Response of respiratory motor output to varying pressure in mechanically ventilated patients

N. Xirouhaki*, E. Kondili*, I. Mitrouska*, N. Siafakas*, D. Georgopoulos*


ABSTRACT: It has been shown in mechanically ventilated patients that pressure support (PS) unloads the respiratory muscles in a graded fashion depending on the PS level. The downregulation of respiratory muscles could be mediated through chemical or load-related reflex feedback.

To test this hypothesis, 8 patients with acute lung injury mechanically ventilated on PS mode (baseline PS) were studied. In Protocol A, PS was randomly decreased or increased by at least 5 cmH2O for two breaths. During this time, which is shorter than circulation delay, only changes in load-related reflex feedback were operating. Sixty trials where PS increased (high PS) for two breaths and 62 trials where PS decreased (low PS), also for two breaths were analysed. Thereafter, the patients were assigned randomly to baseline, low or high PS and ventilated in each level for 30 min (Protocol B). The last 2 min of each period were analysed. Respiratory motor output was assessed by total pressure generated by the respiratory muscles (P_{\text{mus}}), computed from oesophageal pressure (P_{\text{oes}}).

In Protocol A, alteration in PS caused significant changes in tidal volume (VT) without any effect on P_{\text{mus}} waveform except for neural expiratory time (nTE). nTE increased significantly with increasing PS. In Protocol B, P_{\text{mus}} was significantly downregulated with increasing PS. Carbon dioxide tension in arterial blood (P_{\text{aCO}_2}) measured at the end of each period increased with decreasing PS. There was not any further alteration in nTE beyond that observed in Protocol A.

These results indicate that the effect of load-related reflex on respiratory motor output is limited to timing. The downregulation of pressure generated by the respiratory muscles with steady-state increase in pressure support is due to a slow feedback system, which is probably chemical in nature.


Pressure support (PS) is a mode of assisted mechanical ventilation where the ventilator, once triggered by the patient, provides a constant pressure until a predetermined inspiratory flow criterion is reached [1]. PS is widely used as a mode that has the ability to unload the inspiratory muscles, while allowing the patient to retain control on his/her breathing pattern. It is thought that the degree of inspiratory muscle unloading depends on the level of PS. Indeed, several studies have shown that the activity of inspiratory muscles, estimated using indices such as the rate of airway or oesophageal pressure decrease before the ventilator triggering, electromyogram (EMG), transdiaphragmatic pressure, and oxygen cost of breathing, decreases with increasing PS [1–3].

Provided that behavioural response is not an issue, there are three possible mechanisms for this downregulation of respiratory motor output: mechanical, operating via force length and force velocity relationships of respiratory muscles; load compensatory reflexes, and; chemical [4]. Mechanical and reflex feedback systems are referred to as neural control. Neural control is very fast (ms) and thus affects respiratory motor output immediately after a change in PS, whereas chemical feedback influences respiratory muscle activity several seconds later [4]. Slow nonchemical neural responses may be expected: 1) where the stimulus inciting them is changing slowly [4] and; 2) if control system inertia [5, 6] or afterdischarge exists [7–10], masking for some time the effects of mechanical and reflex feedback on respiratory motor output.

Although slower than mechanical and reflex feedback, chemical feedback is by no means slow. Studies in anaesthetized animals have shown that changes in chemical feedback produced by airway occlusion may result in doubling or tripling of the intensity of inspiratory activity within 15–20 s [11]. In humans with a normal cardiovascular system, acute changes in alveolar gas composition significantly alter the activity of inspiratory muscles after 6–9 s [8, 9] which corresponds to circulation delay between the alveoli and the peripheral chemoreceptors [12]. Therefore, any acute change in PS level that alters alveolar ventilation is expected to do so via chemical feedback to the activity of inspiratory muscles relatively quickly (i.e. after 6–9 s). It follows that indices of inspiratory muscle activity obtained several minutes after a change in PS level, as is usually the case in most studies [1–3], may reflect, to an unknown extent, alteration in chemical feedback. On the other hand changes in respiratory muscle activity during the first two to three breaths after the PS change (before the alteration in capillary blood gases reaches the peripheral chemoreceptors) should be determined by changes in neural control and, if it exists, the dumping function of control system inertia or afterdischarge. The pathway through which PS downregulates respiratory motor output in mechanically ventilated patients is currently not clear. This issue is of fundamental
importance for the management of mechanically ventilated patients [13].

The purpose of the present study was to examine the early and late response of respiratory motor output to varying PS level in a homogeneous group of mechanically ventilated patients with acute lung injury. These responses may give some insights into the control of breathing during mechanical ventilation in this group of patients.

