Eur Respir J 1999; 14: 508–516
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

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

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

Response of respiratory motor output to varying pressure support in mechanically ventilated patients. N. Xirouhaki, E. Kondili, I. Mitrouska, N. Siafakas, D. Georgopoulos. ©ERS Journals Ltd 1999.

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 cmH_2O 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_{mus}), computed from oesophageal pressure (P_{oes}).

In Protocol A, alteration in PS caused significant changes in tidal volume (V_T) without any effect on P_{mus} waveform except for neural expiratory time (nt_E). nt_E increased significantly with increasing PS. In Protocol B, P_{mus} was significantly downregulated with increasing PS. Carbon dioxide tension in arterial blood (P_{a,CO_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.

Eur Respir J 1999; 14: 508–516.

*Intensive Care Unit and +Dept of Thoracic Medicine, University Hospital of Heraklion, University of Crete, Heraklion, Crete, Greece

Correspondence: D. Georgopoulos
University Hospital of Heraklion
P.O. Box 1352
Heraklion 711 10
Crete
Greece
Fax: 30 81392636

Keywords: Afterdischarge
chemical feedback
inertia
load
reflex feedback
respiratory muscle pressure

Received: November 26 1998
Accepted after revision May 6 1999

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

For editorial comments see page 487

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^{-1}·min^{-1}) and ventilated on PS mode using Servo 300 (Siemens, Solna, Sweden) or Evita 2 (Dräger, Lübeck, Germany) venti-lators 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-Rudolf 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 (P_{aw}); Micro-Switch 140PC; Honeywell Ltd.) was measured from a side port between the pneumotachograph and the endotracheal tube. Oesophageal pressure (P_{oes}) (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 cmH_2O. 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 (V_T) 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 (P_{a,CO_2}) and inhibit respiratory muscle activity. The absence of respiratory muscle activity was based on specific criteria including, absence of negative deflection of P_{aw} and P_{oes}, 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 P_{aw} and P_{oes} decreased from the maximal value ($P_{aw,peak}$ and $P_{oes,peak}$, respectively) to an apparent plateau ($P_{aw,p}$ and $P_{oes,p}$, respectively). Similarly the end-expiratory P_{aw} ($P_{aw,end}$) and the end-expiratory P_{oes} ($P_{oes,end}$) were recorded after a brief end-expiratory hold maneuvre. The elastance of the respiratory system (E_{rs}) and that of the chest wall (E_{cw}) were computed using the following formulae:

$$E_{rs} = (P_{aw,p} - P_{aw,end})/V_T \quad (1)$$

$$E_{cw} = (P_{oes,p} - P_{oes,end})/V_T \quad (2)$$

The elastance of the lung (E_L) was calculated as the difference between E_{rs} and E_{cw}. The compliance of the respiratory system (C_{rs}), lung (C_L) and chest wall (C_{cw}) was calculated as the inverse of the corresponding value of elastance.

Total resistance of the respiratory system (R_{rs}) and of the chest wall (R_{cw}) was obtained as follows:

$$R_{rs} = (P_{aw,peak} - P_{aw,p})/V'_I \quad (3)$$

$$R_{cw} = (P_{oes,peak} - P_{oes,p})/V'_I \quad (4)$$

where V'_I 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 P_{oes} and transpulmonary pressure (P_{tp}) = (P_{aw} - P_{oes}) 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 ($P_{oes,FRC}$ and $P_{tp,FRC}$, respectively).

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

Data analysis

Pressure generated by the respiratory muscles (P_{mus}) was calculated from P_{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_{mus} is the difference between the pleural pressure (P_{pl}) that would be obtained at the same respiratory volume and flow during passive inflation or deflation, and the P_{pl} actually observed. Thus:

$$P_{mus} = P_{pl}\ (\text{passive}) - P_{pl}\ (\text{actual}) \quad (5)$$

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

$$P_{ple}\ (\text{passive}) = (V \times E_{cw}) + P_{cw,FRC} + (V' \times R_{cw}) \quad (6)$$

