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Acute effects of ventilator settings on respiratory motor output in patients with acute lung injury

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Abstract *Objective*: During assisted mechanical ventilation, changes in ventilator settings may acutely affect the respiratory motor output via the mechanoreceptor reflex feedback system, thus interfering with patient management. This feedback system in mechanically ventilated patients with parenchymal lung injury remains largely unexplored. To investigate this, the early response of respiratory motor output to varying ventilator settings was determined in 13 sedated patients with acute lung injury.
Design: During assist/control and pressure support (PS) ventilation changes in (1) tidal volume (V_T) at fixed inspiratory flow (V'_I), (2) V'_I at fixed V_T and (3) PS level were employed and the response of respiratory motor output was followed for two breaths after the change. Respiratory motor output was assessed by total pressure generated by the respiratory muscles (Pmus), computed from esophageal pressure (Pes).
Results: Neural expiratory time increased with increasing V_T and PS, while it remained constant with V'_I changes. Neural inspiratory time ($T_I n$) increased with decreasing V'_I and PS, but was not affected by V_T changes. None of the changes in ventilator settings influenced significantly the rate of rise of Pmus, used as an index of respiratory drive. The changes in respiratory timing resulted in significant changes in breathing frequency, which increased with decreasing V_T and PS and increasing V'_I. The time integral of Pmus, an index of respiratory effort, increased with increasing $T_I n$. These acute responses were not related to the severity of deterioration of respiratory system mechanics.
Conclusions: We conclude that alterations in commonly used ventilator settings induce acute changes in respiratory timing, without affecting the respiratory drive. These changes, probably mediated via mechanoreceptor reflex feedback, are dependent on the type of the alteration in the ventilator settings.

Keywords Timing · Drive · Reflex feedback · Respiratory muscle pressure

Introduction

During assisted mechanical ventilation, changes in ventilator settings (i.e. level of assist, mechanical inflation time, inspiratory flow) are commonly used in order to achieve various goals, such as better synchrony between the patient and ventilator, less dynamic hyperinflation, reduced work of breathing and more efficient gas exchange [1, 2, 3, 4, 5]. However, the patient who is ventilated on assisted modes of support is not a passive structure but may respond to the alteration in ventilator settings via chemical, mechanoreceptor reflex and behav-

ioral feedback systems [6, 7]. This response may interfere with the planning strategy by reducing or increasing the efficiency of a change in ventilator settings to achieve its goal [6, 7]. It follows that the physician dealing with a mechanically ventilated patient should be aware of the effects of the various feedback systems on respiratory motor output.

Recently, the chemical feedback during assisted mechanical ventilation has been investigated in several studies [8, 9, 10, 11, 12]. These studies showed that chemical feedback, although its operation is affected by the mode of support, has powerful effects on respiratory motor output [8, 9, 10, 11, 12]. On the other hand, at least in humans, very little is known about the function of the mechanoreceptor reflex feedback during assisted mechanical ventilation, as well as its contribution to the prevailing level of respiratory muscle activity. Furthermore, it is not known to what extent various disease states modify the operation of this system. Studies in normal humans and in mechanically ventilated patients with acute respiratory failure due to a variety of diseases have shown that the mechanoreceptor reflex feedback may affect significantly the respiratory timing [12, 13, 14, 15, 16, 17, 18, 19] and, under certain circumstances, the respiratory drive [20]. In the majority of these studies, however, the response of respiratory motor output was not studied in detail [13, 14, 15, 16, 17, 18, 19]. In addition, only one study examined the mechanoreceptor reflex feedback system of a homogeneous group of patients [12]. In this study patients with acute lung injury were ventilated on pressure support mode and the mechanoreceptor reflex response to varying pressure support levels was examined [12]. The effects of other than pressure support level ventilator settings on respiratory motor output in this group of patients are not known.

The aim of the present study was to examine the acute response of respiratory motor output to varying commonly used ventilator settings, such as tidal volume (V_T), inspiratory flow (V'_I) and pressure support (PS), in a group of mechanically ventilated patients with acute lung injury. The acute response, thought to be mediated via a mechanoreceptor reflex feedback system [12, 21], may give some insights into the complex issue of control of breathing during mechanical ventilation in this group of patients.

Methods

Thirteen patients admitted to the Intensive Care Unit for management of acute lung injury were studied. The diagnosis of acute lung injury was based on American-European Consensus Conference criteria [22]. At the time of the study all patients were hemodynamically stable without vasoactive drugs (other than dobutamine < 5 μg·kg·min) and ventilated on pressure support mode through cuffed endotracheal (12 patients) or tracheostomy (1 patient) tubes. The pressure support 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 (1.0–1.5 mg/kg/h). The level of sedation was such as to achieve a score of 3 on Ramsay's scale (response to commands only) [23]. Patients with one of the following characteristics were excluded: (1) previous history of obstructive lung disease (COPD or asthma), (2) chest wall abnormalities, (3) pneumothorax or (4) overt pleural effusion. The study was approved by the hospital ethics committee and informed consent was obtained from the patients or their families.

Flow at the airway opening was measured with a heated pneumotachograph (Hans-Rudolf 3700, Kansas, USA) and a differential pressure transducer (Micro-Switch 140PC, Honeywell, Ontario, Canada), placed between the endotracheal tube and the Y-piece of the ventilator. Flow was electronically integrated to provide volume. Airway pressure (Paw; Micro-Switch 140PC, Honeywell, Ontario, Canada) was measured from a side port between the pneumotachograph and the endotracheal tube. Esophageal pressure (Pes) was measured with an esophageal balloon positioned at the lower third of the esophagus and filled with 0.5 ml of air. The proper position of the balloon was verified using the occlusion test [24]. The response of the pneumotachograph was linear over the experimental range of flow. With the system used to measure Paw and Pes there was no appreciable shift or alteration in amplitude up to 20 Hz. Each signal was sampled at 150 Hz (Windaq Instruments, Ohio, USA) using tubes with low compliance and standard length (50 cm) and stored on a computer disk for later analysis.

The patients were studied in semi-recumbent position (> 45 degrees) in order to obtain as accurate a Pes signal as possible. Initially, the patients were connected to a prototype ventilator (Winnipeg ventilator, University of Manitoba, Winnipeg, Canada) which was able to ventilate them in the volumetric assist/control and pressure support modes. The design and operation of this ventilator has been described in detail previously [11, 25].

Throughout the study PEEP remained constant to a value similar to that applied in pressure support mode before the beginning of the study. Fractional concentration of oxygen (FIO_2)was such as to achieve SaO_2 more than 90%. The study was conducted in the three following randomly applied protocols.

Varying tidal volume protocol

In the varying V_T protocol the patients were ventilated on assist/control with a V_T very similar to that achieved in pressure support mode before the beginning of the study. Inspiratory flow rate (V'_I), given with a square-wave pattern, was set to a value resulting in airway pressure-time waveform with a minimum concavity to the pressure axis during inspiration. The back-up rate of the ventilator was set to zero to insure that all breaths were triggered by the patient. With these settings, ventilatory parameters were recorded for 2 min while blood gases were measured during this period (baseline V_T). Thereafter, V_T was randomly increased (high V_T) or decreased (low V_T) by 150 ml. The actual change, however, was slightly different, averaging 180 ± 60 ml. Each change was maintained for two breaths. Six trials where V_T was decreased for two breaths and six trials where V_T was increased, also for two breaths, were performed in each patient. For a given change in ventilator settings, the target was to analyze at least four satisfactory trials (see below) in each patient. As a result of V_T changes, mechanical inspiratory time varied directly with changes in V_T. Between trials 3 min of baseline V_T ventilation were allowed. At the end of the protocol ventilatory parameters were recorded for 2 min and arterial blood gases were measured again.