Methods

Patients

Eight patients, admitted to the intensive care unit (ICU) for management of acute lung injury (ALI) due to direct lung insults, were studied. At the time of the study all patients were haemodynamically stable without vasoactive drugs (other than dobutamine <5 μg·kg body weight·min⁻¹) and ventilated on PS mode using Servo 300 (Siemens, Solna, Sweden) or Evita 2 (Dräger, Lübeck, Germany) ventilators through cuffed endotracheal or tracheostomy tubes. The PS and positive end-expiratory pressure (PEEP) levels were determined by the primary physician who was not involved in the study. All patients were lightly sedated with propofol.

The level of sedation was such as to achieve a score of 3 in Ramsay’s scale (response to commands only). Patients with one of the following characteristics were excluded: 1) previous history of obstructive lung disease (chronic obstructive pulmonary disease (COPD) or asthma); 2) chest wall abnormalities; 3) pneumothorax; 4) overt pleural effusion, and; 5) abdominal disease. The study was approved by the Hospital Ethics Committee and informed consent was obtained from the patients or their families.

Apparatus

Flow (V') at the airway opening was measured with a heated pneumotachograph (Hans-Rudolph 3700, KS, USA) and a differential pressure transducers (Micro-Switch 140 PC; Honeywell Ltd., Ontario, Canada), placed between the endotracheal tube and the Y-piece of the ventilator. V' was electronically integrated to provide volume (V). Airway pressure (Paw; Micro-Switch 140PC; Honeywell Ltd.) was measured from a side port between the pneumotachograph and the endotracheal tube. Oesophageal pressure (Pos) (Micro-Switch 140PC; Honeywell Ltd.) was measured with an oesophageal balloon positioned at the lower third of the oesophagus and filled with 0.5 mL of air. The proper position of the balloon was verified using the occlusion test [14]. Each signal was sampled at 150 Hz (Windaq Instruments Inc., Akrou, OH, USA) and stored on a computer disk for later analysis.

Protocol

The patients were studied in semi-recumbent position. The study was conducted in three parts. At the first part of the study (Protocol A) the patients were ventilated on PS with the ventilator settings determined by the primary physician (baseline PS). With these settings ventilatory parameters and blood gases were recorded for 2 min (baseline 1). Thereafter, PS was randomly increased (high PS) or decreased (low PS) by at least 5 cmH2O. Each change was maintained for two breaths. At least seven trials where PS was decreased for two breaths and seven trials where PS was increased, also for two breaths, were performed in each patient. Between trials 3–4 min of baseline PS ventilation were allowed. At the end of the first part ventilatory parameters and blood gases were recorded for 2 min again (baseline 2).

In the second part of the study (Protocol B) the patients were ventilated randomly for 30 min with three levels of PS corresponding to those determined at the first part of the study (baseline, low, and high PS). Ventilatory parameters and arterial blood gases were measured at the end of each 30 min period.

Finally, respiratory system mechanics were measured. The patients were placed on volume-control mode and ventilated with a tidal volume (VT) similar to that obtained with baseline PS. Inspiratory flow was given using a square wave flow-time profile. Breathing frequency was adjusted upward in order to lower carbon dioxide tension in arterial blood (Paco2) and inhibit respiratory muscle activity. The absence of respiratory muscle activity was based on specific criteria including, absence of negative deflection of Paw and Pos uniformity of pressure contour, constancy of peak inspiratory pressure from breath to breath and exponential decline of expiratory flow [15]. When passive ventilation was obtained respiratory system mechanics were measured by the technique of rapid airway occlusion [16]. Briefly, to measure the elastance of the respiratory system and to partition it to lung and chest wall components the airways were occluded at end-inspiration until both Paw and Pos decreased from the maximal value (Paw,peak and Pos,peak, respectively) to an apparent plateau (Paw,p and Pos,p, respectively). Similarly the end-expiratory Paw (Paw,end) and the end-expiratory Pos (Pos,end) were recorded after a brief end-expiratory hold manoeuvre.

The elastance of the respiratory system (Ers) and that of the chest wall (Ecw) were computed using the following formulae:

\[ E_{rs} = \frac{(P_{aw,p} - P_{aw,end})}{V_T} \]  
\[ E_{cw} = \frac{(P_{oes,p} - P_{oes,end})}{V_T} \]

The elastance of the lung (Els) was calculated as the difference between Ers and Ecw. The compliance of the respiratory system (Crs), lung (Cl) and chest wall (Ccw) was calculated as the inverse of the corresponding value of elastance.