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

$$P_{mus,t} = (E_{cw} \times V_t) + P_{oes,FRC} + (R_{cw} \times V'_t) - P_{oes,t} \quad (7)$$

where Vt 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_{tp} at end expiration at the point of zero flow ($P_{tp,end}$) and comparing this value with that obtained at passive FRC ($P_{tp,FRC}$). The difference between $P_{tp,end}$ and $P_{tp,FRC}$ 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_{mus} waveform was aligned at the beginning of neural inspiration defined as the time that P_{mus} began to increase rapidly from the value reached during expiration. Neural inspiratory time (ntI) was measured as the interval between the beginning of P_{mus} increase and the point at which P_{mus} started to decline rapidly [18]. Neural expiratory time (ntE) was measured as the remainder of the respiratory cycle, determined from the P_{mus} waveform. Total breath duration was also calculated (t_{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_{mus} waveform. These indices were: 1) peak P_{mus} ($P_{mus,peak}$), the highest value of P_{mus} during inspiration; 2) the rate of increase of P_{mus} during inspiration, the difference between $P_{mus,peak}$ and P_{mus} at the onset of neural inspiration (dp) divided by the corresponding time (dt), *i.e.* dp/dt. 3) the swings of P_{mus} during the respiratory cycle ($P_{mus,sw}$), the difference between $P_{mus,peak}$ and the lowest value of P_{mus} ($P_{mus,nadir}$) 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_{mus} represented, respectively, the pressure time product (P_{tp}) of inspiratory ($P_{tp,i}$) and expiratory ($P_{tp,e}$) muscles. P_{tp} of all respiratory muscles (inspiratory and expiratory, $P_{tp,t}$) was calculated as the sum of $P_{tp,i}$ and $P_{tp,e}$. $P_{tp,i}$, $P_{tp,e}$ and $P_{tp,t}$ were calculated on a per breath basis. The P_{tp} values per min were calculated as the product of the respective P_{tp} 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_{mus} at various study periods P_{mus} was calculated at 5% interval of t_{tot}. Thus in each patient a representative P_{mus} waveform as a function of percentage of t_{tot} 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_{rs} and R_{rs} (including the endotracheal tube resistance) were considerably higher than those observed in healthy control subjects [20]. The increase in E_{rs} and R_{rs} was mainly due to mechanical properties of the lung (E_L and resistance of the lung (RL)). E_{cw} and R_{cw} were within the normal limits [20].

Protocol A

Ventilatory parameters (V_T, t_{tot}) 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

Patient No.	Age yrs	Sex	PS cmH_2O	PEEP cmH_2O	Days onMV
1	73	F	15	5	10
2	58	F	22	10	14
3	55	M	16	5	6
4	85	F	25	5	19
5	62	M	15	8	8
6	75	M	10	5	19
7	60	M	18	5	7
8	75	M	17	5	10
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.

Table 2. – Respiratory system mechanics

Patient No.	E_{rs} $cmH_2O \cdot L^{-1}$	R_{rs} $cmH_2O \cdot L^{-1} \cdot s^{-1}$	E_L $cmH_2O \cdot L^{-1} \cdot s^{-1}$	R_L $cmH_2O \cdot L^{-1} \cdot s^{-1}$	E_{cw} $cmH_2O \cdot L^{-1}$	R_{cw} $cmH_2O \cdot L^{-1} \cdot s^{-1}$
1	41.33	13.50	33.33	12.38	8.00	1.12
2	38.33	12.40	33.33	11.40	5.00	1.00
3	19.39	12.23	14.29	10.13	5.10	2.10
4	32.69	14.50	25.00	13.46	7.69	1.04
5	24.17	9.00	16.67	6.80	7.50	2.20
6	27.60	11.04	25.60	10.39	2.00	0.65
7	19.05	14.00	10.55	12.50	8.50	1.50
8	21.40	13.93	17.50	12.73	3.90	1.20
Mean±SEM	24.05±1.9	12.45±0.8	18.27±2.1	11.00±0.9	5.78±0.9	1.45±0.2

E_{rs} and R_{rs}: respiratory system elastance and resistance, respectively; E_L and R_L: elastance and resistance of the lung respectively; E_{cw} and R_{cw}: elastance and resistance of the chest wall, respectively.