Varying inspiratory flow protocol

In the varying V'_I protocol the patients were ventilated on assist/control with the baseline V_T ventilator settings (baseline V'_I). Thereafter, keeping the V_T constant, V'_I was randomly increased (high V'_I) or decreased (low V'_I) by 0.30 l/s (actual mean change 0.38 ± 0.17 l/s). As a result of these changes, mechanical inspiratory time varied inversely with changes in V'_I. Apart from the manipulated variable, principles similar to those of the varying V_T protocol were followed.

Varying pressure support (PS) protocol

In the varying PS protocol the patients were ventilated on pressure support with ventilator settings identical to those applied on pressure support before the beginning of the study (baseline PS). Thereafter, PS was randomly increased (high PS) or decreased (low PS) by 5 cmH_2O (actual mean change 5.8 ± 0.4 cmH_2O). Apart from the manipulated variable, principles similar to those of the other protocols were applied.

Respiratory system mechanics

At the end of the study the patients were placed on volume-control mode and ventilated with relatively high V_T given with square-wave flow-time profile. In addition, the level of sedation was increased (propofol 6 mg/kg/h plus fentanyl 2.5 μg/kg/h) such as to achieve a score of 6 on Ramsay's scale [23]. Simultaneously, breathing frequency was adjusted upward in order to lower $PaCO_2$ and inhibit respiratory muscle activity. The absence of respiratory muscle activity was based on specific criteria [26]. In patients in whom respiratory muscle activity was not inhibited, a neuromuscular blocking agent was administered (atracurium 25 mg). When passive ventilation was obtained the total respiratory system and lung and chest wall mechanics (resistance and compliance) were measured by the technique of rapid airway occlusion using standard formulas [27]. All the respiratory mechanics data were computed as an average of three measurements obtained by respective maneuvers satisfying passive condition [26].

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 Pes and transpulmonary pressure (Ptp = Paw–Pes) 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 (Pes_{FRC} and Ptp_{FRC}, respectively).

Data analysis

Trials with artifacts in Pes tracing because of swallowing were excluded from the analysis. Furthermore, trials with double triggering (i.e. ventilator was triggered twice by a single inspiratory effort [6]) were also excluded. Double triggering was occasionally observed when the change in ventilator settings resulted in a considerable decrease in mechanical inflation time. At least four trials were analyzed in each patient for a given change in ventilator settings.

Pressure generated by all respiratory muscles (Pmus) was calculated from Pes taking into account the passive elastic and resistive properties of the chest wall. This calculation, which is based on the Campbell diagram, was described in detail earlier [8, 11, 12]. Briefly, at each instant in the respiratory cycle Pmus is the difference between the pleural pressure (Ppl) that would be obtained at the same respiratory volume and flow during passive inflation or deflation and the Ppl actually observed. Thus:

$$Pmus = Ppl\ (passive) - Ppl\ (actual) \quad (1)$$

With passive inflation or deflation the Ppl that would be obtained at given volume (V) and flow (V') is given by:

$$Ppl\ (passive) = V \times Ecw + Pcw_{FRC} + V' \times Rcw \quad (2)$$

where V is volume relative to passive FRC, and Ecw and Rcw are, respectively, the elastance and resistance of the chest wall. Pcw_{FRC} is passive chest wall recoil at passive FRC. The values of Ecw and Rcw obtained at the end of the study were used, while Pcw_{FRC} was assigned a value that equaled Pes_{FRC}. Inspiratory V' and expiratory V' were assigned positive and negative values, respectively. Thus, assuming that Ppl = Pes, at time (t) from the beginning of neural inspiration (see below) Pmus(t) was calculated as follows (Fig. 1):

$$Pmus(t) = Ecw \times V(t) + Pes_{FRC} + Rcw \times V'(t) - Pes(t) \quad (3)$$

where V(t) is volume relative to passive FRC (determined by PEEP level) and V'(t) is flow. The volume was related to passive FRC by calculating Ptp at end expiration (zero flow) and comparing this value (Ptp_{end}) with that obtained at passive FRC (Ptp_{FRC}). The difference between Ptp_{end} and Ptp_{FRC} multiplied by the lung compliance (C_L) should be equal to the difference in lung volumes between passive FRC and end-expiration of the breath of interest (ΔV_{end}) [8, 11, 12, 28].

The breaths preceding the changes in ventilator settings (V_T, V'_I and PS) were averaged to give a single waveform for each of Pmus, Pes, Paw, V and V' (baseline). Thus, a representative baseline breath in the three protocols was obtained for each patient. At least eight breaths in each patient were used to generate the representative baseline breath for a given protocol. Similarly, the first and second breaths following a change in ventilator settings were averaged (average of a minimum of four trials) to give the corresponding representative breaths after the change.

Waveforms of Pmus, Pes, Paw, V and V' were aligned at the beginning of neural inspiration, defined as the time that Pmus began to increase rapidly from the value reached during expiration [8, 11, 12]. Neural inspiratory time (T_In) was measured as the interval between the beginning of Pmus increase and the point at which Pmus started to decline rapidly [8, 11, 12]. Neural expiratory time (T_En) was measured as the remainder of the respiratory cycle, determined from the Pmus waveform. Mechanical inflation (T_Im) and deflation (T_Em) times were measured as the intervals between the beginning and the end of inspiratory and expiratory flow, respectively.

We also calculated various indices of respiratory motor output using the Pmus waveform. These indices were:

1. Peak Pmus ($Pmus_{peak}$); the highest value of Pmus during inspiration.
2. The rate of rise of Pmus (dp/dt); the difference between $Pmus_{peak}$ and Pmus at the onset of neural inspiration divided by the corresponding time.
3. The swings of Pmus during the respiratory cycle ($Pmus_{sw}$); the difference between $Pmus_{peak}$ and the lowest value of Pmus achieved during expiration.

Respiratory muscle effort during the respiratory cycle was quantified using the time integral of respiratory muscle pressure. The

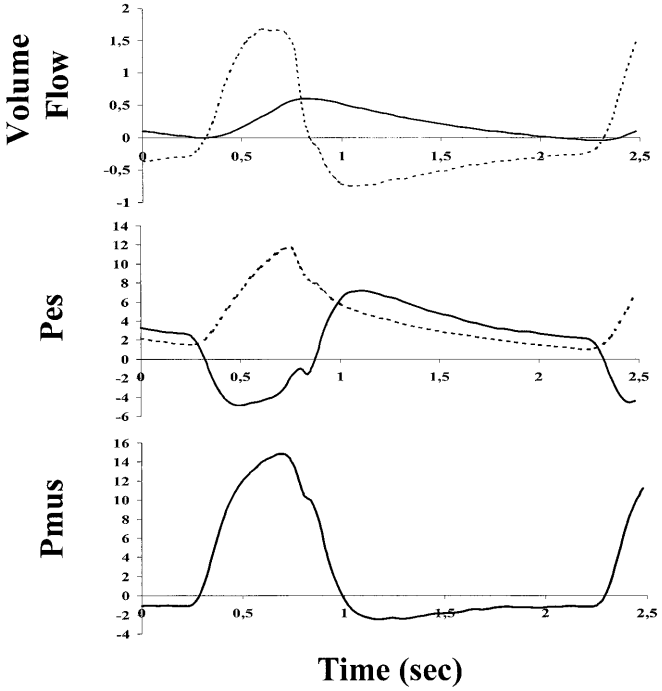

Fig. 1 Upper panel: Volume (l, *continuous line*) and flow (l/s, *dashed line*) as a function of time in a patient receiving assist/control. Volume is related to passive FRC. Middle panel: Actual esophageal *(continuous line)* and estimated esophageal *(dashed line)* pressure as a function of time (cmH_2O). At time (t) estimated esophageal pressure during passive conditions were calculated by Eq. 3 [$Pes_t(passive) = E_{cw} \times V_t + Pes_{FRC} + R_{cw} \times V'_t$]. Lower panel: Pressure developed by the respiratory muscles (Pmus, cmH_2O). At each instant in the respiratory cycle Pmus is the difference between the estimated and the actual esophageal pressure. See text for further detail

