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N. Xirouchaki
D. Georgopoulos

Effects of assisted mechanical ventilation on control of breathing

Effekte der assistierenden mechanischen Beatmung auf die Atmungskontrolle

Zusammenfassung Während der spontanen Atmung wird die Wellenform des Atmungsmuskeldrucks (Pmus) durch ein komplexes System bestimmt, bestehend aus einem Motorarm, einem Kontrollzentrum und verschiedenen Rückkoppelungsmechanismen, welche Informationen zum Kontrollzentrum senden. Während der unterstützten mechanischen Ventilation wird der vom Ventilator gelieferte Druck (Paw) in das System integriert und kann die Wellenform des Pmus ändern, was seinerseits die Funktion des Ventilators modifiziert. Daher stellen die Reaktion des Pmus auf Paw und die Reaktion von Paw auf Pmus die zwei Komponenten sowohl der Patienten-Ventilator-Interaktion als auch der Atmungskontrolle während der mechanischen Ventilation dar. Die Reaktion des Paw auf Pmus ist abhängig von: 1. dem Modus der Ventilationsunterstützung, 2. der Mechanik des Atmungssystems und 3. den Charakteristika der Pmus-Wellenform. Andererseits wird die Reaktion von Pmus auf Paw durch vier Rückkoppelungssysteme vermittelt: 1. das Mechanische, 2. das Chemische, 3. das Reflex, und 4. das Verhaltenssystem. Es ist logisch, daß das System, welches die Atmung kontrolliert, durch die mechanische Ventilation wesentlich modifiziert werden kann. Der Arzt, der einen mechanisch beatmeten Patienten behandelt, soll die Interaktion zwischen der Atmungsanstrengung und der Funktion des Ventilators in Betracht ziehen und sich im Klaren sein, daß die ventilatorische Leistung die verschiedenen Aspekte der Atmungskontrolle spiegeln kann, aber nicht muß.

Schlüsselwörter Atmungsmuskeln – Ventilation – chemische Rückkoppelung – Reflexrückkoppelung – Verhaltensrückkoppelung

Summary During spontaneous breathing, the respiratory muscle pressure (Pmus) waveform is determined by a complex system consisting of a motor arm, a control center, and various feedback mechanisms that convey information to the control center. During assisted mechanical ventilation, the pressure delivered by the ventilator (Paw) is incorporated into the system and may alter the Pmus waveform, which in turn modifies the function of the ventilator. Thus, the response of Pmus to Paw and the response of Paw to Pmus constitute the two components of patient-ventilator interaction as well as of control of breathing during assisted mechanical ventilation. The response of Paw to Pmus depends on: 1) the mode of ventilatory support; 2) the mechanics of the respiratory system, and 3) the characteristics of the Pmus waveform. On the other hand the response of Pmus to Paw is mediated through four feedback systems: 1) mechanical; 2) chemical; 3) reflex, and 4) behavioral. It follows that the system that controls the act of breathing may be considerably modified by mechanical ventilation. The physician dealing with a mechanically ventilated patient should take into account the interaction between the respiratory effort and the function of the ventilator and be aware that the ventilatory output may or may not reflect the various aspects of control of breathing.

Key words Respiratory muscles – Ventilation – Chemical feedback – Reflex feedback – Behavioral

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Prof. Dr. D. Georgopoulos (✉)
N. Xirouchaki
Intensive Care Unit
University Hospital
P.O. Box 1352
GR-Heraklion 71110/Crete
Greece
E-mail: georgop@med.uch.gr

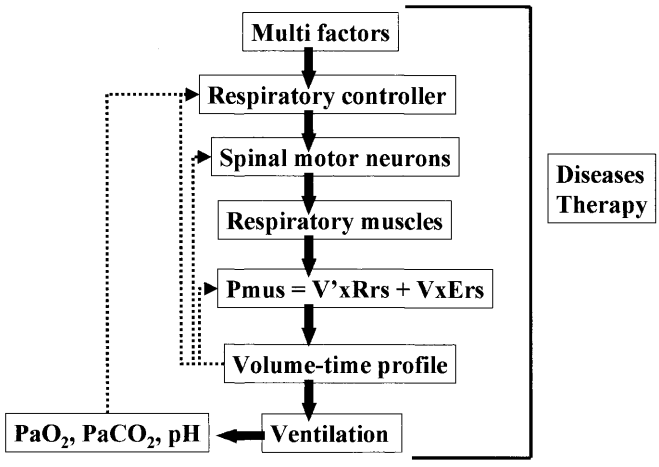

Fig. 1 Schematic representation of the system that controls the act of breathing. Dotted lines indicate various feedback systems. See text for details

Introduction

The respiratory control system consists of a motor arm, which executes the act of breathing, a control center located in the medulla, and a number of mechanisms that convey information to the control center [1, 35]. Based on the information the control center activates spinal motor neurons subserving respiratory muscles, with intensity and rate that varies substantially between breaths. The activity of spinal motor neurons is conveyed, via peripheral nerves, to respiratory muscles, which contract and generate pressure (Pmus). Pmus is dissipated to overcome resistance and elastance of the respiratory system (inertia is assumed to be negligible) and this combination determines volume-time profile and, thus, ventilation. Volume-time profile affects Pmus via force-length and force-velocity relationships of respiratory muscles (mechanical feedback), whereas it modifies the activity of spinal motor neurons and control center via afferents from various receptors located in the airways, chest wall or respiratory muscles (reflex feedback). Inputs generated from other sources (i.e., behavioral, temperature, postural) may also modify the function of the control center. On the other hand, ventilation and gas exchange properties of the lung determine arterial blood gases (PaO_2, $PaCO_2$) which, in turn, affect the activity of control center, via peripheral and central chemoreceptors (chemical feedback). This system can be influenced at any level by diseases or therapeutic modalities (Fig. 1).

During mechanical ventilation, the pressure provided by the ventilator (Paw) is incorporated into the system [7]. Therefore, in mechanically ventilated patients the driving pressure for inspiratory flow (P_{TOT}) is the sum of Pmus and Paw [7, 33]. P_{TOT} is dissipated to overcome resistance (Rrs) and elastance (Ers) of the respiratory system, determining the volume-time profile according to the equation of motion:

$$P_{TOT} = Pmus + Paw = V' \times Rrs + V \times Ers ,$$

where V′ and V are flow and volume relative to passive FRC, respectively.