Sixty trials where PS increased to 23.0±1.4 cmH_2O for two breaths and 62 trials where PS decreased to 11.1±1.5 cmH_2O, also for two breaths, were analysed. In all patients the two breaths after the PS change were completed in <6.5 s (mean duration 5.45±0.4 s and 4.80±0.4 s, respectively, with high and low PS). The alterations in PS caused significant changes in V_T (table 3). Compared to breaths preceding the PS change (baseline), none of the indices of P_{mus} reflecting respiratory drive changed upon PS transition (table 3, fig. 1a). On the other hand, t_{tot} increased and decreased, respectively, with increasing and decreasing PS. The increase was significant at high PS. The t_{tot} response was mainly due to nt_E (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 P_{mus} waveform (expressed as percentage of t_{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 P_{mus} 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 P_{mus} waveform. P_{mus} 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 t_{tot} increased with increasing PS due to nt_E increase. The magnitude of nt_E changes (Δnt_E, expressed as percentage changes from nt_E with baseline PS) was comparable to those observed in protocol A. Furthermore, there was a significant relationship between Δnt_E in Protocol B with Δnt_E in Protocol A (y=0.99x–0.52, r=0.83, p<0.001). A similar significant relationship was observed in t_{tot} changes (Δt_{tot}, y=0.60x–1.35, r=0.72, p<0.001). With high PS nt_I/t_{tot} decreased significantly. Compared to baseline and high PS, P_{a,CO_2}

Table 3. – Breath characteristics in Protocol A

	Low		Baseline	High	
	1st	2nd		1st	2nd
V_T L	0.47±0.06*+	0.49±0.06*+	0.58±0.06	0.72±0.07*	0.72±0.07*
dP/dt $cmH_2O \cdot s^{-1}$	10.51±1.6	10.70±1.5	10.58±1.3	10.13±1.5	9.84±1.2
$P_{mus,sw}$ cmH_2O	6.86±0.7	6.94±0.6	6.21±0.8	6.44±0.7	6.40±0.7
$P_{mus,peak}$ cmH_2O	5.71±0.6	5.79±0.6	5.40±0.6	5.54±0.6	5.68±0.7
$P_{mus,nadir}$ cmH_2O	-1.16±0.3	-1.15±0.2	-0.81±0.2	-0.90±0.2	-0.72±0.2
PtP im·min^{-1} $cmH_2O \cdot s^{-1} \cdot min^{-1}$	89.1±11.7	98.8±15.6	88.9±12.2	90.3±10.7	95.0±18.1
PtPtot·min^{-1} $cmH_2O \cdot s^{-1} \cdot min^{-1}$	107.8±10.5	116.8±17.1	100.7±12.7	101.4±10.8	108.9±18.5
t_{tot} s	2.44±0.2+	2.36±0.2+	2.46±0.2	2.70±0.2*	2.75±0.2*
nt_I s	0.66±0.04	0.66±0.04	0.66±0.04	0.74±0.07	0.71±0.07
nt_E s	1.79±0.2+	1.70±0.2+	1.80±0.2	1.96±0.2*	2.05±0.2*
nt_I /t_{tot}	0.28±0.02	0.29±0.02	0.28±0.02	0.28±0.02	0.26±0.02
$t_{I,ext}$ s	0.16±0.04+	0.16±0.04+	0.18±0.04	0.19±0.07	0.26±0.07*
V EELV/FRC L	-0.10±0.02	0.00±0.02	0.03±0.01	0.06±0.02	0.06±0.02

+: Significantly different than pressure support (PS); *: significantly different than baseline PS. V_T: tidal volume; dP/dt: the rate of pressure generated by the respiratory muscles (P_{mus}) increase during inspiration; $P_{mus,sw}$: P_{mus} swings during the respiratory cycle; $P_{mus,peak}$: peak P_{mus} during inspiration; $P_{mus,nadir}$: the lowest P_{mus} during expiration; PtP im·min^{-1}: pressure time product of inspiratory muscles per minute; PtPtot·min^{-1}: pressure time product of all (inspiratory and expiratory) respiratory muscles per minute; t_{tot}: total breath duration; nt_I and nt_E: neural inspiratory and expiratory time respectively; nt_I /t_{tot}: duty cycle; $t_{I,ext}$: time that mechanical inflation extents into neural expiration; V EELV/FRC: end expiratory lung volume (EELV) relative to passive functional residual volume (FRC).