time integral of positive and negative Pmus represented the pressure time product of inspiratory (PTPi) and expiratory (PTPe) muscles, respectively [29]. PTP of all respiratory muscles (inspiratory and expiratory, PTPtot) was calculated as the sum of PTPi and PTPe. PTPi, PTPe and PTPtot were calculated on a per breath basis. The PTP values per minute were calculated as the product of the respective PTP per breath and breathing frequency.

Data were analyzed by analysis of variance for repeated measurements (ANOVA), followed by Tukey's test, if the *F* value was significant, and regression analysis where appropriate. A p less than 0.05 was considered statistically significant. All values are expressed as mean ± SD.

Results

The main clinical characteristics, baseline ventilator settings and respiratory system mechanics are shown in Tables 1 and 2. For the whole group the mean values of the elastance (Ers) and airflow resistance of the respiratory system (Rrs) (including the endotracheal tube resistance) were considerably higher than those observed in healthy normal subjects [27]. The increase in Ers and Rrs was mainly due to mechanical properties of the lung, while the elastance (Ecw) and resistance (Rcw) of the chest wall were slightly above the normal limits (Table 2).

For a given protocol ventilatory parameters and arterial blood gases with baseline ventilator settings did not differ between the beginning and the end of the protocol, indicating the patients' stability during the time that the trials were performed. Independent of the protocol, none of the breath characteristics differed significantly between the first and second breaths after the change in ventilator settings and, therefore, for clarity of presentation these two breaths were averaged. In all patients the two breaths following a change in ventilator settings were completed in less than 6.5 s.

Varying tidal volume protocol

Sixty-seven satisfactory trials (no swallowing artifacts, no double triggering) where V_T increased to 0.71 ± 0.12 l for two breaths and 59 where V_T decreased to 0.35 ± 0.08 l, also for two breaths, were analyzed (baseline V_T 0.52 ± 0.1 l). T_{TOT} varied directly with V_T changes (Table 3). The T_{TOT} response was mainly due to T_En (Table 3, Fig. 2), whereas T_In remained relatively constant. As a result T_In/T_{TOT} increased with decreasing V_T. There was no relationship between the T_En response to V_T changes ($\Delta T_En/\Delta V_T$) and respiratory system mechanics (multiple regression, $p > 0.05$). Respiratory effort per breath increased slightly with increasing V_T, due mainly to expiratory effort. The volume relative to passive FRC at the end of neural inspiration (V_{th}) and the time that mechanical inflation extended into neural expiration (T_{ext}) varied directly with changes in V_T. V_T changes did not affect ΔV_{end} significantly.

With low V_T, the end of mechanical inspiration (end of inspiratory flow) occurred before the end of neural inspiration in three patients. This was the case in one patient with baseline V_T. With high V_T, the end of neural inspiration occurred before the end of mechanical inspiration in all patients.

There was a significant linear relationship between the changes induced by V_T alterations in T_{ext} (ΔT_{ext}) and T_En (ΔT_En) (Fig. 3). ΔT_En was also linearly related to V_T changes (ΔV_T) ($\Delta T_En = 0.06 + 1.08\Delta V_T$; $r = 0.87$, $p < 0.01$).

Varying inspiratory flow protocol

Sixty-five trials where V'_I increased to 1.49 ± 0.44 l/s for two breaths and 66 where V'_I decreased to 0.77 ± 0.28 l/s, also for two breaths, were analyzed (baseline V'_I 1.10 ± 0.3 l/s). V'_I had a significant effect on T_{TOT}; T_{TOT}

Table 1 Patients' characteristics and baseline ventilator settings (*M* male, *F* female, *PEEP* positive end-expiratory pressure, *PS* pressure support level, F_IO_2 fractional concentration of oxygen, PaO_2 and $PaCO_2$ partial pressure of arterial oxygen and carbon dioxide, respectively, *MV* mechanical ventilation, *ALI* acute lung injury, *AIP* acute interstitial pneumonia)

Patient No.	Age (years)	Sex	PEEP (cmH_2O)	PS	F_IO_2 (%)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	Days on MV	Cause of ALI
1	78	M	6	20	0.30	60.1	45.6	3	Pneumonia
2	69	M	5	18	0.60	67.8	40.5	5	Aspiration
3	40	F	5	15	0.60	114.2	42.1	25	Sepsis
4	65	M	5	12	0.50	63.7	52.9	7	Sepsis
5	38	M	5	12	0.40	67.0	47.0	7	Pneumonia
6	80	M	5	17	0.50	90.0	38.3	5	Sepsis
7	64	M	9	14	0.50	91.0	41.0	4	Pneumonia
8	45	M	6	13	0.50	87.0	35.10	8	Pneumonia
9	76	F	7	30	0.60	69.0	63.9	10	Sepsis
10	61	F	6	16	0.50	85.8	37.0	2	Pneumonia
11	70	F	10	22	0.60	62.0	37.0	5	Pancreatitis
12	40	M	8	15	0.40	65.0	44.2	6	Sepsis
13	62	M	9	18	0.50	70.0	42.1	3	AIP
Mean	60.6		6.6	16.9	0.50	76.4	43.6	6.9	
SD	15.0		1.8	5.0	0.09	16.0	7.8	5.9	

Table 2 Respiratory system mechanics (*Ers*, E_L, *Ecw* elastance of respiratory system, lung and chest wall, respectively, *Rrs*, R_L, *Rcw* airflow resistance of respiratory system, lung and chest wall, respectively, *PEEPi* intrinsic positive end-expiratory pressure (above PEEP)

Patient No.	Ers cmH_2O/l	Rrs $cmH_2O/l/s$	EL cmH_2O/l	RL $cmH_2O/l/s$	Ecw cmH_2O/l	Rcw $cmH_2O/l/s$	PEEPi cmH_2O
1	9.8	15.9	3.8	13.4	6.0	2.5	0.0
2	25.8	14.9	15.1	12.4	10.7	2.5	1.1
3	38.0	12.6	31.2	11.6	6.8	1.1	0.8
4	30.8	16.6	26.7	14.9	4.1	1.7	0.0
5	17.5	8.0	12.5	6.0	5.0	2.0	0.6
6	21.5	12.1	14.7	11.2	6.8	0.9	0.6
7	12.3	7.2	5.0	6.2	7.3	1.0	0.8
8	29.3	15.4	23.8	13.9	5.5	1.5	0.3
9	30.2	17.1	25.2	16.7	5.0	0.4	5.0
10	25.6	17.2	18.1	16.2	7.5	1.0	1.1
11	28.1	14.5	18.7	13.8	9.4	0.7	1.3
12	29.1	11.0	22.6	9.2	6.5	1.8	0.5
13	24.6	13.3	16.4	10.3	8.2	3.0	0.0
Mean	24.8	13.5	18.0	12.0	6.8	1.5	0.9
SD	7.8	3.3	8.1	3.4	1.8	0.8	1.3

varied inversely to V'_I changes (Table 4). This response was mainly due to T_In (Fig. 4), while T_En remained relatively constant. As a result T_In/T_{TOT} decreased with increasing V'_I. There was no relationship between the T_In response to V'_I changes ($\Delta T_In/\Delta V'_I$) and respiratory system mechanics (multiple regression, $p > 0.05$). T_{ext} increased slightly with decreasing V'_I. V_{th} and ΔV_{end} remained relatively stable.