The volume-time profile, via mechanical, chemical, reflex, and behavioral feedback systems, affects Pmus waveform, which, depending on several factors (see below), alters Paw waveform. It is obvious that the response of Paw to Pmus and that of Pmus to Paw constitute the two components of control of breathing during mechanical ventilation. The interaction between these two components may alter either the system itself or its expression, leading to serious consequences concerning the management of mechanically ventilated patients [7].

Determinants of Paw during assisted mechanical ventilation

The waveform of Paw depends on three factors: 1) the mode of mechanical ventilation, 2) the mechanics of the respiratory system, and 3) the characteristics of Pmus waveform.

Mode of mechanical ventilation

There are several modes of assisted mechanical ventilation [33, 36]. These can be classified in three categories: 1) *assist volume control* (AVC), where the ventilator, once triggered, delivers a pre-set tidal volume with a pre-set flow-time profile, 2) *pressure support* (PS), where the ventilator delivers a pre-set pressure, and 3) *proportional assist ventilation* (PAV), where the ventilator delivers pressure which is proportional (the proportionality is pre-set) to instantaneous flow and volume and, thus, to Pmus. With AVC mechanical inflation time is determined, theoretically, by the ventilator, whereas with PS it is influenced both by the patient and ventilator [33]. On the other hand, with PAV, mechanical inflation time is controlled mainly by the patient [36]. However, PAV mode is under intense investigation and it is not available for general use. In this article, the peculiar relationship between Paw and Pmus in the PAV mode will be used as a tool to clarify some important aspects of control of breathing relevant to mechanical ventilation.

The operational principles of each ventilator mode determine the relationship between Paw and Pmus (Figs. 2–4). With AVC there is a negative relationship between Paw and Pmus, whereas with PS there is no relationship and with PAV there is a positive one. Thus, in mechanically ventilated patients the ventilatory output can not be interpreted properly if the mode of ventilatory support is not taken into account. During assisted ventilation,

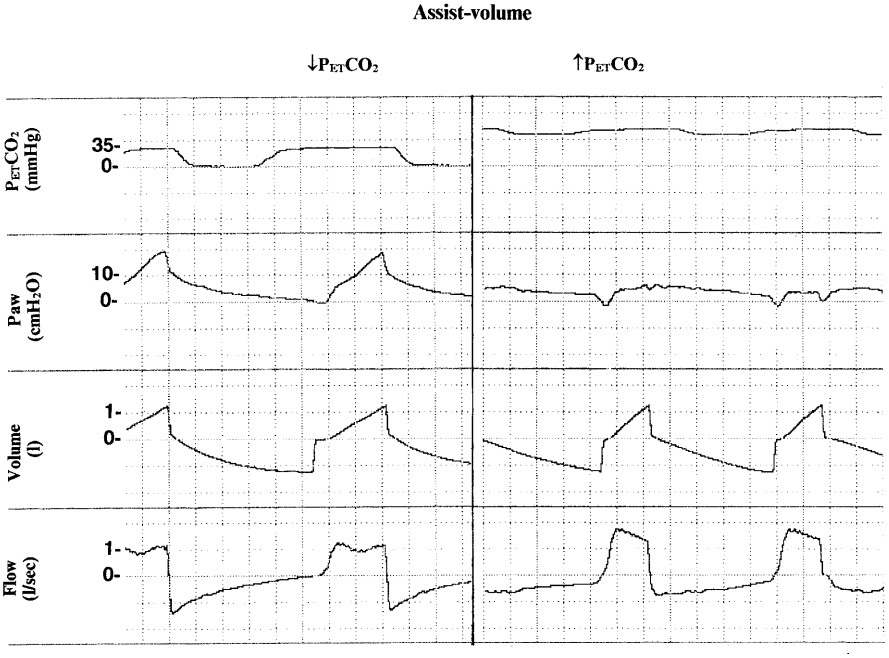

Fig. 2 Partial pressure of end-tidal CO_2 ($P_{ET}CO_2$), airway pressure (Paw) volume, and flow in a patient ventilated on assist volume control (AVC). Note the decrease in Paw when the patient's respiratory effort was stimulated by CO_2. With this mode there is a negative relationship between the patient's effort and Paw. Observe also that due to high inspiratory effort the patient was able to increase inspiratory flow above the pre-set level and, thus, to achieve the pre-set V_T sooner. This was due to the fact that the ventilator was not able to decrease Paw during inflation below a minimum value

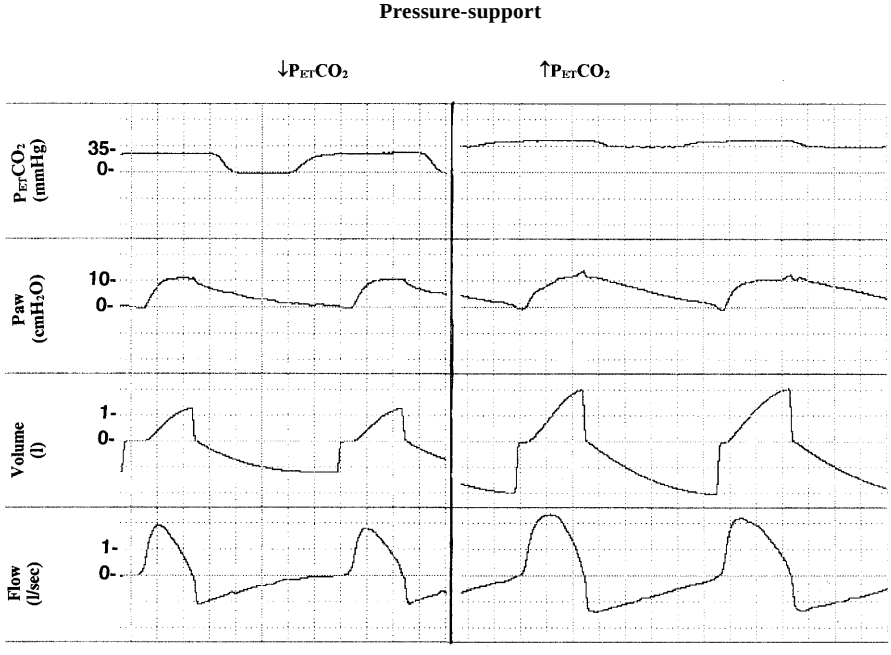

Fig. 3 Partial pressure of end-tidal CO_2 ($P_{ET}CO_2$), airway pressure (Paw) volume, and flow in a patient (same patient as in Fig. 2) ventilated on pressure support (PS). Note that Paw remained constant and independent of the patient's respiratory effort

changes in ventilatory output may not reflect corresponding changes in patient effort (Figs. 2–4).