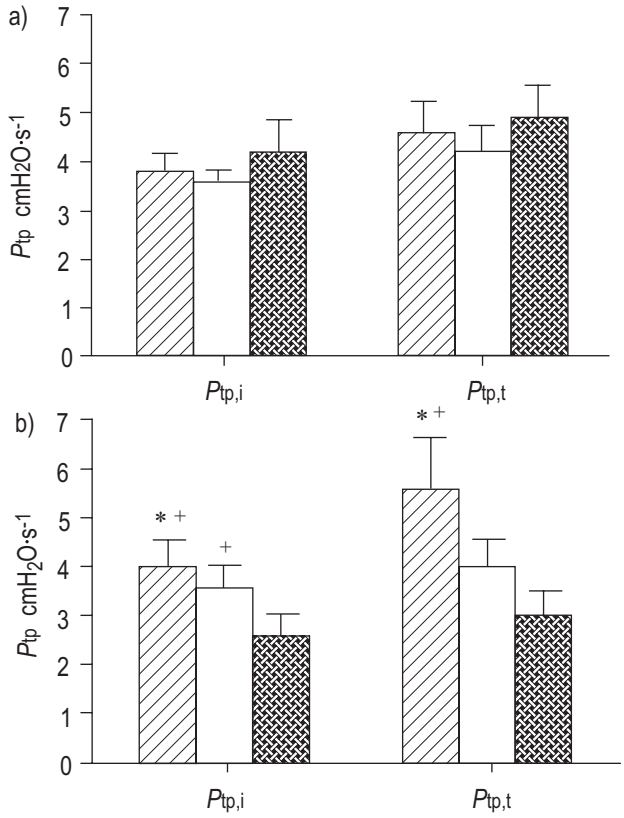

Fig. 1. – a) Protocol A. Mean±SEM pressure time product (Ptp) of inspiratory (Ptp,i) and all respiratory (Ptp,t) muscles of the breaths preceding the pressure support (PS) change. b) Protocol B. Mean±SEM Ptp of Ptp,i and Ptp,t muscles with steady state PS. *: significantly different from baseline; +: significantly from high PS. ○: baseline PS; ▨: low PS; ▩: high PS.

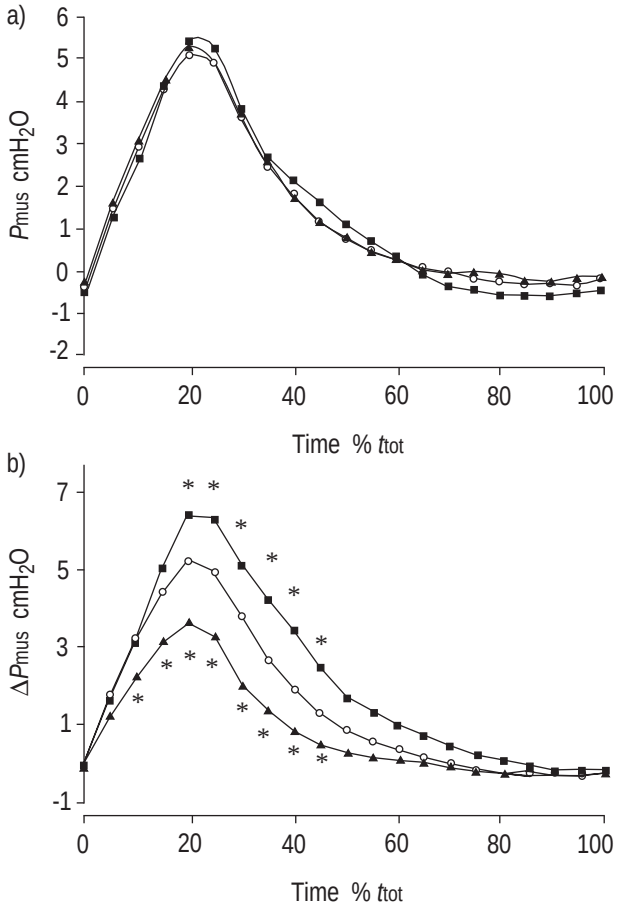

Fig. 2. – a) Protocol A. Average total pressure generated by the respiratory muscles (Pmus) waveform of the breaths preceding the pressure support (PS) change (baseline PS, ○) and that of the second breath after the decrease (■) or increase (▲) of PS. The traces were aligned at onset of neural inspiration (zero time). To correct for total breath duration ($t$tot) variability between breaths Pmus was expressed as a percentage of $t$tot. Each symbol represents the mean value of Pmus at that point. Observe the similarity of Pmus waveform at different PS levels. b) Protocol B. Average change in Pmus from that at the end of neural expiration (ΔPmus) with steady-state PS. ΔPmus was averaged during the last 2 min of each 30 min period. The traces were aligned at onset of neural inspiration (zero time). To correct for $t$tot variability between breaths ΔPmus was expressed as a percentage of $t$tot. Standard error bars have been omitted for clarity. *Significantly different from baseline at a given percentage of $t$tot. ○: baseline PS; ▲: high PS; ■: low PS.