Total resistance of the respiratory system (Rrs) and of the chest wall (Rcw) was obtained as follows:

\[ R_{rs} = \frac{(P_{aw,peak} - P_{aw,p})}{V_T} \]  
\[ R_{cw} = \frac{(P_{oes,peak} - P_{oes,p})}{V_T} \]

where V'T was the flow immediately before the end-inspiratory occlusion.

Furthermore, the ventilator frequency was reduced to zero and the patients were permitted to exhale passively until cessation of expiratory flow was evident. At this point Poes and transpulmonary pressure (Pdp) = (Paw - Poes) were recorded and assumed to reflect the corresponding pressures across the chest wall and the lung at passive functional residual capacity (FRC) determined by the PEEP level (Poes,FRC and Pdp,FRC, respectively).

All the respiratory system mechanics data were computed as an average of three measurements obtained by respective manoeuvres satisfying passive conditions.
Data analysis

Pressure generated by the respiratory muscles ($P_{\text{mus}}$) was calculated from $P_{\text{oes}}$ taking into account the passive elastic and resistive properties of the chest wall. This calculation, which is based on the diagram in Campbell [17], was described in detail earlier [18]. Briefly, at each instant in the respiratory cycle $P_{\text{mus}}$ is the difference between the pleural pressure ($P_{\text{pl}}$) that would be obtained at the same respiratory volume and flow during passive inflation or deflation, and the $P_{\text{pl}}$ actually observed. Thus:

$$P_{\text{mus}} = P_{\text{pl}} \text{ (passive)} - P_{\text{pl}} \text{ (actual)}$$

(5)

With passive inflation or deflation the $P_{\text{pl}}$ that would be obtained at a given volume ($V$) and flow ($V'$) is given by:

$$P_{\text{ple}} \text{ (passive)} = (V \times E_{\text{cw}}) + P_{\text{oes}} \text{.FRC} + (V' \times R_{\text{cw}})$$

(6)

where $V$ is volume relative to passive FRC, and $E_{\text{cw}}$ and $R_{\text{cw}}$ are, respectively, elastance and resistance of the chest wall. $P_{\text{oes}}\text{.FRC}$ is passive chest wall recoil at passive FRC. The values of $E_{\text{cw}}$ and $R_{\text{cw}}$ obtained at the end of the study were used, while $P_{\text{oes}}\text{.FRC}$ was assigned a value that equaled $P_{\text{oes}}\text{.FRC}$. Inspiratory $V'$ and expiratory $V'$ were assigned positive and negative values, respectively. Thus, at time ($t$) from the beginning of neural inspiration (see below) $P_{\text{mus}}(t)$ was calculated as follows:

$$P_{\text{mus}}(t) = (E_{\text{cw}} \times V_{t}) + P_{\text{oes}}\text{.FRC} + (R_{\text{cw}} \times V'_{t}) - P_{\text{oes}}(t)$$

(7)

where $V_{t}$ and $V'_{t}$ are, respectively, volume relative to passive FRC (determined by PEEP level) and flow. The volume was related to passive FRC by calculating $P_{\text{pl}}$ at end expiration at the point of zero flow ($P_{\text{pl},\text{end}}$) and comparing this value with that obtained at passive FRC ($P_{\text{pl},\text{FRC}}$). The difference between $P_{\text{pl},\text{end}}$ and $P_{\text{pl},\text{FRC}}$ multiplied by the CL should be equal to the difference in lung volumes between passive FRC and end-expiration of the breath of interest [18, 19].

$P_{\text{mus}}$ waveform was aligned at the beginning of neural inspiration defined as the time that $P_{\text{mus}}$ began to increase rapidly from the value reached during expiration. Neural inspiratory time (nI) was measured as the interval between the beginning of $P_{\text{mus}}$ increase and the point at which $P_{\text{mus}}$ started to decline rapidly [18]. Neural expiratory time (nE) was measured as the remainder of the respiratory cycle, determined from the $P_{\text{mus}}$ waveform. Total breath duration was also calculated (tot). Mechanical inflation time was measured as the interval between the beginning and the end of inspiratory flow.

Various indices of respiratory drive were also calculated using the $P_{\text{mus}}$ waveform. These indices were: 1) peak $P_{\text{mus}}$ ($P_{\text{mus,peak}}$), the highest value of $P_{\text{mus}}$ during inspiration; 2) the rate of increase of $P_{\text{mus}}$ during inspiration, the difference between $P_{\text{mus,peak}}$ and $P_{\text{mus}}$ at the onset of neural inspiration (dp) divided by the corresponding time (dt), i.e. dp/dt. 3) the swings of $P_{\text{mus}}$ during the respiratory cycle ($P_{\text{mus,SW}}$), the difference between $P_{\text{mus,peak}}$ and the lowest value of $P_{\text{mus}}$ ($P_{\text{mus,nadir}}$) achieved during expiration.

