10 and 12 of each period, and we consistently found that respiratory parameters stabilized before minute 8 of each period. In addition, our statistical evaluation takes into account the order in which subjects received IPS and IPS + CO2. This order failed to significantly influence the results.

When PETCO2 was kept normal during IPSV via CO2 inhalation, RR increased nonsignificantly, Ve increased slightly but significantly, Vt remained unchanged, and respiratory motor output indexes showed nonsignificant increases. The increase in Ve was \( \sim 0.2 \text{l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1} \), which is a relatively weak response. Some previous studies found no significant change in Ve until PETCO2 reached hypercapnic levels (12, 25), whereas Georgopoulos et al. (9) observed, as in our study, a weak ventilatory response (of \( \sim 0.35 \text{l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1} \)) in the hypercapnic range and a much stronger ventilatory response in the hypercapnic range (see Fig. 4 in Ref. 9).

Nonchemical inhibition of inspiratory activity was not observed in a study of PAV performed by Georgopoulos et al. (10). They demonstrated that during PAV the decrease in respiratory motor output was due only to the change in PETCO2. Direct comparison of our study to that by Georgopoulos et al. is difficult. First, the study by Georgopoulos et al. was performed during a dynamic condition of ventilatory CO2 response, whereas our condition was static. Second, Georgopoulos et al. evaluated their subjects in a hypercapnic range, from 50 to 59 Torr, whereas we evaluated IPSV in hypocapnic and normocapnic conditions (differences in CO2 responses between the hypocapnic and hypercapnic ranges have been discussed above). Third, PAV and IPSV are obviously not similar modes of ventilation. For example, after the initial active triggering phase during IPSV, inspiration can be virtually passive and Vt can be above physiological values despite minimal inspiratory activity (2), whereas during PAV the assistance is proportional to respiratory muscle activity and Vt depends on the duration and the strength of respiratory muscle activity. These differences in experimental techniques and ventilatory modes may account for the apparent discrepancy between our findings and those of Georgopoulos et al.

Nonchemical inhibition of inspiratory activity has been observed during CMV. Puddy et al. (23) observed a small, nonchemical inhibition of inspiratory activity during CMV. However, their conclusion was based only on an analysis of the respiratory rhythm. Henke et al. (11) reported that returning PETCO2 to the spontaneous level by adding CO2 to the inspired air during mechanical hyperventilation did not completely restore respiratory activity to the level observed during spontaneous breathing. Altose et al. (1), Simon et al. (27, 29), and others (13, 18, 22) found that, after suppression of inspiratory activity by mechanical hyperventilation, the level of PETCO2 at which inspiratory activity was detectable was several Torr above the eupneic PETCO2. This suggests a nonchemical inhibitory effect of CMV similar to that seen during IPSV. Some of these studies were performed in sleeping subjects (11, 13, 27), indicating that these nonchemical inhibitory effects are largely of peripheral origin and do not depend on higher brain centers.

In keeping with these studies, we suggest that the thoracic displacement imposed by IPSV exerts a nonchemical inhibitory influence, the origin of which is probably in peripheral afferents. In our study, the reduction in inspiratory activity during IPSV was due primarily to a reduction in the duration of inspiratory activity as assessed on the basis of eTt (see Fig. 3; compared with control periods, IPS + CO2 was associated with a decrease in eTt and with a nonsignificant decrease in the peak of electrical activity). Reduction in inspiratory activity may also be due to the reduction in the slope of the inspiratory activity, according to the significant decrease in \( \Delta Pd_{250} \) and \( \Delta Pd_{500} \) and to the nonsignificant decrease in the EMGd peak. This leads us to believe that the lung inflation and Vt-to-mTt ratio increase induced by IPSV during neural inspiration reduce and/or terminate neural inspiration.

Among studies done to investigate the mechanism of nonchemical inhibition of mechanical ventilation in humans, some compared the response to mechanical ventilation between normal subjects and patients with loss of a sensory pathway (15, 18, 28, 29). The nonchemical inhibition associated with mechanical ventilation persisted in C4–C5 quadriplegics with intercostal deafferentation (28). Studies in lung-transplant patients with bilateral vagal denervation yielded conflicting results: persistence of nonchemical inhibition during mechanical ventilation was observed by Simon et al. (29) and by Leevers et al. (15) but not by Lofaso et al. (18). Thus the pathways of nonchemical inhibition associated with mechanical ventilation remain unclear.

In conclusion, our data support the existence of nonchemical inhibition of inspiratory activity during IPSV. This may explain why IPSV is effective in patients with imminent failure of respiratory muscles in the absence of any concomitant improvement in arterial blood-gas values.
REFERENCES