increased significantly with low PS. With high PS P_{a,CO_2} was slightly, but nonsignificantly, lower than that 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 Ptp at end expiration and CL (see *Methods* section). Changes in end-expiratory Ptp 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 CO_2 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-inspiratory 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 cmH_2O. 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 elastance 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 be not 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 cmH_2O. It has been demonstrated that the lower inflection point is greatly minimized or even obviated 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, LEEVERS 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 t_{tot} and nt_E 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 decreasng stimulus intensity [8, 10]. Furthermore, STP or control system inertia has been observed following manipulations resulting in V_T that were close to $\geq$1 L [5–8, 10], considerably higher than that during spontaneous breathing. In the current study V_T during baseline was ~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

Table 4. – Arterial blood-gases and breath characteristics in Protocol B

	Low	Baseline	High
P_{a,CO_2} mmHg	48.2±5.0*$^{+}$	44.8±4.7	44.1±4.4
P_{a,O_2} mmHg	81.5±4.3	81.3±5.7	78.1±3.1
V_T L	0.55±0.05^{+}	0.57±0.05	0.62±0.06
dP/dt $cmH_2O \cdot s^{-1}$	13.45±2.2^{+}	10.28±1.3	6.85±1.3
$P_{mus,sw}$ cmH_2O	8.43±1.3*$^{+}$	6.02±0.7	4.25±0.8
$P_{mus,peak}$ cmH_2O	6.87±1.2*$^{+}$	5.38±0.6	3.61±0.7*
$P_{mus,nadir}$ cmH_2O	-1.51±0.6	-0.64±0.2	-0.64±0.2
PtP $im \cdot min^{-1}$ $cmH_2O \cdot s^{-1} \cdot min^{-1}$	112.0±27.5^{+}	84.0±8.8	52.7±10.7
$PtP_{tot} \cdot min^{-1}$ $cmH_2O \cdot s^{-1} \cdot min^{-1}$	152.2±30.1^{+}	102.4±15.1	63.9±12.5
t_{tot} s	2.35±0.2^{+}	2.51±0.2	2.75±0.2
ntI s	0.66±0.04	0.67±0.04	0.62±0.04
ntE s	1.69±0.2^{+}	1.84±0.2	2.13±0.1*
ntI /t_{tot}	0.30±0.08^{+}	0.28±0.07^{+}	0.23±0.03
$t_{I,ext}$ s	0.16±0.04	0.19±0.04	0.28±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. P_{a,O_2} and P_{a,CO_2}: oxygen and carbon dioxide respectively, tension of arterial blood. See table 3 for other abbreviations. 1 mmHg=0.133 kPa.

blood gas composition to reach peripheral chemoreceptors [12]. This reflex response of ntE to varying PS could be due to two factors. Firstly, for a given P_{mus} lung volume changed as a function of PS level; it increased with increasing PS (V_T increased by ~50% from low to high PS, whereas PS remained constant). This response caused the V_T/P_{mus} 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 ntI would be expected with high PS, as a result of the high V_T. There are at least two reasons, however, that may account for this apparent nondependency of ntI on V_T. 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 ntI on V_T progressively decreases as ntI without volume feedback decreases, as it occurs in the presence of various stimuli that increase breathing frequency [4, 31]. Secondly, the V_T 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 P_{mus} 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 P_{a,CO_2} observed with different PS might not be able to elicit the P_{mus} responses observed. Indeed, compared to baseline, P_{a,CO_2} 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 P_{a,CO_2} 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 P_{a,CO_2} [4, 34]. It follows that chemical feedback cannot be discounted on the grounds that P_{a,CO_2} did not change significantly. Furthermore, there were no discernible immediate changes in P_{mus} 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 P_{mus} 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 CO_2 effects [35].

Is it possible that a slowly evolving reflex response may partly contribute to P_{mus} 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 V_T failed to modify P_{mus} waveform. The V_T increased by ~50% from low to high PS, yet P_{mus} 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 (BIPAP) [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

proportional to the decrease in respiratory drive (estimated using the change in oesophageal pressure before triggering, dp/dt) during intervening breaths. These results indicate that inspiratory activity was preprogrammed and it was rela-tively insensitive to the breath-by-breath changes in load seen during SIMV or BIPAP. It has been suggested that chemical feedback and intrinsic mechanical properties of the respiratory system could be a critical factor for this breath programming [13, 39].