Mechanics of respiratory system

The mechanical properties of the respiratory system (and ventilator tubings) play a crucial role in the response of Paw to Pmus. These properties may influence Paw independent of Pmus, leading to patient-ventilator asynchrony. Abnormal respiratory system mechanics is the main cause of asynchrony between Pmus and Paw. Usually asynchrony between Pmus and Paw waveforms is mainly due to the phenomenon of dynamic hyperinflation and can be observed with all modes of support [5, 24, 28, 29, 37, 38]. Dynamic hyperinflation is a common finding in patients with obstructive lung disease [28]. It is caused by several factors such as low elastic recoil, high ventilatory demands, increased expiratory resistance, and short expiratory time [28]. When dynamic hyperinflation is

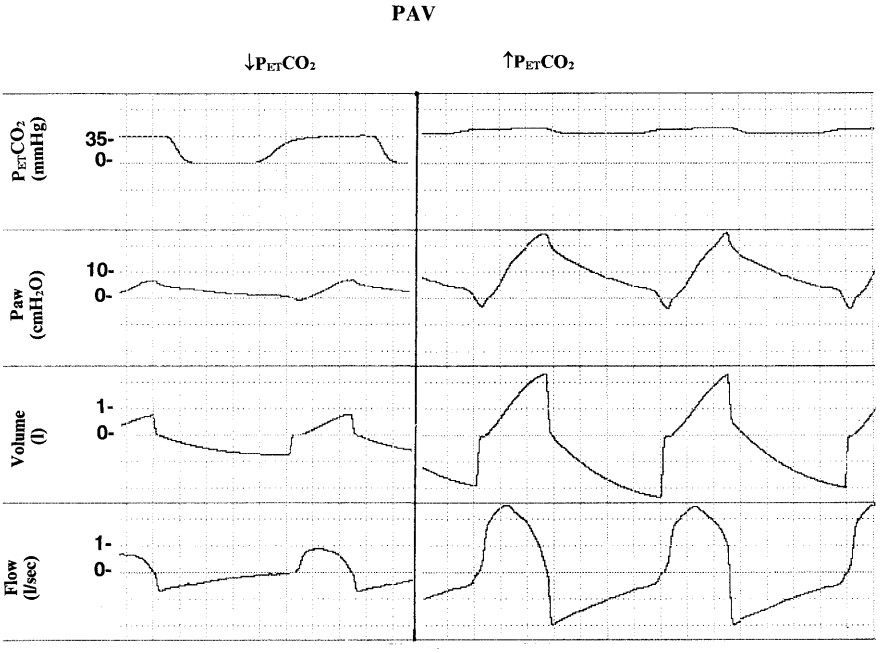

Fig. 4 Partial pressure of end-tidal CO_2 ($P_{ET}CO_2$), airway pressure (Paw) volume, and flow in a patient (same patient as in Fig. 2) ventilated on proportional assist ventilation (PAV). Note that CO_2 stimulation caused an increase in Paw. With this mode there is a positive relationship between the patient's effort and Paw

present, end-expiratory lung volume is above passive FRC or the volume determined by external PEEP (PEEPe) and, therefore, elastic recoil pressure at end-expiration is positive. This positive elastic recoil pressure, referred to as intrinsic PEEP (PEEPi), represents an elastic threshold load for the patient and may lead to ineffective efforts during assisted mechanical ventilation (failure to trigger the ventilator) (Fig. 5).

Ineffective efforts have been observed both with AVC and PS, particularly when the patient has tachypnea (short expiratory time) and the assist level (volume or pressure) is relatively high. With PAV the likelihood of ineffective efforts is considerably reduced [26, 38]. This is mainly due to the fact that with PAV the end of mechanical inflation time occurs at the end of neural inspiration because, by design, Paw is linked to Pmus. Therefore, mechanical inflation time can not be extended to neural expiratory time, which is available for lung deflation.

The phenomenon of ineffective efforts considerably influences the interpretation of ventilatory output in relation to the control of breathing during assisted mechanical ventilation. In the presence of ineffective efforts, ventilator frequency does not reflect a patient's spontaneous breathing rate. Furthermore, with ineffective efforts, significant alteration in patient respiratory effort occurs due to changes in feedback loop. For example the patient shown in Fig. 5 decreased his breathing frequency with increasing inspiratory flow, most likely because chemical feedback was altered as a result of better synchrony between patient and ventilator. Indeed, at high inspiratory flow rate, minute ventilation increased from 6.2 l/min to 9.4 l/min, causing a decrease in $PaCO_2$, which might be associated with a drop in the patient's spontaneous breathing frequency.

Characteristics of Pmus waveform

The characteristics of Pmus waveform influence the Paw in a complex way, depending on several factors related both to patient and ventilator. Although extensive review of these factors is beyond the scope of this article, some examples may be helpful to understand how the characteristics of Pmus may affect ventilator function.

