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Patient–ventilator interaction

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The respiratory control system consists of a motor arm, which executes the act of breathing, a control centre in the medulla oblongata and a number of pathways that convey information to the control centre.[2] [69] On the basis of this information, the control centre activates spinal motor neurones serving respiratory muscles, with an intensity and rate that can vary substantially between breaths. The activity of spinal motor neurones is carried by peripheral nerves to the respiratory muscles, which contract and generate pressure (P_{mus}). According to the equation of motion for the respiratory system, P_{mus} is dissipated to overcome the resistance (R_{rs}) and elastance (E_{rs}) of the respiratory system (inertia is assumed to be negligible), as follows:

$$P_{mus}=(R_{rs}\times\dot{V})+(E_{rs}\times V) \qquad (1)$$

where V is volume relative to passive functional residual capacity (FRC) and $\dot{V}$ is flow. Equation 1 determines volume in relation to time and, depending on the frequency of activation of the respiratory muscles, ventilation. Volume changes with time can affect P_{mus} via the force–length and force–velocity relationships of the respiratory muscles (mechanical feedback), and can modify the activity of spinal motor neurones and the control centre via afferents from receptors in the airways, chest wall or respiratory muscles (reflex feedback). Inputs from other sources (e.g. behavioural, temperature, postural) may also modify the function of the control centre. In addition, ventilation and gas exchange in the lung determine arterial blood gas composition (Pa_{O_2}, Pa_{CO_2}). These variables affect the activity of the control centre via peripheral and central chemoreceptors (chemical feedback). This system can be affected at any site by disease or treatment.

During mechanical ventilation, the pressure provided by the ventilator (P_{aw}) is added to the muscle pressure.[21] In mechanically ventilated patients the driving pressure for inspiratory flow (P_T) is the sum of P_{mus} and P_{aw}.[21] [54] According to the equation of motion, P_T is dissipated to overcome the resistance (R_{rs}) and elastance (E_{rs}) of the respiratory system, determining the volume time profile as follows:

$$P_T=P_{mus}+P_{aw}=(\dot{V}\times R_{rs})+(V\times E_{rs}) \qquad (2)$$

The change in volume affects the pattern of P_{mus} through mechanical, chemical, reflex and behavioural feedback systems, which can then alter the waveform of P_{aw} (Fig. 1). During assisted mechanical ventilation there is interaction between the patient and ventilator. This interaction depends on (i) the response of the ventilator (i.e. P_{aw}) to patient effort (i.e. P_{mus}) and (ii) the response of the patient to ventilator delivered breath (Fig. 1).[21]

Response of the ventilator to patient effort

This depends on factors related to the ventilator and the patient.[54] The ventilator-related factors are (i) the triggering variable, (ii) the variable that controls gas delivery, and (iii) the cycling off criterion. Patient-related factors are (i) the mechanics of the respiratory system and (ii) the characteristics of the P_{mus} waveform.

Ventilator-related factors

For given mechanical properties of the respiratory system and P_{mus} waveform, the response of the ventilator to patient effort is greatly influenced by the ventilator variables.

Trigger variable

The trigger variable is usually pressure or flow.[51] With pressure triggering, in order to trigger the ventilator and initiate the inspiratory flow, the patient must decrease the pressure in the ventilator circuit to a preset value, which will then open a demand valve. With flow triggering, the patient triggers the ventilator when the respiratory muscles generate a certain preset inspiratory flow.[51] With pressure triggering, the inspiratory muscles contract isometrically, and with flow
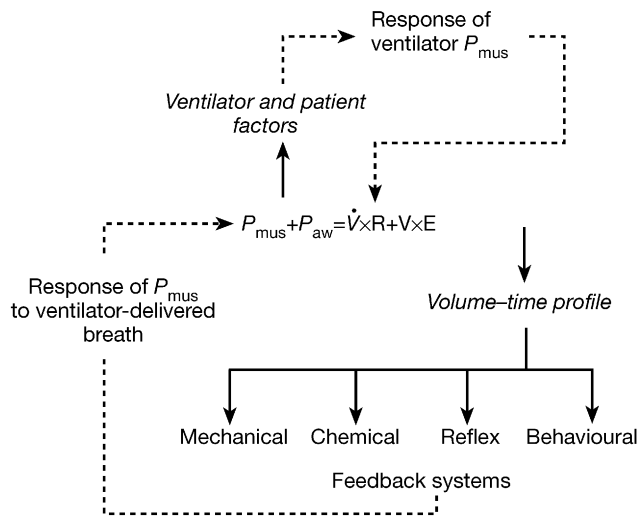
Fig 1 Variables that influence patient–ventilator interaction. Dotted lines indicate various feedback systems. P_{mus}=respiratory muscle pressure; P_{aw}=ventilator pressure; $\dot{V}$=flow; V=volume relative to passive functional residual capacity; R and E=resistance and elastance of respiratory system, respectively. See text for details.