The results of this study appear to contradict with those obtained by FAUROUX *et al.* [41] in normal conscious humans and BONMARCHAND *et al.* [3] in COPD patients. FAUROUX *et al.* [41] observed that during normocapnic PS respiratory drive decreased compared to spontaneous breathing. BONMARCHAND *et al.* [3] increased the initial flow rate during PS by decreasing the attack time of achieving the predetermined PS level and observed a decrease in respiratory drive, although end-tidal carbon dioxide tension ($P\mathrm{CO_2}$) ($P_{\mathrm{ET,CO_2}}$) decreased minimally. Direct comparison between these studies and the current study is difficult due to differences in experimental design as well as in the patients studied. In the study of FAUROUX *et al.* V_T during PS was approximately double that during spontaneous breathing. Perhaps an inhibitory input is generated with very high volumes of ventilation. Furthermore, conscious healthy humans were studied and, thus, behavioural response to these high values of V_T cannot be entirely excluded. In the study of BONMARCHAND *et al.* CO_2 stimulus was not controlled during the various study periods. Indeed, mean $P_{\mathrm{ET,CO_2}}$ and mean airway occlusion pressure ($P0.1$) (an index of inspiratory drive) differed by 0.319 kPa, 5.19 *versus* 5.51 (2.4 mmHg, 39 *versus* 41.4) and 1.4 $\mathrm{cmH_2O}$, 2.2 *versus* 3.6, respectively, between the highest and lowest initial inspiratory flow rate ($T0.1$ and $T1.25$ periods in their study where data from all patients were reported). This gives a $P0.1/P_{\mathrm{ET,CO_2}}$ ratio of 0.58 $\mathrm{cmH_2O{\cdot}mmHg}$ (1 mmHg=0.133 kPa), which is similar to the $P0.1$ response to CO_2 challenge observed in COPD patients [42]. Notwithstanding that $P_{\mathrm{ET,CO_2}}$ in COPD patients may not accurately reflect $P_{\mathrm{a,CO_2}}$, these findings indicate that the downregulation of respiratory drive might be related to chemical feedback.

LEEVERS and coworkers [5, 6] have shown in both awake and sleeping humans the occurrence of apnoea after isocapnic artificial ventilation indicating a nonchemical mediated inhibition of respiratory activity. However, in these studies the V_T during mechanical ventilation was at least twice that during spontaneous breathing, again raising the issue of high V_T for nonchemical inhibition.

Nevertheless, the results of LEEVERS and coworkers [5, 6] have been challenged by other studies [23, 24]. Currently, the issue of neuromechanical inhibition remains highly controversial [23].

Studies in anesthetized dogs and cats have shown that positive pressure breathing diminishes respiratory drive as assessed 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 work, V_T during PS was several folds higher than that during spontaneous breathing indicating that very high lung volume may be necessary for the reflex inhibition of respiratory drive.

Recently VIALE *et al.* [40] studied the time course of the effects of PS on respiratory muscle activity in patients with COPD. When the patients were placed on PS only mean P_{di} decreased within the first two breaths. The other indices of respiratory drive such as oesophageal occlusion pressure (P_{oes},0.1) and diaphragmatic electromyogram (EMGdi) decreased several seconds later, in line with the findings of the current study. VIALE *et al.* [40] interpreted their results as indicating that PS unloads the inspiratory muscles from the first breath. Notwithstanding that patients with obstructive lung disease were studied and only one trial was analysed in each patient, the interpretation of the change in mean P_{di} is complicated. In the study of VIALE *et al.* [40] mean P_{di} was calculated using the inspiratory time based on inspiratory flow tracing. In mechanically ventilated patients, particularly in the presence of obstructive lung disease, mechanical events do not reflect neural events [13]. Furthermore, mechanical feedback, due to considerably higher flow and volume with PS, and end-expiratory lung volume changes were not taken into account in P_{di} interpretation. Finally, P_{di} waveform was not reported.

The findings of the current study may have clinical implications for mechanically ventilated patients. If chemical feedback dominates the response of respiratory mus-cles to pressure support then the degree of downregulation with pressure support will depend on the individual sen-sitivity to chemical stimuli. their relation to alveolar ventilation and the magnitude of carbon dioxide tension in arterial blood change. For a given increase in alveolar ventilation downregulation will be greater in patients with high sensitivity to carbon dioxide tension in arterial blood and/or high initial carbon dioxide tension in arterial blood (due to the shape of the carbon dioxide tension in arteriae blood-alveolar ventilation relationship). In awake patients this may cause a considerable reduction in the sense of dyspnoea and greater acceptability of mechanical ventilation, an issue of great importance for invasive and noninvasive ventilatory support. This, however, needs to be studied. In addition, it should be stated that patients were studied with acute lung injury over a limited range of pressure support. Thus, it is not known whether these findings may apply in other groups of patients and at higher pressure support levels.