In three patients with high V'_I the end of mechanical inspiration occurred before the end of neural inspiration. This was the case in one patient with low V'_I and in two patients with baseline V'_I.

Inspiratory flow did not affect the rate of Pmus increase during inspiration (dp/dt). On the other hand, $Pmus_{sw}$ and $Pmus_{peak}$ were significantly affected by the V'_I changes; both parameters varied inversely to V'_I changes. Respiratory effort increased significantly with decreasing V'_I. There was a significant linear relationship between the changes induced by V'_I alterations in T_In (ΔT_In) and PTPin (ΔPTPin) ($\Delta PTPin = 0.18 + 9.12\Delta T_In$; $r = 0.71$, $p < 0.01$).

Varying pressure support protocol

Sixty trials where PS increased to $22.6 \pm 5.6\ cmH_2O$ for two breaths and 62 where PS decreased to $11.0 \pm 4.0\ cmH_2O$, also for two breaths, were analyzed (baseline PS $16.9 \pm 5.0\ cmH_2O$). These PS changes caused significant alterations in V_T and peak inspiratory

Table 3 Breath characteristics in the varying V_T protocol (V_T tidal volume, $V'_I peak$ peak inspiratory flow, $V_T/T_I m$ mean inspiratory flow, $T_I m$ mechanical inspiratory time, T_{TOT} total breath duration, $T_I n$ neural inspiratory time, $T_E n$ neural expiratory time, $T_I n/T_{TOT}$ duty cycle, *dp/dt* the rate of increase of respiratory muscle pressure *(Pmus)* during inspiration, $Pmus_{sw}$ Pmus swings during the respiratory cycle, $Pmus_{peak}$ peak Pmus during inspiration, *PTPin*, *PTPtot* pressure time product of inspiratory and all respiratory muscles per breath, respectively, *PTPin/min*, *PTPtot/min* pressure time product of inspiratory and all respiratory muscles per minute, respectively, V_{th} volume relative to passive FRC at the end of neural inspiration, T_{ext} time that mechanical inflation extents into neural expiration, ΔV_{end} end expiratory lung volume relative to passive FRC)

	Low V_T	Baseline	High V_T	*p*
V_T (l)	0.35 ± 0.1[a,b]	0.52 ± 0.1	0.71 ± 0.1[a]	< 0.001
V'_Ipeak (l/s)	1.09 ± 0.3	1.10 ± 0.3	1.11 ± 0.3	
V_T/T_Im (l/s)	0.70 ± 0.2	0.75 ± 0.2	0.80 ± 0.3	
T_Im (s)	0.52 ± 0.1[a,b]	0.71 ± 0.1	0.93 ± 0.2[a]	< 0.001
T_{TOT} (s)	2.09 ± 0.3[a,b]	2.21 ± 0.3	2.48 ± 0.4[a]	< 0.001
T_In (s)	0.58 ± 0.1	0.57 ± 0.1	0.59 ± 0.1	
T_En (s)	1.51 ± 0.3[a,b]	1.64 ± 0.3	1.90 ± 0.4[a]	< 0.001
$T_I n/T_{TOT}$	0.28 ± 0.1[b]	0.26 ± 0.1	0.24 ± 0.1[a]	< 0.001
dP/dt (cmH_2O/s)	17.3 ± 10.7	18.2 ± 12.3	18.2 ± 11.3	
$Pmus_{sw}$ (cmH_2O)	8.8 ± 3.7	9.4 ± 3.8	9.8 ± 3.7	
$Pmus_{peak}$ (cmH_2O)	8.0 ± 4.7	8.4 ± 5.5	8.6 ± 5.7	
PTPin (cmH_2O·s)	4.3 ± 2.5	4.0 ± 2.7	4.6 ± 2.9	
PTPtot (cmH_2O·s)	6.3 ± 2.8[b]	6.4 ± 2.6	7.3 ± 2.6[a]	< 0.01
PTPin/min (cmH_2O·sec/min)	127.4 ± 82.0	114.4 ± 83.9	115.8 ± 74.1	
PTPtot/min (cmH_2O·sec/min)	184.0 ± 80.0	179.3 ± 77.5	181.1 ± 64.1	
V_{th} (l)	0.26 ± 0.2[b]	0.28 ± 0.1	0.31 ± 0.2	< 0.05
T_{ext} (s)	0.08 ± 0.1[a,b]	0.22 ± 0.2	0.44 ± 0.2[a]	< 0.001
DV_{end} (l)	0.04 ± 0.1	–0.01 ± 0.1	–0.02 ± 0.1	

[a] Significantly different from baseline
[b] Significantly different from high V_T

flow (Table 5). T_{TOT} varied directly with PS changes. This response was due to T_En (Fig. 5). There was no relationship between the T_En response to volume changes due to PS alteration ($\Delta T_E n/\Delta V_T$) and respiratory system mechanics (multiple regression, $p > 0.05$). T_In, $T_I n/T_{TOT}$ and respiratory effort increased significantly with decreasing PS (Table 5). Similar to varying the V'_I protocol, there was a significant linear relationship between the changes induced by PS alterations in T_In ($\Delta T_I n$) and PTPin (ΔPTPin) ($\Delta PTPin = -0.18+2.59\Delta T_I n$; $r = 0.62$, $p < 0.01$).

The volume relative to passive FRC at the end of neural inspiration (V_{th}) and T_{ext} decreased significantly with decreasing PS. ΔV_{end} remained relatively constant. In all patients, independent of PS level, the end of neural inspiration occurred before the end of mechanical inspiration.

Similar to varying V_T protocol, there was a significant linear relationship between the changes induced by PS alterations in T_{ext} (ΔT_{ext}) and T_En ($\Delta T_E n$) (Fig. 6). ΔT_En was also linearly related to ΔV_T ($\Delta T_E n = 0.03+1.50\Delta V_T$; $r = 0.92$, $p < 0.01$).

Discussion

The main finding of the present study is that changing commonly used ventilator settings in mechanically ventilated patients with acute lung injury caused an immediate alteration of respiratory timing, while the rate of rise of inspiratory muscle activity (an index of respiratory drive) remained largely unaffected. The response was quite consistent between patients and independent of the severity of deterioration of respiratory system mechanics.