Respiratory muscle effort during the respiratory cycle was quantified using the time integral of respiratory muscle pressure. The time integral of positive and negative $P_{\text{mus}}$ represented, respectively, the pressure time product ($P_{\text{p}}$) of inspiratory ($P_{\text{p,i}}$) and expiratory ($P_{\text{p,e}}$) muscles. $P_{\text{p}}$ of all respiratory muscles (inspiratory and expiratory, $P_{\text{p,i}}$) was calculated as the sum of $P_{\text{p,i}}$ and $P_{\text{p,e}}$. $P_{\text{p,i}}$, $P_{\text{p,e}}$ and $P_{\text{p}}$ were calculated on a per breath basis. The $P_{\text{p}}$ values per min were calculated as the product of the respective $P_{\text{p}}$ per breath and breathing frequency.

In the first part of the study (Protocol A) the breath variables preceding the PS change (either high or low) were averaged to give the baseline values. Similarly, the variables of the first and second breath following an increase in PS and the first and second breath following a decrease in PS were averaged to give the corresponding characteristics of the two representative breaths (first and second) after a change in PS. In the second part of the study (Protocol B) breaths during the last 2 min of each 30 min period were averaged to give the breath variables with steady state baseline, low and high PS.

Furthermore, in order to examine the shape of $P_{\text{mus}}$ at various study periods $P_{\text{mus}}$ was calculated at 5% interval of htot. Thus in each patient a representative $P_{\text{mus}}$ waveform as a function of percentage of htot was obtained at the various periods of the study.

Data were analysed by analysis of variance for repeated measurements (ANOVA), followed by Tukey’s test if the F-value was significant. A p<0.05 was considered statistically significant. Values are expressed as mean±SEM.

Results

The main clinical characteristics, the baseline ventilator settings and the respiratory system mechanics of the patients are shown in tables 1 and 2. Aspiration was the cause of ALI in two patients (patients 1 and 7) and pneumonia in the remaining. Five patients were orotracheally intubated and three had tracheostomies (patients 2, 4 and 6). The mean values of $E_{\text{rs}}$ and $R_{\text{rs}}$ (including the endotracheal tube resistance) were considerably higher than those observed in healthy control subjects [20]. The increase in $E_{\text{rs}}$ and $R_{\text{rs}}$ was mainly due to mechanical properties of the lung ($E_{\text{l}}$ and resistance of the lung (RL)). $E_{\text{cw}}$ and $R_{\text{cw}}$ were within the normal limits [20].

Protocol A

Ventilatory parameters ($V_{t}$, htot) and arterial blood gases with baseline PS did not differ between the beginning (baseline 1) and the end (baseline 2) of the Protocol A, indicating the patients’ stability during the time that the trials were performed. The ventilatory parameters during the two baseline periods were similar to those obtained by averaging the breaths preceding the PS change.

Table 1. – Patients’ characteristics and baseline ventilator settings

<table>
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<th>Patient No.</th>
<th>Age yrs</th>
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<th>PEEP cmH2O</th>
<th>Days onMV</th>
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<td>M</td>
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Mean±SEM 67.9±3.75  17.3±1.6  5.9±0.7  11.6±1.8

PS: pressure support; PEEP: positive end-expiratory pressure; MV: mechanical ventilator; F: female; M: male.
Sixty trials where PS increased to 23.0±1.4 cmH2O for two breaths and 62 trials where PS decreased to 11.1±1.5 cmH2O, also for two breaths, were analysed. In all patients the two breaths after the PS change were completed in <6.5 s (mean duration 5.4±0.4 s and 4.8±0.4 s, respectively, with high and low PS). The alterations in PS caused significant changes in Vt (table 3). Compared to breaths preceding the PS change (baseline), none of the indices of Pmus reflecting respiratory drive changed upon PS transition (table 3, fig. 1a). On the other hand, tOT increased and decreased, respectively, with increasing and decreasing PS. The increase was significant at high PS. The tOT response was mainly due to nS (table 3). Either with high or low PS none of the various breath parameters differed between the first and second breath after the PS change. Figure 2a shows the Pmus waveform (expressed as percentage of tOT) obtained by averaging the breaths preceding the PS change and that of the second breath after the increase or decrease of PS. The shape of the Pmus waveform was remarkably similar at all PS levels.