The initial rate of Pmus increase interacts with the triggering function of the ventilator. A low rate of the initial increase of Pmus, as it occurs with a concave upwards shape of Pmus or low respiratory drive (i.e., low $PaCO_2$, sedation, sleep), increases the time delay between onset of a patient's inspiratory effort and ventilator triggering and promotes asynchrony (see above). At presence of dynamic hyperinflation this increased triggering time, particularly when it is associated with relatively short neural inspiratory time and low peak Pmus, may result in ineffective efforts with all the consequences described above (Fig. 5). Alternatively, an increase in intensity of inspiratory effort, as it occurs for example with an increase in metabolic rate, high $PaCO_2$ or decrease in the level of sedation, is manifested in the rate of rise of Pmus as well as in the peak Pmus. This may cause a decrease in the time delay, thus, promoting patient-ventilator synchrony. On the other hand, if the patient inspiratory effort is vigorous and longer than mechanical inflation time, the ventilator may be triggered more than once (double triggering) during the same inspir-

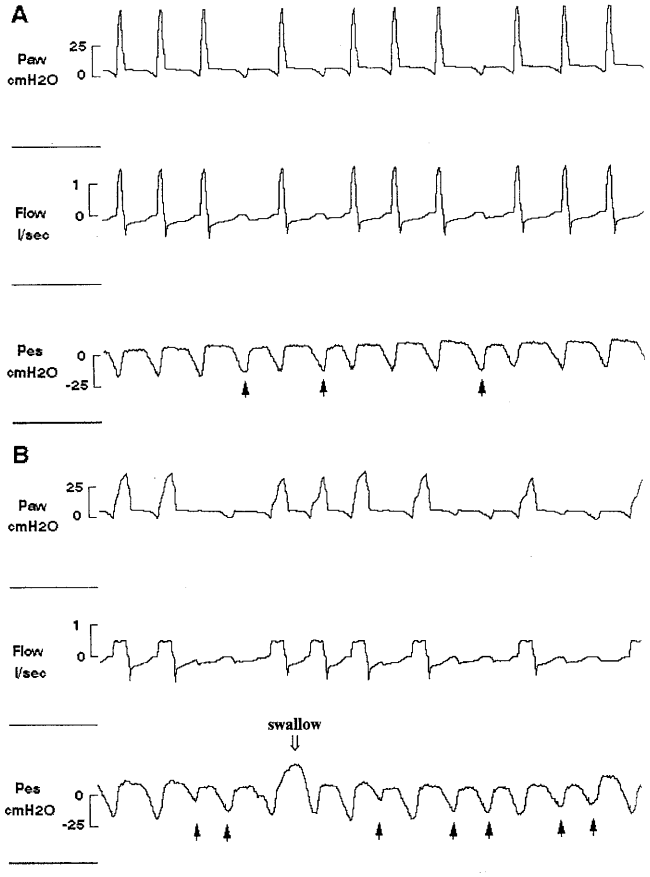

Fig. 5 Airway pressure (Paw), flow, and esophageal pressure (Pes) in a patient with chronic obstructive lung disease ventilated on assist volume control mode with two different inspiratory flow rates (V_I), 90 l/min (Fig. 5A) and 30 l/min (Fig. 5B). Tidal volume (V_T) was kept constant (0.55 l). Ineffective efforts are indicated by arrows. Observe the time delay between the onset of inspiratory effort (abrupt decrease in Pes) and the ventilator triggering. By increasing the time available for expiration (increase in inspiratory flow at constant V_T, Fig. 5A) the number of ineffective efforts was reduced and as a result the rate of the ventilator increased

atory effort. This may occur when at the end of mechanical inspiration Pmus continues to increase and, because inspiratory flow is zero or is reversed, it is dissipated to overcome only the elastic recoil. Thus, during mechanical expiration there might be a situation where Pmus is greater than elastic recoil, causing airway pressure to decrease below PEEP and this triggers the ventilator. Short mechanical inflation time and low eleastic recoil at end-inspiration may promote re-triggering. It follows that changes in the characteristics of Pmus waveform may influence ventilator rate and ventilatory output even in the absence of a change in the patient's respiratory frequency. Alteration in ventilatory output may secondarily modify patient effort through various feedback loop changes [7].

Determinants of Pmus during assisted mechanical ventilation

The waveform of Pmus during assisted mechanical ventilation is determined mainly by four feedback systems: 1) mechanical, 2) chemical, 3) reflex, and 4) behavioral.

Mechanical feedback

Mechanical feedback describes the effects of length (i.e., volume) and velocity of contraction (i.e., flow) of respiratory muscles, as well as of geometrical factors on Pmus. For a given neural output to inspiratory muscles, Pmus decreases with increasing lung volume and flow [39]. Therefore, for similar level of muscle activation, Pmus should be smaller during mechanical ventilation than during spontaneous breathing if pressure provided by the ventilator results in greater flow and volume. The influence and consequences of mechanical feedback during mechanical ventilation have not been studied. It is likely that the effects of mechanical feedback on Pmus in mechanically ventilated patients are relatively small, due to low values of operating volume and flow.

Chemical feedback

Chemical feedback refers to the response of the respiratory system to PaO_2, $PaCO_2$, and pH. In spontaneously breathing normal subjects chemical feedback is an important determinant of respiratory motor output both during wakefulness and during sleep. Two crucial questions are raised at this point: 1) To which extent does mechanical ventilation alter the contribution of chemical feedback in determining Pmus? 2) Is the effectiveness of chemical feedback to compensate for changes in chemical stimuli modified by mechanical ventilation?

Contribution of chemical feedback in determining Pmus during mechanical ventilation

Several years ago Milic-Emili and Tyler studied in normal subjects the ventilatory response to CO_2 with different resistive loads and observed that, for a given PCO_2, the work output of inspiratory muscles did not change appreciably with the load [20]. Data in patients during constant flow synchronized intermittent mandatory ventilation (SIMV) and biphasic positive airway pressure (BIPAP) have shown that, for a given level of assist, inspiratory effort did not differ between spontaneous and mandatory breaths [16, 18, 34]. Recently Leung et al. [17] studied the respiratory effort of patients ventilated with SIMV or a combination of SIMV and pressure support. Compared to SIMV alone, when PS was added to a given level of SIMV, inspiratory