This study may be faulted for using pressure measurements to infer changes in respiratory muscle activation as opposed to actually measuring respiratory activity. It is believed that the uncertainties associated with this approach [see ref. 11, 12 for review], are much more acceptable than the uncertainties associated with recording respiratory activity under these experimental conditions. The only practicable method available to monitor respiratory muscle activation in humans is electromyography (EMG) via esophageal or body surface electrodes. Given that the diaphragm excursion was expected to change with positive pressure breathing, the physical relation between electrode and muscle would also change with uncertain outcome on the measured signal. To this end, one must add the substantial confounding effect of different muscle lengths on measured EMG (for the same activation) even with implanted electrodes [30, 31]. These uncertainties would make it impossible to ascertain whether a reduction of 50 % or more in measured EMG was not technical in origin.

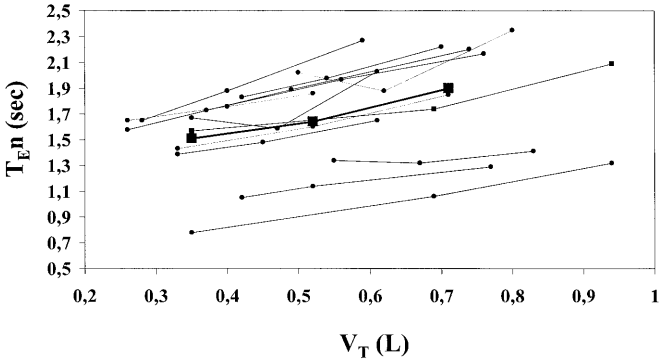

Fig. 2 Varying V_T protocol: Individual responses of neural expiratory time (T_En) to changes in V_T

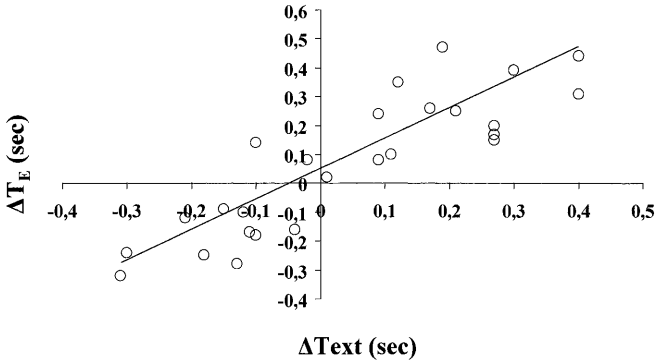

Fig. 3 Varying VT protocol: Relation between the changes (compared to baseline V_T) in time interval between the end of inspiratory flow (end of ventilator inflation phase) and the end of neural inspiratory time (ΔT_{ext}) and those of neural expiratory time (ΔT_En). ($y = 0.02+0.96x$, $r = 0.88$, $p < 0.01$)

We believe that the mechanoreceptor reflex feedback system is the most plausible pathway for mediating the observed response of respiratory timing. This feedback system is very fast (milliseconds) [7, 21] and, thus, affects respiratory output immediately after a change in ventilator settings. Chemical feedback was not an issue because the duration of the two breaths after the change in ventilator settings was less than 6.5 s in all patients. This was not sufficient time for changes in capillary blood gas composition to reach peripheral chemoreceptors [32]. Other non-chemical mechanisms, such as short-term post-stimulus potentiation (afterdischarge) [33] and control system inertia [34], are unlikely to influence the results under our experimental conditions. This issue has been discussed previously and will not be repeated [see ref. 12]. In addition, behavioral feedback in these sedated patients, although not entirely excluded, was unlikely to alter the response significantly. Compared to baseline, changes in flow and volume were relatively small and the elicited responses were quite consistent within patients, suggesting that the response observed was not voluntarily influenced by these lightly sedated patients.

Our results reconfirmed the dependency of neural expiratory time on V_T during pressure support ventilation in patients with acute lung injury [12]. Furthermore, the present study demonstrated that this dependency is not limited to this mode of support. Similar to pressure support, neural expiratory time changed with alteration in V_T during assist/control. This response of neural expiratory time to varying V_T could be due to at least one factor. On both modes T_{ext} increased significantly with increasing V_T. It has been shown that when lung emptying is delayed during neural expiration, as was the case with increasing V_T, expiratory duration is prolonged, a response that is mediated via vagal volume feedback [35, 36]. This is further supported by the significant rela-

Table 4 Breath characteristics in varying V'_I protocol (See Table 3 for abbreviations and significant differences)

	Low V'_I	Baseline	High V'_I	*p*
V_T (l)	0.51 ± 0.1	0.52 ± 0.1	0.52 ± 0.1	
V'_Ipeak (l/s)	0.77 ± 0.3[a,b]	1.10 ± 0.3	1.49 ± 0.4[a]	< 0.001
V_T/T_Im (l/s)	0.63 ± 0.2[a,b]	0.74 ± 0.2	0.84 ± 0.2[a]	< 0.001
T_Im (s)	0.88 ± 0.2[a,b]	0.73 ± 0.1	0.63 ± 0.1[a]	< 0.001
T_{TOT} (s)	2.32 ± 0.3[b]	2.24 ± 0.3	2.17 ± 0.3	< 0.01
T_In (s)	0.66 ± 0.1[a,b]	0.61 ± 0.1	0.54 ± 0.1[a]	< 0.001
T_En (s)	1.66 ± 0.3	1.63 ± 0.3	1.63 ± 0.3	
T_In/T_{TOT}	0.29 ± 0.1[b]	0.27 ± 0.1	0.25 ± 0.1[a]	< 0.001
dp/dt (cmH_2O/s)	17.9 ± 11.0	18.1 ± 10.8	19.2 ± 12.4	
$Pmus_{sw}$ (cmH_2O)	12.8 ± 5.6[b]	11.6 ± 5.3	11.1 ± 5.9	< 0.001
$Pmus_{peak}$ (cmH_2O)	9.8 ± 5.9[b]	8.9 ± 5.2	8.3 ± 5.4	< 0.001
PTPin (cmH_2O·s)	5.0 ± 2.9[a,b]	4.3 ± 2.6	3.8 ± 2.5	< 0.001
PTPtot (cmH_2O·s)	7.8 ± 3.1[a,b]	6.9 ± 2.8	6.4 ± 3.2	< 0.001
PTPin/min (cmH_2O·sec/min)	133.6 ± 79.3[b]	118.6 ± 71.5	105.9 ± 64.8	< 0.01
PTPtot/min (cmH_2O·sec/min)	203.1 ± 75.4[b]	187.7 ± 76.4	176.2 ± 77.4	< 0.01
V_{th} (l)	0.28 ± 0.1	0.30 ± 0.1	0.30 ± 0.1	
T_{ext} (s)	0.30 ± 0.3[a,b]	0.18 ± 0.2	0.15 ± 0.2	< 0.001
DV_{end} (l)	0.01 ± 0.1	–0.02 ± 0.1	–0.01 ± 0.1	

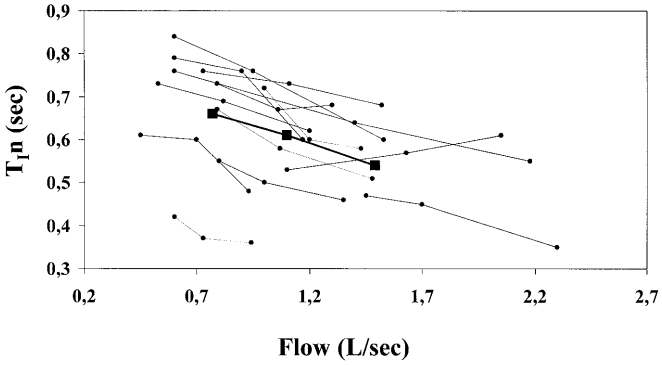

Fig. 4 Varying V'_I protocol: Individual responses of neural inspiratory time ($T_I n$) to changes in inspiratory flow