Compared to baseline PS, increasing and decreasing PS resulted in a slight increase and decrease, respectively, in the time that mechanical inflation extended into neural expiration. These changes, however, were only significant in the second breath with high PS (table 3). End expiratory lung volume increased and decreased slightly with increasing and decreasing PS, respectively. Neither change, however, was significant (table 3).

**Protocol B**

Contrary to protocol A, steady-state changes in PS caused significant alterations in Pmus waveform. Pmus was significantly down regulated with increasing the pressure support, as indicated by the various indices of respiratory drive and the shape of Pmus waveform (table 4, figs. 1b and 2b). Similar to Protocol A tOT increased with increasing PS due to nS increase. The magnitude of nS changes (∆nS, expressed as percentage changes from nS with baseline PS) was comparable to those observed in protocol A. Furthermore, there was a significant relationship between ∆nS in Protocol B with ∆nS in Protocol A (γ=0.99±0.52, r=0.83, p<0.001). A similar significant relationship was observed in tOT changes (ΔtOT, γ=0.60±1.35, r=0.72, p<0.001). With high PS nS/tOT decreased significantly. Compared to baseline and high PS, PaCO2

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### Table 2: Respiratory system mechanics

<table>
<thead>
<tr>
<th>Patient No.</th>
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<th>Rs</th>
<th>Rcw</th>
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</table>

Ets and Rs: respiratory system elastance and resistance, respectively; E: elastance and resistance of the lung respectively; Ecw and Rcw: elastance and resistance of the chest wall, respectively.

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### Table 3: Breath characteristics in Protocol A

<table>
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*: Significantly different than pressure support (PS); *: significantly different than baseline PS. Vt: tidal volume; dP/dt: the rate of pressure generated by the respiratory muscles (Pmus) increase during inspiration; Pmus,sw: Pmus swings during the respiratory cycle; Pmus,peak: peak Pmus during inspiration; Pmus,nadir: the lowest Pmus during expiration; PIP im-min⁻¹: pressure time product of inspiratory muscles per minute; PIPtot-im⁻¹: pressure time product of all (inspiratory and expiratory) respiratory muscles per minute; tot: total breath duration; nI and nE: neural inspiratory and expiratory time respectively; nI /tot: duty cycle; EELV: time that mechanical inflation extents into neural expiration; V EELV/FRC: end expiratory lung volume (EELV) relative to passive functional residual volume (FRC).
increased significantly with low PS. With high PS $P_a CO_2$ was slightly, but nonsignificantly, lower than at baseline PS. At all PS levels oxygen tension in arterial blood ($P_a O_2$) remained relatively constant. The time that mechanical inflation extended to neural expiration increased with increasing PS. However, these changes were not significant. End expiratory lung volume remained similar at all PS levels.

**Discussion**

**Critiques of the method**

End-expiratory lung volume was related to passive FRC using the $P_T$ at end expiration and CL (see Methods section). Changes in end-expiratory $P_T$ from this were assumed to reflect changes in end-expiratory lung volume [18, 19]. This method has been used previously to estimate end-expiratory lung volume change due to expiratory muscle recruitment during CO2 rebreathing [18, 19]. Assuming that, at zero flow, mouth pressure equals alveolar pressure and chest wall or lung compliance did not change during the study, this method may detect end-expiratory lung volume changes even at high levels of respiratory drive. The patients did not have obstructive lung disease, making the existence of expiratory flow limitation during tidal expiration unlikely and, thus, the assumption that at zero flow mouth pressure equals alveolar pressure should be valid. Also, the patients were stable throughout the study, indicating that major changes in chest wall or lung compliance during the experiment were unlikely.

CL was measured at end-inspiration with the technique of rapid airway occlusion. These patients, however, may exhibit a nonlinear behaviour of the static pressure-volume ($P-V$) of the lung and, thus, end-expiratory CL might be higher than that at end-expiration [21, 22], overestimating the change in end-expiratory lung volume. Nevertheless, the patients were studied in semi-recumbent position, several days after the primary lung insult and with PEEP ranging 5–10 cmH2O. All these factors force the $P-V$ curve relationship to be linear, decreasing the possible error in estimating the end-expiratory lung volume change [21, 22]. Furthermore, in the patients end-inspiratory CL was quite low and any difference in end-expiratory lung volume change due to further decrease in CL at low lung volumes should be minimal. Finally, if overestimation of
end-expiratory lung volume change occurred it would be of comparable magnitude at all PS studied, because in these patients with nonobstructive lung disease and high elas	ance of the respiratory system significant changes in end-expiratory lung volume as a result of different PS were unlikely. Nevertheless, errors in estimation of end-expiratory lung volume should affect the peak and nadir values of $P_{mus}$ and the $P_{tp,i}$ and $P_{tp,e}$. The $P_{tp}$ of all respiratory muscles as well as the other indices of respiratory drive or timing should not be affected.