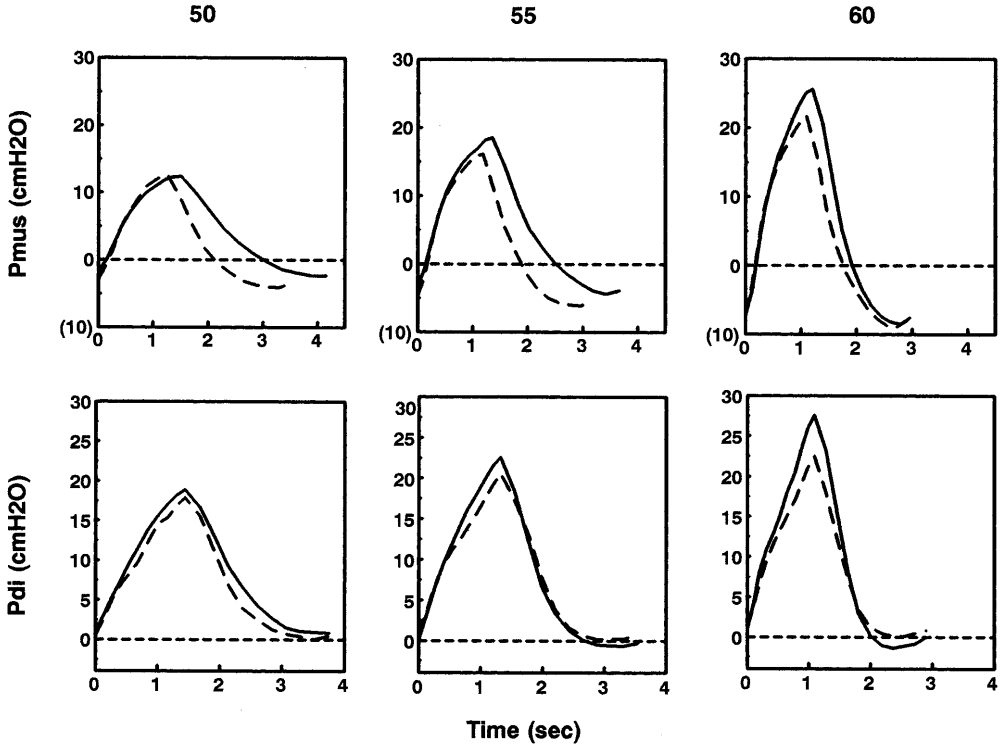

Fig. 6 Average time course of transdiaphragmatic pressure and pressure generated by all respiratory muscles (Pmus) (Pdi) at three levels of $P_{ET}CO_2$, (50, 55, and 60 mmHg) with (dashed lines) and without (solid lines) mechanical ventilatory support. The traces were aligned at the onset of neural inspiration (zero time). Mechanical ventilatory support was achieved using proportional assist ventilation (the assist level was such as to decrease the elastance and resistance of respiratory system by 50%). Observe the similarity of Pdi and Pmus with and without mechanical ventilation particularly at low $P_{ET}CO_2$. At high $P_{ET}CO_2$, Pdi and Pmus at the end of inspiration were slightly lower due to mechanical feedback (force-length and force-velocity relationships of respiratory muscles). (Modified from Georgopoulos et al. [18] with permission)

pressure-time product (an index of inspiratory work of breathing) 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 esophageal pressure before triggering, dp/dt) during intervening breaths. These results indicate that inspiratory activity was pre-programmed and relative insensitive to changes in load between mandatory and spontaneous breaths during SIMV or BIPAP. Chemical feedback could be a critical factor for this breath programming. Using a closed circuit experimental set-up we demonstrated that, when the chemical stimulus was rigorously controlled, unloading of the respiratory muscles by mechanical ventilation (proportional assist ventilation, 50% reduction of the normal load) did not result in down-regulation of respiratory muscle activation [8]. The waveforms of transdiaphragmatic pressure and pressure generated by all respiratory muscles (Pmus) did not differ significantly with and without unloading (Fig. 6). These results indicate that the neuromuscular output was tightly linked to CO_2 (i.e., to chemical stimulus) and not to load reduction. It follows that mechanical ventilation, which can be viewed as a type of respiratory muscle unloading, does not alter significantly the contribution of chemical feedback to the prevailing levels of respiratory muscle activity. Chemical feedback remains an important determinant of Pmus even in mechanically ventilated patients.

Effectiveness of chemical feedback during mechanical ventilation

Although mechanical ventilation per se does not alter significantly the contribution of chemical feedback in determining Pmus, its effectiveness to compensate for changes in chemical stimuli may be modified [7]. This issue is of fundamental importance to understand the concept of control of breathing during mechanical ventilation. However, the effectiveness of chemical feedback may differ between wakefulness and sleep (or anesthesia). For this reason the effectiveness of chemical feedback during mechanical ventilation will be described separately during wakefulness and during sleep or anesthesia.

Wakefulness. Recent studies have examined the ventilatory response to CO_2 in mechanically ventilated normal conscious subjects [8, 9, 25, 30]. These studies demonstrated that, as it occurs during spontaneous breathing, changes in $PaCO_2$ resulted in a progressive increase in the intensity of respiratory effort (Pmus) with initially no change in respiratory rate. Respiratory rate increased, to a much lesser extent, when $PaCO_2$ approached values well above eucapnic level. It is of interest to note that this response pattern was observed independent of the mode of mechanical ventilation, indicating that there is no fundamental difference in response to CO_2 between various modes of ventilatory support [8, 9, 25, 30].