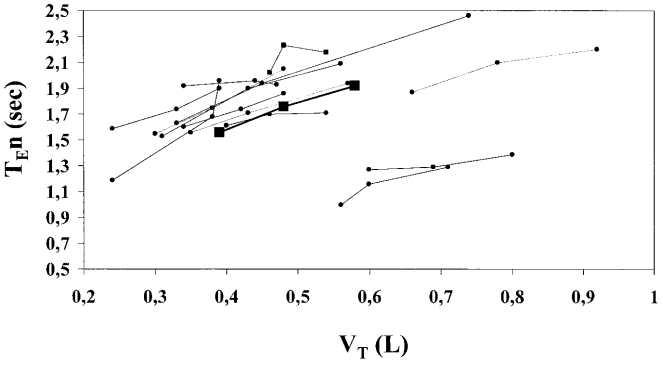

Fig. 5 Varying PS protocol: Individual responses of neural expiratory time ($T_E n$) to changes in PS which resulted in V_T alterations

tionship between the change in T_{ext} and the change in neural expiratory time, observed both with assist/control and pressure support modes. It is of interest to note that the intercept and slope of the relationship were very similar between the two modes.

In the varying V'_I protocol neural expiratory time remained relatively constant, presumably because, contrary to the other two protocols, T_{ext} changed slightly and only at low V'_I. Indeed, by pooling the data from all protocols, the relationship between ΔT_{ext} and $\Delta T_E n$ remained highly significant ($y = -0.01+0.90x$, $r = 0.77$). Nevertheless, ΔT_{ext} was mainly dependent on V_T changes (ΔV_T) and thus, as was expected, $\Delta T_E n$ was also significantly related to ΔV_T. It follows that our study did not prove with certainty a cause and effect relationship between ΔT_{ext} and $\Delta T_E n$. Indirect evidence in normal humans, however, indicates that a critical factor for neural expiratory time prolongation might not be the V_T but rather the time of continuing inflation during neural expiration [15]. Indeed, Laghi et al. [15] have shown, in normal humans, that alterations in delivered V_T at a constant mechanical inspiratory time did not cause significant changes in breathing frequency. This was not the case if mechanical inflation time was allowed to vary [15]. Notwithstanding the fact that neural breathing pattern was not examined, these results indicate that mechanical inflation time and, therefore, the relation between mechanical and neural inspiratory time may influence respiratory timing.

In a recent study Fernandez et al. [16] demonstrated in awake normal subjects that decreasing inspiratory flow at constant V_T caused an immediate increase in neural inspiratory time whereas neural expiratory time remained relatively constant. As a result, breathing frequency decreased significantly with decreasing inspiratory flow. The present study showed that patients with acute lung injury responded similarly; in the varying V'_I protocol neural inspiratory time increased with decreasing inspiratory flow, whereas neural expiratory time remained constant, resulting in a significant de-

Table 5 Breath characteristics in varying PS protocol (See Table 3 for abbreviations and significant differences)

	Low PS	Baseline	High PS	*p*
V_T (l)	0.39 ± 0.1[a,b]	0.48 ± 0.1	0.58 ± 0.2[a]	< 0.001
V'_Ipeak (l/s)	0.87 ± 0.2[a,b]	1.10 ± 0.2	1.29 ± 0.2[a]	< 0.001
$V_T/T_I m$ (l/s)	0.55 ± 0.3[a,b]	0.63 ± 0.2	0.71 ± 0.2[a]	< 0.001
$T_I m$ (s)	0.76 ± 0.1[b]	0.78 ± 0.1	0.84 ± 0.2	< 0.02
T_{TOT} (s)	2.17 ± 0.4[b]	2.26 ± 0.4	2.40 ± 0.3[a]	< 0.001
$T_I n$ (s)	0.60 ± 0.2[a,b]	0.49 ± 0.1	0.49 ± 0.2	< 0.001
$T_E n$ (s)	1.56 ± 0.3[a,b]	1.76 ± 0.3	1.92 ± 0.3[a]	< 0.001
$T_I n/T_{TOT}$	0.28 ± 0.1[a,b]	0.22 ± 0.1	0.20 ± 0.1	< 0.001
dp/dt (cmH_2O/s)	15.6 ± 9.8	16.2 ± 9.2	15.1 ± 7.7	
$Pmus_{sw}$ (cmH_2O)	8.0 ± 3.4	7.9 ± 3.3	7.6 ± 3.2	
$Pmus_{peak}$ (cmH_2O)	7.5 ± 4.8	7.2 ± 4.6	6.5 ± 4.3	
PTPin (cmH_2O·s)	3.9 ± 2.2[b]	3.7 ± 2.2	3.4 ± 2.2	< 0.01
PTPtot (cmH_2O·s)	5.1 ± 3.1	5.0 ± 3.1	5.0 ± 3.1	
PTPin/min (cmH_2O·sec/min)	118.8 ± 68.3[a,b]	102.7 ± 66.7	88.1 ± 60.7	< 0.001
PTPtot/min (cmH_2O·sec/min)	147.0 ± 85.7[b]	143.9 ± 78.5	125.6 ± 74.7	< 0.001
V_{th} (l)	0.35 ± 0.2[b]	0.39 ± 0.3	0.43 ± 0.3	< 0.01
T_{ext} (s)	0.27 ± 0.1[a,b]	0.39 ± 0.2	0.47 ± 0.3	< 0.001
DV_{end} (l)	0.04 ± 0.1	0.02 ± 0.1	0.01 ± 0.1	

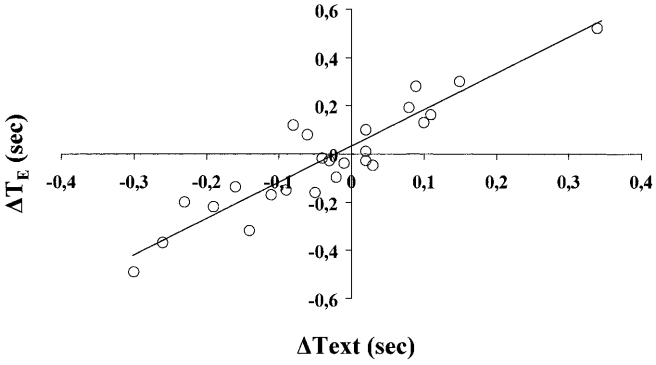

Fig. 6 Varying PS protocol. Relation between the changes (compared to baseline PS) in time interval between the end of inspiratory flow (end of ventilator inflation phase) and the end of neural inspiratory time (ΔT_{ext}) and those of neural expiratory time ($\Delta T_E n$) ($y = 0.03+1.50x$, $r = 0.92$, $p < 0.01$)

crease in breathing frequency. Furthermore, we showed that neural inspiratory time was also relatively sensitive to pressure support changes in this group of patients. Indeed, neural inspiratory time, although it remained constant between high and baseline pressure support, increased significantly at low pressure support. The changes in inspiratory flow and/or volume at the end of neural inspiration observed in both protocols could mediate the response. V_{th} was lower with low pressure support level, whereas it remained relatively constant in the varying V'_I protocol. However, in the varying V'_I protocol mechanical inflation terminated before the end of neural inspiration in several cases, making the interpretation of V_{th} complicated; V_{th} probably underestimated, particularly at high V'_I, the actual volume at the end of neural inspiration. This did not occur with pressure support. Notwithstanding the difficulties in measuring actual V_{th} in the varying V'_I protocol, volume at the end of neural inspiration was lower with low pressure support and, thus, based on vagal volume feedback, neural inspiratory time should be prolonged [7, 21].