$P_{mus}$ was calculated using the values of $E_{cw}$ and $R_{cw}$, which were measured at the end of the study. These values were assumed to be constant throughout the respiratory cycle. This assumption, however, may not be, particularly for $E_{cw}$, valid [21, 22]. It has been shown that in mechanically ventilated critically ill patients the static $P-V$ curve of the chest wall may exhibit a lower inflection point [21, 22]. If this was the case $P_{mus}$ should be underestimated at low lung volume. Although the $P-V$ curve of the chest wall was not measured, it is believed that for several reasons errors in $P_{mus}$ calculation due to the presence of lower inflection point should be small, if any. Firstly the patients were studied in semi-recumbent position. Lower inflection point in chest wall $P-V$ curve is volume related and it has been observed in supine position, which is well known to decrease FRC [21, 22]. Secondly, all patients had external PEEP, the magnitude of which ranged 5–10 cmH2O. It has been demonstrated that the lower inflection point is greatly minimized or even obliterated by this range of PEEP, due to end-expiratory lung volume increases [22]. Thirdly, patients were excluded if they had abdominal disease, overt pleural effusion or chest wall abnormalities, conditions that may alter the intrinsic mechanical properties of the chest wall and exaggerate the nonlinear behaviour of the chest wall static $P-V$ curve [21]. Finally, because end-expiratory lung volume did not differ at various study conditions, if underestimation of $P_{mus}$ occurred at low lung volumes it should be of similar magnitude with different PS.

Transdiaphragmatic pressure ($P_{di}$) could be another index of respiratory motor output. This index does not necessitate the assumptions used for $P_{mus}$, although the measurement of gastric pressure may impose some problems in $P_{di}$ interpretation, particularly if alteration in abdominal wall compliance during the respiratory cycle occurs. Nevertheless, it was interesting to examine the response of all respiratory muscles to varying PS. $P_{di}$ is a measurement of the pressure output of the diaphragm and therefore $P_{di}$ waveform could not give information regarding the response of other respiratory muscles to PS. On the other hand calculated $P_{mus}$ represents a global index of the activity of all respiratory muscles (inspiratory and expiratory muscles). It is believed that in these selected patients $P_{mus}$ waveform is a better reflection of respiratory muscle activity than $P_{di}$.

Response of respiratory motor output to varying pressure support

The main findings of the present study are: 1) changing the PS level in mechanically ventilated patients with high mechanical load of the respiratory system did not cause any significant immediate alteration of respiratory drive; 2) total breath duration increased with increasing PS due to an increase in neural expiratory time. The response was evident within two breaths after the PS change; 3) steady-state changes in PS significantly influenced respiratory drive; the various indices of respiratory drive decreased with increasing PS, and 4) there was not any further alteration in breath timing beyond that observed within two breaths after the PS change.

It has been shown that after abrupt cessation of a nonspecific respiratory stimulus ventilatory output declines gradually to prestimulus levels [7–10]. This phenomenon is referred to as short-term poststimulus potentiation (STP) or afterdischarge, and is attributed to activation of a brainstem mechanism, with slow dynamics, that drives ventilation for some time, independent of chemical feedback. Furthermore, Leuvers and coworkers [5, 6] observed that complete inhibition of respiratory motor output with normocapnic mechanical ventilation displays a "memory-like" effect or control system inertia, as indicated by the significant prolongation of expiratory time after discontinuation of mechanical ventilation. These findings, however, were not observed in other studies [23, 24]. Nevertheless, the above observations indicate that if these mechanisms (STP or control system inertia) were operating during the two breaths following the acute PS changes, then the effects of reflex feedback on respiratory motor output would be dampened. It is believed that the contribution of the above mentioned mechanism on the response observed is minimal for at least three reasons. Firstly, control system inertia or STP affects both respiratory drive and timing [5–10]. The present study showed that within two breaths total and net increased and decreased, respectively, with increasing and decreasing PS and that these changes remained constant during steady-state PS alteration. It follows that control system inertia or STP did not dampen breath timing changes. Thus, if these mechanisms were operating they would specifically affect the respiratory drive. No data in humans support such a specific effect. Secondly, studies indicate that the manifestation of STP is influenced by the intensity of the stimulus that initiates it; STP is attenuated with decreasing stimulus intensity [8, 10]. Furthermore, STP or control system inertia has been observed following manipulations resulting in $P_{t}$ that were close to \( \pm 1 \) L [5–8, 10], considerably higher than that during spontaneous breathing. In the current study $P_{t}$ during baseline was \( \sim 0.6 \) L and no stimulus was applied. This condition is unlikely to activate a significant STP. Thirdly, studies in humans ventilated on assist volume control, where inspiratory flow rate was changed abruptly, did not show any hard evidence of the existence of STP or control system inertia [25, 26]. Indeed, the changes induced by alteration in inspiratory flow were observed immediately upon flow transition without adaptation of the response in the subsequent breaths. The experimental design of the above studies, as far as the acute response to ventilator settings is concerned, is similar to that used in the present study. On the other hand, STP or control system inertia have been observed by studies using different experimental designs and, thus, it is not known if these findings may apply in the current study.