References

1. Brochard L, Harf A, Lorino H, Lemaire F. Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. *Am Rev Respir Dis* 1989; 139: 513–521.
2. Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator mode on triggering, patient effort, and dyspnoea. *Am J Respir Crit Care Med* 1997; 155: 1940–1948.
3. Bonmarchand G, Chevron V, Chopin C, *et al*. Increased initial flow rate reduces inspiratory work of breathing during pressure support ventilation in patients with exacerbation of chronic obstructive pulmonary disease. *Intensive Care Med* 1996; 22: 1147–1154.
4. Younes M. Mechanisms of respiratory load compensation. *In*: Dempsey JA, Pack AI, ed. Regulation of Breathing. Lung Biology in Health and Disease. Vol. 19. Marcel Dekker, New York, 1996; pp. 867–922.

5. Leevers AM, Simon P, Xi L, Dempsey JA. Apnoea following normocapnic mechanical ventilation in awake mammals: a demonstration of control system inertia. *J Physiol* 1993; 472: 749–768.
6. Leevers AM, Simon P, Dempsey JA. Apnoea after normocapnic mechanical ventilation during NREM sleep. *J Appl Physiol* 1994; 77: 2079–2085.
7. Tawadrous FD, Eldridge FL. Posthyperventilation breathing patterns after active hyperventilation in man. *J Appl Physiol* 1974; 37: 353–356.
8. Georgopoulos D, Giannouli E, Tsara V, Argiropoulou P, Patakas D, Anthonisen NR. Respiratory short-term poststimulus potentiation (after-discharge) in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1992; 146: 1250–1255.
9. Georgopoulos D, Mitrouska I, Koletsos K, *et al*. Poststimulus ventilation in patients with brain damage. *Am J Respir Crit Care Med* 1995; 152: 1627–1632.
10. Fregosi RF. Short-term potentiation of breathing in humans. *J Appl Physiol* 1991; 71: 892–899.
11. Younes M, Arkinstall W, Milic-Emili J. Mechanism of rapid ventilatory compensation to added elastic loads. *J Appl Physiol* 1973; 35: 443–453.
12. Lange RL, Horgan JD, Botticelli JT, Tsagaris T, Carlisle RP, Kuida H. Pulmonary to arterial circulatory transfer function: importance in respiratory control. *J Appl Physiol* 1996; 21: 1281–1291.
13. Georgopoulos D, Roussos C. Control of breathing in mechanically ventilated patients. *Eur Respir J* 1996; 9: 2151–2160.
14. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. *Am Rev Respir Dis* 1982; 126: 788–791.
15. Prechter GC, Nelson SB, Hubmayr RD. The ventilatory recruitment threshold for carbon dioxide. *Am Rev Respir Dis* 1990; 141: 758–764.
16. Pelosi P, Cereda G, Foti M, Giacomini M, Pesenti A. Alterations of lung and chest wall mechanics in patients with acute lung injury: effects of positive end-expiratory pressure. *Am J Respir Crit Care Med* 1995; 152: 531–537.
17. Campbell EJM. The respiratory muscles and the mechanics of breathing. London, Loyd-Luke 1958.
18. Georgopoulos D, Mitrouska I, Webster K, Bshouty Z, Younes M. Effects of respiratory muscle unloading on the ventilatory response to CO_2. *Am J Respir Crit Care Med* 1997; 155: 2000–2009.
19. Yan S, Sliwinski P, Gauthier AP, *et al*. Effect of global inspiratory muscle fatigue on ventilatory and respiratory muscle responses to CO_2. *J Appl Physiol* 1993; 75: 1371–1377.
20. D′Angelo E, Robatto FM, Calderini E, *et al*. Pulmonary and chest wall mechanics in anesthetized paralyzed humans. *J Appl Physiol* 1991; 70: 2602–2610.
21. Ranieri MV, Brienza N, Santostasi S, *et al*. Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome. Role of abdominal distension. *Am J Respir Crit Care Med* 1997; 156: 1082–1091.
22. Mergoni M, Martelli A, Volpi A, Primavera S, Zuccoli P, Rossi A. Impact of positive end-expiratory pressure on chest wall and lung pressure-volume curve in acute respiratory failure. *Am J Respir Crit Care Med* 1997; 156: 846–854.