The ventilatory response pattern to chemical stimuli has important consequences as far as the effectiveness of chem-

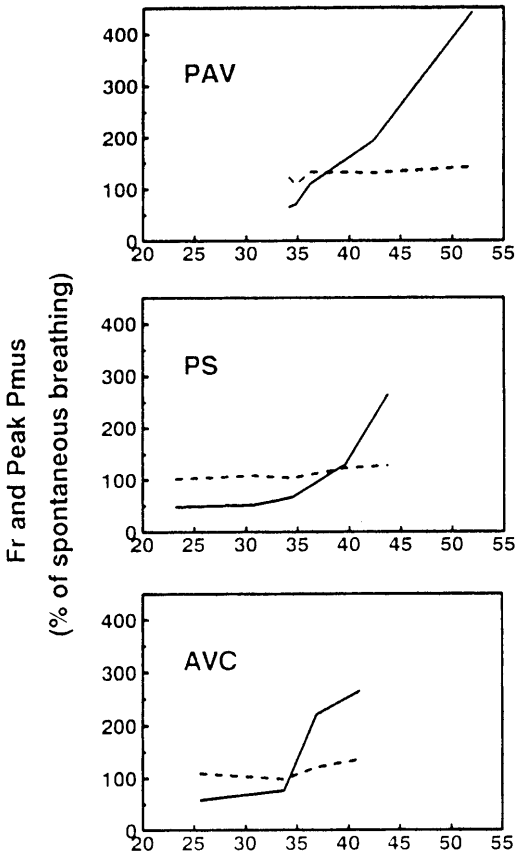

Fig. 7 Breathing frequency (Fr, dashed lines) and peak inspiratory muscle pressure (peak Pmus, solid lines) as a function of end-tidal PCO_2 ($P_{ET}CO_2$) in a patient ventilated on three modes of ventilatory support. Fr and peak Pmus were expressed as % of the values observed during spontaneous breathing. PAV; proportional assist ventilation. PS; pressure support. AVC; assist volume control. See text for further details

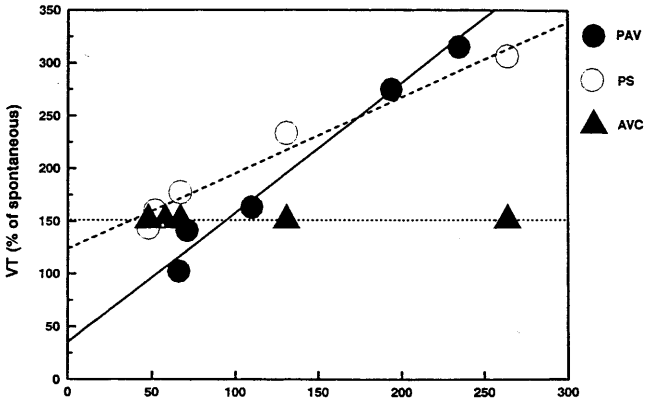

Fig. 8 Same patient as in Fig. 7. Relationships between V_T and peak Pmus (% of spontaneous breathing) during different modes of support. Regression lines were constructed by the least square method. See Fig. 7 for abbreviations

ical feedback is concerned. Recently, we studied in normal conscious humans the effectiveness of chemical feedback during various modes of assisted ventilatory support [21]. Figure 7 shows ventilatory output as a function of $PaCO_2$ in a representative patient with relatively normal respiratory system mechanics ventilated with different modes of assisted mechanical ventilation. On each mode the patient was ventilated with the highest comfortable level of assist, corresponding to 80% reduction of patient resistance and elastance with PAV, 10 cm H_2O pressure with PS, and 1.2 l V_T with AVC. When the patient was stable on each mode, inspired CO_2(F_ICO_2) was increased in steps and the response of the respiratory system to this CO_2 challenge was observed. Several important points are illustrated by the figure: 1) The starting PCO_2 point was considerably lower with PS and AVC than with PAV; a significant respiratory alkalosis was observed with PS and AVC but not with PAV. 2) Breathing frequency remained relatively stable compared to baseline level (spontaneous breathing) over a wide range of PCO_2. The patient continued to trigger the ventilator rhythmically despite severe hypocapnia. 3) At zero F_ICO_2 and independent of the mode of ventilatory support, the intensity of respiratory effort, as expressed by peak Pmus (Pmus was calculated using esophageal pressure measurements and the Campbell diagram), decreased to approximately 50% of baseline and increased progressively with increasing CO_2 stimulus. Fig. 8 shows the relationship between the intensity of patient effort, expressed by peak Pmus, and V_T in the same patient. As is expected with AVC, V_T is constant and independent of Pmus. With PS, V_T increased with increasing Pmus. However, even when Pmus decreased to 50% of baseline, V_T was approximately 40% higher than that during spontaneous breathing. This is because with PS, in the absence of active termination of inspiration, the V_T has a minimum value, which depends on the PS level, mechanical properties of respiratory system, and cycling-off criterion [37, 38]. On the other hand, with PAV the decrease of Pmus to 60% of baseline was able to maintain V_T at the baseline level, thus, avoiding a significant drop in PCO_2. It follows that modes of ventilatory support that permit the intensity of patient effort to be expressed on the V_T delivered by the ventilator increase the effectiveness of chemical feedback to regulate $PaCO_2$ and particularly to prevent respiratory alkalosis, an important cause of arrhythmia and weaning failure. Thus, the effectiveness of chemical feedback increases progressively as we switch from AVC to PS to PAV. The above considerations are also supported by the study of Puntillo et al. [26]. These investigators studied the variability of various ventilatory parameters observed over 12 h in patients with acute respiratory failure. The patients were studied one day during PS and the following day during PAV. Compared to PS, with PAV arterial blood gases during the 12 h period of observation were maintained within narrower limits. This was likely due to the increased ability of patients to change V_T in response to alteration in

ventilatory demands; with PAV the variability of V_T was significantly greater, while that of breathing frequency was significantly less than the values observed during PS.

Various disease states may alter the principles described above. This remains an unexplored area and much work needs to be done. We have shown in conscious patients with the sleep apnea syndrome and in patients with brain damage that a drop in $PaCO_2$ due to brief (40 s) hypoxic hyperventilation, resulted, contrary to normals, in significant hypoventilation and in some cases triggered periodic breathing [10, 11]. This hypoventilation was interpreted as evidence indicating a defect or reduced effectiveness of short-term post-stimulus potentiation, a brain stem mechanism promoting ventilatory stability [12]. In which case level of assist that causes a significant decrease in $PaCO_2$ may promote unstable breathing, a situation closely resembling that observed during sleep (see below).