The immediate increase in neural expiratory time with increasing PS is most probably reflex in origin. Chemical feedback was not an issue because in all patients the duration of the two breaths after the PS change was \( <6.5 \) s, which was not sufficient time for changes in capillary...
blood gas composition to reach peripheral chemoreceptors [12]. This reflex response of nfi to varying PS could be due to two factors. Firstly, for a given Pmus lung volume changed as a function of PS level: it increased with increasing PS (Pt increased by ~50% from low to high PS, whereas PS remained constant). This response caused the Vtv/Pmus ratio (an index of the gain of the respiratory system) to increase by ~60%. This increase can be viewed as a considerable decrease in the elastic load faced by the respiratory muscles. It is believed that decreasing the elastic load may decrease breathing frequency via a reflex mechanism, probably mediated through chest wall afferents [4, 27, 28]. Secondly, the mechanical inflation tended to extend into neural inspiration for a longer time with increasing PS. It has been shown that when lung emptying is delayed during expiration, as it was the case with increasing PS, expiratory duration is prolonged, a response that is mediated via vagal volume feedback [4, 29, 30].

Neural inspiratory time remained constant at all PS levels studied. Based on vagal volume feedback a shorter nif would be expected with high PS, as a result of the high Vtv. There are at least two reasons, however, that may account for this apparent nondependency of nif on Vtv. Firstly, the patients studied breathed at a relatively high rate; breathing frequency averaged 24 breaths min\(^{-1}\) with baseline PS. It has been shown that for a given respiratory drive the dependence of nif on Vtv progressively decreases as nif without volume feedback decreases, as it occurs in the presence of various stimuli that increase breathing frequency [4, 31]. Secondly, the Vtv ranged 0.47–0.72 L. In humans the effect of vagal volume feedback on neural inspiratory time has been demonstrated at much higher volumes (i.e. above 1 L) [32, 33].

Contrary to short-term protocol, steady-state changes in PS caused significant alterations in Pmus waveform. On the other hand neural inspiratory and expiratory time remained relatively similar to levels observed immediately after the PS change. It is believed that this pressure downregulation is mediated through chemical feedback. One could argue that the small changes in Paco2 observed with different PS might not be able to elicit the Pmus responses observed. Indeed, compared to baseline, Paco2 decreased by <0.133 kPa (<1 mmHg) with high PS, yet indices of respiratory drive changed by ~30%. However, the load compensatory ability of chemical feedback is enormous; small changes in Paco2 which may be difficult to detect, are able to mount a considerable response by the respiratory muscles. For example, a 30% increase in peak respiratory muscle pressure can be the cause of <0.266 kPa (<2 mmHg) increase in Paco2 [4, 34]. It follows that chemical feedback cannot be discounted on the grounds that Paco2 did not change significantly. Furthermore, there were no discernible immediate changes in Pmus when PS changed for two breaths, indicating that the up- or downregulation of the respiratory muscle activity observed after a steady-state change in PS, was mediated with a slow feedback system. Chemical feedback is such a system [4]. Finally, the Pmus waveform points at chemical feedback as the prominent mechanism. It was observed that steady-state increase and decrease in PS caused, respectively, a decrease and increase in the rate of rise of inspiratory activity with little change in neural inspiratory time. This response pattern is characteristic of CO2 effects [35].