It is not known to what extent this mechanism contributes to the response of neural inspiratory time. It is of interest to note that the patients breathed at a relatively high rate; on both modes, mean breathing frequency was approximately 27 breaths/min at baseline. It has been shown that the dependency of neural inspiratory time on volume progressively decreases as neural inspiratory time without volume feedback decreases [37], as it occurs in the presence of various stimuli that increase breathing frequency, a common finding in patients with acute lung injury. Therefore, the effect of vagal feedback on neural inspiratory time is likely to be weak in the patients studied. Finally, a specific effect of inspiratory flow on neural inspiratory time mediated by flow-sensitive vagal receptors, as suggested by Fernandez et al. [16] in normal awake humans, might also be the pathway for the observed response. Our study design does not permit further clarification of the predominant mechanism.

In the varying PS protocol neural inspiratory time did not differ between high and baseline pressure support, although peak inspiratory flow changed significantly. According to the above analysis we would expect a decrease in neural inspiratory time with increasing pressure support. It is not known why this did not occur. Compared to the varying V'_I protocol, the decelerating flow-time profile and the relatively small increase in peak inspiratory flow from baseline to high pressure support may account for the stable neural inspiratory time. In addition, neural inspiratory time during baseline PS was quite low (0.49 s) and it is possible that at these levels neural inspiratory time may be relatively insensitive to changes in inspiratory flow. For example, if a curvilinear relationship between inspiratory flow and neural inspiratory time exists then a given change in inspiratory flow causes a smaller change in neural inspiratory time when this is short rather than long.

The changes in neural inspiratory and expiratory time resulted in significant alteration in breathing frequency. Breathing frequency decreased with decreasing inspiratory flow (V'_I protocol) and with increasing tidal volume (V_T protocol) and pressure support (PS protocol). This response of breathing frequency to varying inspiratory flow and tidal volume has previously been observed in normal subjects during wakefulness and sleep [13, 15, 16, 17, 18, 19], and in patients with acute lung injury mechanically ventilated on pressure support [12]. To our knowledge this is the first study showing the early neural breathing pattern response to varying commonly used ventilator settings in patients with parenchymal lung injury. Our results indicate that the changes in breathing frequency were mediated via alteration in neural inspiratory and expiratory time, depending on the type of ventilator setting change. It is of interest to note that the response of respiratory timing was observed in patients with relatively normal (i.e. Ers < 20 cmH_2O/l), as well as in those with severe impairment of, respiratory system mechanics. Indeed, independent of the protocol, there was no relationship between the response of respiratory timing and respiratory system mechanics, suggesting that the degree of impairment of neuroventilatory coupling is not a main determinant of the response.

We believe that, from all calculated indices of respiratory motor output, the rate of rise of Pmus during inspiration (dp/dt) represented the best index of respiratory drive [7]. Indeed, contrary to other indices, such as $Pmus_{peak}$, $Pmus_{sw}$ and PTPin, this index is not affected by changes in respiratory timing. However, dp/dt should be influenced by changes in the force-length and force-velocity relationship of respiratory muscles due to dif-

ferent flow and volume [20]; dp/dt should be underestimated with higher flow and/or volume. Nevertheless, the gain of this reflex is such (11 cmH_2O/l for force-length and 0.2 $cmH_2O \cdot l \cdot s$ for force-velocity) [20] that the expected changes in Pmus, and thus in dp/dt, should be relatively small in the range of volume and flow studied. This reflex is of clinical importance at much higher flow and volumes [8, 20].

Our study demonstrated that dp/dt remained relatively constant, suggesting that if anything happens, respiratory drive should be slightly increased with increasing flow and volumes. To the extent that delivering higher volume and/or flow may reflect a decrease in the mechanical load faced by the respiratory muscles, our results indicate that acute reduction in mechanical load does not result in reflex downregulation of respiratory muscle activity in patients with acute lung injury. Increases in neither tidal volume nor inspiratory flow were able to decrease immediately the respiratory drive, as indicated by the constancy of dp/dt. This was evident both on assist/control and pressure support modes. These results are in accordance with studies suggesting that, at least in this range of tidal volume and inspiratory flow, the acute load response of respiratory muscles is minimal and limited to timing [8, 12, 38].

The increase in neural inspiratory time with decreasing inspiratory flow, observed in the varying V'_I and PS protocols, resulted in a significant increase in inspiratory effort, as indicated by the significant relationship between the change in $T_I n$ and the change in PTPin/breath demonstrated in both protocols. Thus, inspiratory muscle energy consumption is probably increased by low inspiratory flow. On the other hand, in the varying V_T protocol neural inspiratory time did not change with V_T alterations, resulting in relatively stable inspiratory effort. These results indicated that inspiratory effort and, therefore, the energy consumption of inspiratory muscles, are sensitive to neural inspiratory time alterations. The reduction of the inspiratory work of breathing with increasing inspiratory flow demonstrated by several studies [2, 3, 39, 40] might be partly mediated by the flow-dependent reflex decrease of neural inspiratory time.

The early response of respiratory motor output was studied in sedated patients with acute lung injury. The similar response in normal subjects during wakefulness and sleep [13, 15, 16, 17, 18, 19] indicates that this type and level of sedation may not, at least qualitatively, modify the response. On the other hand it is not known if the strength of the reflexes involved is influenced by the level or type of sedation. In addition, patients with acute lung injury mainly due to pneumonia and sepsis were studied and it is not known if these results may apply in other groups of patients. For example, it has been suggested that the vagal volume feedback in patients with COPD is rather weak [7]. If this is the case, different acute responses to manipulation in ventilator settings would be expected. In addition, in the patients studied, alteration in ventilator settings did not result in dynamic hyperinflation, which might be an important determinant of respiratory motor output [6, 7]. Further studies are needed to resolve all these issues.

Our study does not intend to provide suggestions for ventilator strategies. The main purpose was to study the mechanoreceptor reflex feedback in mechanically ventilated patients with acute lung injury. However, notwithstanding that the final response of respiratory motor output is influenced by several other factors and largely unpredictable [6, 7], the findings of the current study may have clinical implications for mechanically ventilated patients with acute lung injury. The effects of ventilator settings on breathing frequency should be taken into account when respiratory rate is interpreted during mechanical ventilation. For example, during the weaning phase high breathing frequency may be caused by the reflex response of the respiratory system to ventilator settings and not due to weaning failure. At that point it is important to consider that the reflex response of respiratory timing may not show any adaptation in the long term [12]. Finally, low inspiratory flow rate may increase the energy consumption of inspiratory muscles via a mechanoreceptor reflex increase in neural inspiratory time and this, in critically ill patients, may lead to inspiratory muscle fatigue with serious consequences for patient-ventilator interaction and weaning outcome.