Recently Ranieri et al. [27] studied the response to added dead space in patients with abnormal respiratory system mechanics (high resistance and elastance) ventilated either on PS or PAV. Addition of dead space (i.e., CO_2 challenge) during PAV resulted in an increase in V_T with no change in breathing frequency. This response pattern was similar to that observed in normals. With PS in the same patients, dead space resulted in an increase in rate with little change in V_T, while they experienced more discomfort. However, because with PS the ability of patients, particularly in the presence of abnormal respiratory system mechanics, to increase V_T is limited [37, 38], it is likely that the increase in rate reflects greater respiratory distress (i.e., behavioral feedback).

Sleep – Anesthesia. It is well known that removal of the wakefulness drive to breathe as it occurs during sleep or under anesthesia increases the dependence of respiratory rhythm on $PaCO_2$ [4, 6, 23, 33, 40]. Under these circumstances a drop in $PaCO_2$ by 3–4 mmHg causes apnea. An assist level that is associated with a relatively high V_T increases the likelihood of apneas and may trigger periodic breathing [23, 24]. The occurrence of periodic breathing is clearly an indication of over-assist. Periodic breathing may cause significant hypoxemia, an issue that should be considered seriously in critically ill patients. Reducing the assist level to the point where breathing becomes stable may improve oxygenation and sleep quality. Periodic breathing has been observed with PS and AVC modes of ventilatory support [4, 23, 32]. On the other hand, it has been shown that unstable breathing did not occur with PAV despite the fact that the subjects were ventilated at the highest assist level (90% assist) [19]. This is due to the fact that with PAV there is a tight link between Pmus and Paw [36]. It follows that modes of ventilatory support that decrease the V_T in response to any reduction in Pmus promote ventilatory stability. It should be mentioned that in the presence of active lung disease (i.e., pneumonia, ARDS) inputs to respiratory controller from other than chemical sources (i.e., reflex feedback) may not permit chemical feedback to prevent respiratory alkalosis during sleep or under anesthesia.

In summary, the operation of chemical feedback during assisted mechanical ventilation depends on *1) the mode of mechanical ventilatory support, 2) the sleep/awake stage, and 3) disease state*.

Reflex feedback

Reflex feedback plays an important role in the control of breathing [1, 35]. The characteristics of each breath are influenced by various reflexes, which are related to lung volume or flow and mediated by receptors located in the respiratory tract, lung, and chest wall [2, 31, 35]. Mechanical ventilation may stimulate these receptors by changing flow and volume [7]. In addition, changes in ventilatory settings that inevitably associated with volume and flow changes may also elicit Pmus responses mediated by various reflexes [7, 37, 38]. Table 1 summarizes the effects of these reflexes on Pmus waveform and highlights some possible consequences during mechanical ventilation. A few examples may help the reader to follow Table 1. Assume, for example, that the patient is ventilated on pressure support and the pressure support level is increased (1^{st} column of the Table 1). This results in higher V_T (2^{nd} column) which, through the vagal volume feedback reflex (3^{rd} column), will decrease the neural inspiratory and expiratory time as well as the peak pressure developed by the inspiratory muscles. As a consequence (4^{th} column), the patient may exhibit dynamic hyperinflation (higher volume must be exhaled in shorter time). Dynamic hyperinflation together with the reduced peak inspiratory pressure may lead to ineffective effort. Decreasing the assist level (1^{st} column) may increase neural inspiratory time and peak inspiratory pressure (3^{rd} column) and under certain circumstances may lead to the phenomenon of double triggering (4^{th} column). Consider another patient who has high abdominal pressure (i.e., pancreatitis). The increased abdominal pressure (1^{st} column) increases the elastance of chest wall (2^{nd} column). The change in chest wall elastance modifies the activity of chest wall reflexes (3^{rd} column), leading to tachypnea. Tachypnea, particulary in patients with increased expiratory resistance, may cause (4^{th} column) patient-ventilator asynchrony (i.e., ineffective efforts). Finally, assume that the PEEP level is increased in a patient ventilated on assisted modes (1^{st} column). This results in sustained increased of lung volume (2^{nd} column) which, through vagal volume related reflexes, increases the neural expiratory time and causes recruitment of expiratory muscles (3^{rd} column). The longer expiratory time and activation of expiratory muscles may decrease the expiratory lung volume, thus limiting the PEEP-induced lung volume change (4^{th} column).

Notwithstanding that the final response may be unpredictable depending on the magnitude and type of lung vol-

Table 1 Examples of changes in ventilator settings and clinical status, the reflex response of the patient respiratory effort and possible consequences during MV

Example	Change	Response	Possible consequences during MV
		Vagal volume related reflexes	
↑ assist level	↑ V_T	↓ T_In, ↓ T_En, ↓ Peak $Pmus_I$	↑ dynamic hyperinflation, ineffective effort
↓ assist level	↓ V_T	↑ T_In, ↑ T_En, ↑ Peak $Pmus_I$	double triggering
↑ resistance	delayed of lung emptying	↑ T_En, ↑ $Pmus_E$	↓ dynamic hyperinflation
$T_I m > T_I n$	mechanical inflation during T_En	↑ T_En, ↑ $Pmus_E$	↓ dynamic hyperinflation
↑ PEEP	sustained increased of lung volume	↑ T_En, ↑ $Pmus_E$	↓ PEEP-induced lung volume change
$T_I m < T_I n$	withdrawn of lung volume during neural inspiration	↑ T_In	double triggering
		Chest wall reflexes	
↑ abdominal pressure	↑ E_{CW}	↑ Fr	↑ patient-ventilator asynchrony
		Flow-related reflexes	
↓ T_Im at constant V_T	↑ inspiratory flow	↓ T_In, ↓ T_En	↑ dynamic hyperinflation