Is it possible that a slowly evolving reflex response may partly contribute to Pmus down- or upregulation observed with steady-state changes in PS? Slow reflex responses may be expected where the stimulus inciting them is changing slowly. In the current study PS change was applied abruptly and not progressively. Inspiratory muscle fatigue associated with low PS could also elicit a slowly evolving reflex response. However the development of inspiratory muscle fatigue should cause faster, shallower efforts. On the other hand, deeper efforts were observed with no further change in frequency. Furthermore, the patients did not exhibit any clinical signs indicating inspiratory muscle fatigue during the study periods. Nevertheless, the possibility of the existence of a hitherto unidentified neural mechanism that affects respiratory drive and evolves over many seconds or minutes cannot be entirely excluded.

The results of this study indicate that in patients with abnormal mechanical load of the respiratory system load-related influences of neural afferents on respiratory muscle pressure are minimal; a change in the mechanical load brought about by PS that resulted in a considerable alteration in Vtv failed to modify Pmus waveform. The Vtv increased by ~50% from low to high PS, yet Pmus wave-form was almost identical. These findings are in accord-ance with studies in normal humans during wakefulness or sleep, demonstrating a lack of nonchemical load response of respiratory muscle activity [18, 36, 37]. Indirect evidence in the literature indicates that this might be also the case in patients with high mechanical load of the respiratory system [38–40]. Data in patients during constant flow synchronized intermittent mandatory ventilation (SIMV) [38, 39] or biphasic positive airway pressure (BPAP) [40], have shown that for a given level of assistance, inspiratory effort did not differ between spontaneous and mandatory breaths. Recently Leung et al. [2] studied the respiratory effort of patients ventilated on SIMV and on a combination of SIMV and PS. Compared to SIMV alone, when PS was added to a given level of SIMV inspiratory pressure-time product (an index of inspiratory work of breathing) was decreased both in mandatory and intervening breaths. This additional reduction during mandatory breaths was

| Table 4. – Arterial blood-gases and breath characteristics in Protocol B |
|---------------------------|---------------------------|---------------------------|
|                           | Low                       | Baseline                   | High                      |
| Pco2 mmHg                | 48.2±5.0*                 | 44.8±4.7                  | 44.1±4.4                 |
| Paco2 mmHg               | 81.5±4.3                  | 81.3±5.7                  | 78.1±3.1                 |
| Pt L                     | 0.55±0.05                 | 0.57±0.05                 | 0.62±0.06                |
| dp/dt cmH2O s\(^{-1}\)  | 13.4±5.2*                 | 10.2±8.1                  | 6.85±1.3                 |
| Pmus,tw cmH2O           | 8.4±1.3*                  | 6.02±0.9                  | 4.25±0.8                 |
| Pmus,peak cmH2O         | 6.87±1.2*                 | 5.38±0.6                  | 3.61±0.7*                |
| Pmus,nadir cmH2O        | -1.51±0.6                 | -0.64±0.2                 | -0.64±0.2                |
| Ptv im\(^{-1}\)         | 120±27.5                  | 84.0±8.8                  | 52.7±10.7                |
| Ptv/cmH2O s\(^{-1}\)    | 152.6±30.1*               | 102.4±15.1                | 63.9±12.5                |
| Ptv/cmH2O s\(^{-1}\)    | 2.35±0.2*                 | 2.51±0.2                  | 2.75±0.2                 |
| Ptv/cmH2O s\(^{-1}\)    | 1.69±0.2*                 | 1.84±0.2                  | 2.13±0.1*                |
| Ptv/cmH2O s\(^{-1}\)    | 0.30±0.08                 | 0.28±0.07                 | 0.23±0.03                |
| Ptv/cmH2O s\(^{-1}\)    | 0.16±0.04                 | 0.19±0.04                 | 0.26±0.04                |
| V EELV/FRC L            | -0.01±0.02                | 0.00±0.02                 | 0.02±0.01                |

*: significantly different than high pressure support (PS); *: significantly different than baseline PS. Pco2 and Paco2: oxygen and carbon dioxide respectively, tension of arterial blood. See table 3 for other abbreviations. 1 mmHg = 0.133 kPa.
The CO2 stimulus was not controlled during the various study entirely excluded. In the study of Bonmarchand et al. [42] observed in COPD patients [42]. Notwithstanding that currently, the issue of neuromechanical inhibition remains 6] have been challenged by other studies [23, 24]. Cur-

However, in the previous studies, contrary to the present

assessing by diaphragmatic EMG [43, 44]. The decrease was proportional to positive pressure level and attributed to 1) the hypocapnia resulting from increased ventilation and 2) the stimulation of vagal afferents. The contribution of hypocapnia appeared to be more powerful. In the current study no strong evidence that anything other than chemoreceptor inputs contribute significantly to the response of respiratory drive to PS change was found. However, in the previous studies, contrary to the present

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References


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