References

1. Connors AF, McCaffree RD Jr, Gray BA (1981) Effect of inspiratory flow rate on gas exchange during mechanical ventilation. Am Rev Respir Dis 124: 537–543
2. Marini J, Capps J, Culver BH (1985) The inspiratory work of breathing during assisted mechanical ventilation. Chest 87: 612–618
3. Sassoon CSH, Mahutte C, Simmons D, Light R (1988) Work of breathing and airway occlusion pressure during assist-mode mechanical ventilation. Chest 93: 571–576
4. Georgopoulos D, Mitrouska I, Markopoulou K, Patakas D, Anthonisen NR (1995) Effects of breathing patterns on mechanically ventilated patients with chronic obstructive pulmonary disease and dynamic hyperinflation. Intensive Care Med 21: 880–886

5. Leung P, Jubran A, Tobin MJ (1997) Comparison of assisted ventilator modes on triggering, patient effort and dyspnea. Am J Respir Crit Care Med 155: 1940–1948
6. Georgopoulos D, Rouusos C (1996) Control of breathing in mechanically ventilated patients. Eur Respir J 9: 2151–2160
7. Younes M, Georgopoulos D (1998) Control of breathing relevant to mechanical ventilation. In: Marini J, Slutsky A (eds) Physiological basis of ventilatory support: lung biology in health and disease, Vol. 118. Marcel Dekker, New York, pp 1–74
8. Georgopoulos D, Mitrouska I, Webster K, Bshouty Z, Younes M (1997) Effects of respiratory muscle unloading on the ventilatory response to CO_2. Am J Respir Crit Care Med 155: 2000–2009
9. Patrick W, Webster K, Puddy A, Sanii R, Younes M (1995) Respiratory response to CO_2 in the hypocapnic range in conscious humans. J Appl Physiol 76: 2058–2086
10. Georgopoulos D, Mitrouska I, Bshouty Z, Webster K, Patakas D, Younes M (1997) Respiratory response to CO_2 during pressure support ventilation in conscious normal humans. Am J Respir Crit Care Med 156: 146–154
11. Mitrouska I, Xirouchaki N, Patakas D, Siafakas N, Georgopoulos D (1999) Effects of chemical feedback on respiratory motor and ventilatory output during different modes of assisted mechanical ventilation. Eur Respir J 13: 873–882
12. Xirouchaki N, Kondili E, Mitouska I, Siafakas N, Georgopoulos D (1999) Response of respiratory motor output to varying pressure support in mechanically ventilated patients. Eur Respir J 14: 508–516
13. Puddy A, Younes M (1992) Effect of inspiratory flow rate on respiratory motor output in normal humans. Am Rev Respir Dis 146: 787–789
14. Corne S, Gillespie D, Roberts D, Younes M (1997) Effect of inspiratory flow rate on respiratory rate in intubated ventilated patients. Am J Respir Crit Care Med 156: 304–308
15. Laghi F, Karamchandani K, Tobin MJ (1999) Influence of ventilator settings in determining respiratory frequency during mechanical ventilation. Am J Respir Crit Care Med 160: 1766–1770
16. Fernandez R, Mendez M, Younes M (1999) Effect of ventilator flow rate on respiratory timing in normal humans. Am J Respir Crit Care Med 159: 710–719
17. Tobert DG, Simon PM, Stroetz RW, Hubmayr RD (1997) The determinants of respiratory rate during mechanical ventilation. Am J Respir Crit Care Med 155: 485–492
18. Georgopoulos D, Mitrouska I, Bshouty Z, Anthonisen NR, Younes M (1996) Effects of NREM sleep on the response of respiratory motor output to varying inspiratory flow. Am J Respir Crit Care Med 153: 1624–1630
19. Georgopoulos D, Mitrouska I, Bshouty Z, Webster K, Anthonisen NR, Younes M (1996) Effects of breathing route, temperature and volume of inspired gas and airway anesthesia on the response of respiratory motor output to varying inspiratory flow. Am J Respir Crit Care Med 153: 168–175
20. Corne S, Webster K, Younes M (2000) Effects of inspiratory flow on diaphragmatic motor output in normal subjects. J Appl Physiol 89: 481–492
21. Younes M (1996) Mechanisms of respiratory load compensation. In: Dempsey JA, Pack AI (eds) Regulation of breathing. lung biology in health and disease, Vol. 19. Marcel Dekker, New York, pp 867–922
22. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R and the Consensus Committee (1994) The American-European Consensus Conference on ARDS. Am J Respir Crit Care Med 149: 818–824
23. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R (1974) Controlled sedation with alphaxalone-alphadalone. BMJ 2: 656–659
24. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J (1982) A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis 126: 788–791
25. Younes M, Puddy A, Roberts D, Light RB, Quesada A, Taylor K, Oppenheimer L, Cramp H (1992) Proportional assist ventilation. Results of an initial clinical trial. Am Rev Respir Dis 145: 121–129
26. Prechter GC, Nelson SB, Hubmayr RD (1990) The ventilatory recruitment threshold for carbon dioxide. Am Rev Respir Dis 141: 758–764
27. D'Angelo E, Robatto FM, Calderini E, Tavola M, Bono D, Torril G, Milic-Emili J (1991) Pulmonary and chest wall mechanics in anesthetized paralyzed humans. J Appl Physiol 70: 2602–2610
28. Yan S, Sliwinski P, Gauthier AP, Lichros I, Zakynthinos S, Macklem PT (1993) Effect of global inspiratory muscle fatigue on ventilatory and respiratory muscle responses to CO_2. J Appl Physiol 75: 1371–1377
29. Jubran A, Van De Graaf WB, Tobin M (1995) Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152: 129–136
30. McKenzie DK, Gandevia SG (1986) Changes in human diaphragmatic electromyogram with positive pressure breathing. Neurol Sci Lett 70: 86–90
31. Brancatisano AS, Kelly SM, Tully A, Loring SH, Engel LA (1989) Postural changes in spontaneous and evoked regional diaphragmatic activity in dogs. J Appl Physiol 66: 1699–1705
32. Lange RL, Horgan JD, Botticelli JT, Tsagaris T, Carlisle RP, Kuida H (1996) Pulmonary to arterial circulatory transfer function: importance in respiratory control. J Appl Physiol 21: 1281–1291
33. Tawadrous FD, Eldridge FL (1974) Posthyperventilation breathing patterns after active hyperventilation in man. J Appl Physiol 37: 353–356
34. Leevers AM, Simon P, Xi L, Dempsey JA (1993) Apnoea following normocapnic mechanical ventilation in awake mammals: a demonstration of control system inertia. J Physiol 472: 749–768
35. Remmers JE, Bartlett D Jr (1977) Reflex control of expiratory airflow and duration. J Appl Physiol 42: 80–87
36. Gautier H, Remmers JE, Bartlett D Jr (1973) Control of the duration of expiration. Respir Physiol 18: 205–221
37. Bradley GW, Von Euler C, Marttila I, Roos B (1973) Steady-state effects of CO_2 and temperature on the relationship between lung volume and inspiratory duration (Hering-Breuer threshold curve). Acta Physiol Scand 92: 351–363
38. Meza S, Giannouli E, Younes M (1998) Control of breathing during sleep assessed by proportional assist ventilation. J Appl Physiol 84: 3–12
39. Marini JJ, Rodriquez RM, Lamb V (1986) The inspiratory workload of patient initiated mechanical ventilation. Am Rev Respir Dis 134: 902–909
40. Ward ME, Corbeil C, Gibbons W, Newman S, Macklem PT (1988) Optimization of respiratory muscle relaxation during mechanical ventilation. Anesthesiology 69: 29–34