T_In, T_En; neural inspiratory and expiratory time, respectively. T_Im; ventilator inspiratory time. E_{CW}; chest wall elastance. Fr; breathing frequency. $Pmus_I$, $Pmus_E$; inspiratory and expiratory muscle pressure, respectively. V_T; tidal volume. MV; mechanical ventilation

ume change, the level of consciousness and the relative strength of the reflexes involved, reflex feedback should be taken into account when ventilatory strategies are planned. However, very few studies have examined specifically the operation of reflex feedback during mechanical ventilation and much work is clearly needed in this field. It is our opinion that this feedback, under certain circumstances, may be of importance for the management of mechanically ventilated patients. For example, it has been shown that increasing inspiratory flow rate causes tachypnea [13, 14]. This response was also observed during NREM sleep, although its magnitude was reduced. This observation confirms that the response is mediated via a reflex pathway (i.e., not a behavioral response) and that its potency is related to the level of vigilance. The response was equally strong in quadriplegic, indicating that it is not mediated by rib cage receptors, and was also preserved in patients with double lung transplants [15]. The latter observation does not exclude a vagal mechanoreceptor response, since many of these receptors are located above the resection line, while there is a possibility of regeneration. The excitatory effect of inspiratory flow on breathing frequency has two important clinical implications. First, an increase in flow rate intended to reduce inflation time and provide more time for expiration in order to reduce the dynamic hyperinflation (i.e., in patients with obstructive lung disease) [15] may be detrimental and elicit the opposite response (i.e., decrease in expiratory time) (Fig. 9). Indeed, in a recent study in patients ventilated on the assist volume controlled mode, Corn et al. [3] increased inspiratory flow rate at constant tidal volume and observed a significant increase in breathing frequency. As a result of the change in breathing frequency, expiratory time showed a variable response to changes in flow rate, with some patients actually demonstrating a reduced expiratory time with higher flow rates. Second, an increase in inspiratory flow rate may lead to hyperventilation and respiratory alkalosis, important causes of arrhythmia and weaning difficulties.

Behavioral feedback

The effects of behavioral feedback on control of breathing in mechanically ventilated patients are unpredictable depending on several factors related to an individual patient and the Intensive Care Unit (ICU) environment. Alteration of ventilator settings, planned to achieve a particular goal (i.e., reduction of dynamic hyperinflation), might be ineffective in awake patients due to behavioral feedback. Finally, behavioral feedback may change considerably from time to time due to changes in the level of sedation, sleep/awake state, patient status, and stimuli of ICU environment. However, the several factors that are involved in behavioral feedback complicate the study and interpretation of the effects of this feedback on the system that controls breathing in mechanically ventilated patients.

Composite response of Pmus to Paw

The above considerations indicate that the final response of Pmus to Paw is complex and influenced by several factors. Changes in ventilator settings alter Pmus in a way that depends on the 1) instantaneous flow and volume changes, 2) magnitude of PaO_2, $PaCO_2$, and pH changes, 3) individual sensitivity to chemical stimuli, 4) disease states, 5) level of consciousness, and 6) type and strength of various reflexes involved in the response. The unpredictable effects of behavioral feedback further complicate the situation. All these determinants of Pmus may modify the ventilatory outcome intended for the change in ventilator settings.

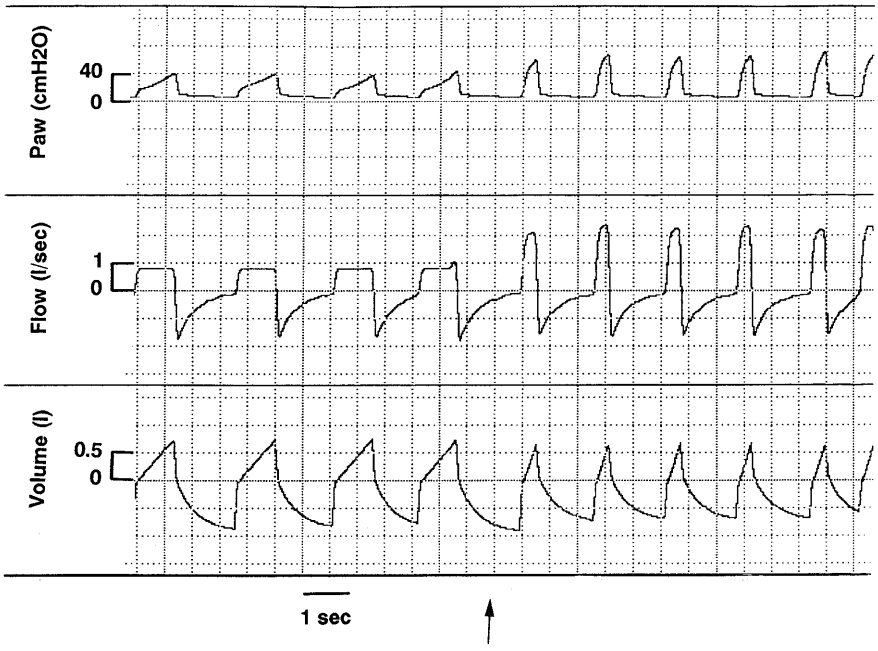

Fig. 9 Airway pressure (Paw), airflow, and volume (inspiration positive) in a patient with obstructive lung disease ventilated on assist volume-controlled mode. Arrow indicates the point at which constant inspiratory flow increased from 30 l/min to 90 l/min (tidal volume was kept constant). Notice that within one breath after a change in V_I from 30 l/min to 90 l/min total breath duration decreased considerably (from 2.1 to 1.63 s). Therefore, despite the decrease in inspiratory time (from 0.9 to 0.4 s), expiratory time did not increase proportionally, but remained relatively constant (from 1.2 to 1.23 s). The excitatory effect of V_I on the rate of inspiratory effort counterbalanced the beneficial effect of high V_I on expiratory time

Conclusion

The pressure provided by the ventilator considerably alters the expression of the system that controls breathing. During mechanical ventilation the respiratory system is under the influence of two pumps, the ventilator pump (i.e., Paw) controlled by the physician's brain and the patient's own respiratory muscle pump (Pmus) controlled by the patient's brain. In order for the final ventilatory output to be appropriate for the current status of the patient, a harmony between the function of these two brains is essential. To achieve this harmony, the physician dealing with a mechanically ventilated patient should be aware that: 1) Paw by changing the driving pressure for inspiratory flow modifies the volume-time profile, which via various feedback systems affects Pmus; 2) Paw is influenced by the mode of mechanical ventilatory support, the mechanics of the respiratory system, and the Pmus waveform, and 3) as a result of the Paw-Pmus interaction, the various aspects of control of breathing may be masked and/or modulated by mechanical ventilation.

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