23. Datta AK, Shea SA, Homer RL, Guz A. The influence of induced hypocapnia and sleep on the endogenous rhythm in humans. *J Physiology* 1991; 440: 17–33.
24. Puddy A, Patrick W, Webster K, Younes M. Respiratory control during volume-cycled ventilation in normal humans. *J Appl Physiol* 1996; 80: 1749–1758.
25. Puddy A, Younes M. Effect of inspiratory flow rate on respiratory motor output in normal humans. *Am Rev Respir Dis* 1992; 146: 787–789.
26. Georgopoulos D, Mitrouska I, Bshouty Z, Webster K, Anthonisen NR, Younes M. Effects of breathing route, temperature and volume of inspired gas and airway anesthesia on the response of respiratory output to varying inspiratory flow. *Am J Respir Crit Care Med* 1996; 153: 168–175.
27. Younes M, Youssef M. Effect of five human anesthetics on respiratory control in cats. *J Appl Physiol* 1978; 44: 596–606.
28. Remmers JE. Inhibition of inspiratory activity by intercostal muscle afferents. *Respir Physiol* 1970; 10: 358–383.
29. Remmers JE, Bartlett D Jr. Reflex control of expiratory airflow and duration. *J Appl Physiol* 1977; 42: 80–87.
30. Gautier H, Remmers JE, Bartlett D Jr. Control of the duration of expiration. *Respir Physiol* 1973; 18: 205–221.
31. Bradley GW, Von Euler C, Marttila I, Roos B. Steady state effects of CO_2 and temperature on the relationship between lung volume and inspiratory duration (Hering-Breuer threshold curve). *Acta Physiol Scand* 1974; 92: 351–363.
32. Widdicombe JG. Respiratory reflexes in man and other mammalian species. *Clin Sci* 1961; 21: 163–170.
33. Iber C, Simon P, Skatrud JB, Mahowald MW, Dempsey JA. The Breuer-Hering reflex in humans: effects of pulmonary denervation and hypocapnia. *Am J Respir Crit Care Med* 1995; 152: 217–224.
34. Younes M, Riddle W. A model for the relationship between respiratory neural and mechanical outputs. I. Theory. *J Appl Physiol* 1981; 51: 963–978.
35. Euler CV, Marttila I, Remmers JE, Trippenbach T. Effects of lesions in the parabrachial nucleus on the mechanisms for central and reflex termination of inspiration in the cat. *Acta Physiol Scand* 1976; 96: 324–337.
36. Milic-Emili J, Tyler JM. Relation between work output of respiratory muscles and end-tidal CO_2 tension. *J Appl Physiol* 1963; 18: 497–504.
37. Meza S, Giannouli E, Younes M. Control of breathing during sleep assessed by proportional assist ventilation. *J Appl Physiol* 1998; 84: 3–12.
38. Marini JJ, Smith TC, Lamb VJ. External output and force generation during synchronized intermittent mechanical ventilation. *Am Rev Respir Dis* 1998; 138: 1169–1179.
39. Imsand C, Feihl F, Perret C, Fitting JW. Regulation of inspiratory neuromuscular output during synchronized intermittent mechanical ventilation. *Anesthesiology* 1994; 80: 13–22.
40. Viale JP, Duperret S, Mahul P, *et al*. Time course evolution of ventilatory responses to inspiratory unloading in patients. *Am J Respir Crit Care Med* 1998; 428–434.
41. Fauroux B, Isabey D, Desmarais G, Brochard L, Harf A, Lofaso F. Nonchemical influence of inspiratory pressure support on inspiratory activity in humans. *J Appl Physiol* 1998; 85: 2169–2175.
42. Tobin MJ, Gardner WN. Monitoring of the control of breathing. *In:* Tobin MJ, ed. Principles and Practice of Intensive Care Monitoring. McGraw-Hill, Inc., 1998; pp. 415–464.
43. Tan CSH, Simmons DH. Effect of assisted ventilation on respiratory drive of normal anesthetized dogs. *Respir Physiol* 1981; 43: 287–297.
44. Shams H, Scheid P. Respiratory response to positive inspiratory pressure in the cat: effects of CO_2 and vagal integrity. *J Appl Physiol* 1995; 79: 1704–1710.