Fig 2 Flow–time waveform in two patients ventilated with a Vision ventilator on pressure support mode. Inspiration is down and expiration is up. Open arrows indicate the flow shape signal, generated by offsetting (0.25 litre s^{-1}) and delaying (300 ms) the actual flow (thick line) during inspiration and expiration. Closed arrows indicate the electronic signal rising in proportion to actual inspiratory flow (thick line) in each breath. (A) Mechanical breath triggered and terminated by the shape method. During expiration the actual flow decreased abruptly (due to the onset of inspiratory effort), crossed the flow shape signal and triggered the ventilator. During inspiration the acute decrease in inspiratory flow caused the actual flow to cross the flow shape signal and terminated the pressure delivery (cycling off) before the electronic signal equalled the actual flow. (B) Mechanical breath triggered by the volume method and terminated by the spontaneous expiratory threshold. During expiration the actual flow did not cross the flow shape signal (the actual flow crossed the shape signal after the triggering). The ventilator was triggered when 6 ml of volume was inspired. During expiration the electronic signal equalled the actual flow and terminated the pressure delivery (cycling off) before the actual flow crossed the shape signal flow.[43] See text for details.

triggering contraction is isotonic. It is generally believed that triggering of the ventilator is better with flow than with pressure.[1 3 23 49] The clinical significance is unclear in terms of the work of breathing and patient–ventilator interaction. Pressure sensors in current ventilators are much improved, reducing any difference between flow- and pressure-triggering systems.[5 46 55] Recent studies in patients with different diseases show that the difference in the work of breathing between flow and pressure triggering is of minimal clinical significance.[1 24 59]

Recently, a new microprocessor-controlled positive pressure ventilatory assist system has been introduced (BiPAP Vision; Respironics, Pittsburg, PA, USA) with new algorithms to trigger the ventilator. They are designed to improve patient–ventilator interaction, with the flow waveform mainly used to trigger the ventilator. Triggering occurs either when patient effort generates inspiratory flow, causing 6 ml of volume to accumulate above baseline flow (volume method), or when the patient inspiratory effort distorts the expiratory flow waveform sufficiently, whichever occurs first. The latter method of triggering is referred to as the shape signal method. This method is based on the generation of a new flow signal (flow shape signal) by offsetting the signal from the actual flow by 0.25 litre s^{-1} and delaying it for 300 ms. The intentional delay causes the flow shape signal to be slightly behind the patient's flow rate. As a result, a sudden decrease in expiratory flow from an inspiratory effort will cross the shape signal and this creates a signal for ventilator triggering (Fig. 2). Similarly, the flow waveform can be used to terminate the mechanical breath (Fig. 2). We found that the flow waveform method of ventilator triggering was more sensitive to patient effort than the flow triggering with less ineffective effort from the
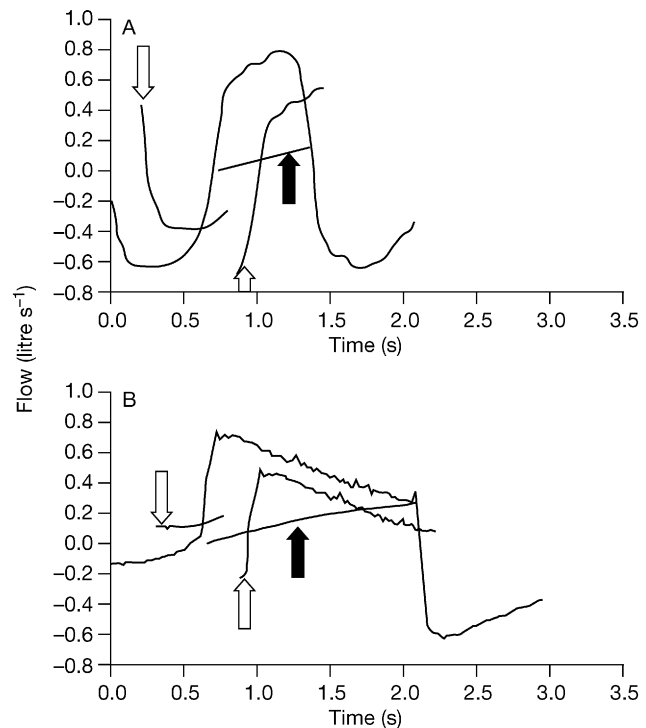
patient.[43] An active lung model showed that, at controlled levels of dynamic hyperinflation and inspiratory effort, the simulated patient effort required to trigger the ventilator was ~50% less with the shape method than with flow triggering.[43]

Ideally, during assisted support the triggering of the ventilator should be the result of inspiratory muscle contraction. In some circumstances, however, a mechanical breath may be triggered without an inspiratory effort (autotriggering). Autotriggering is well known and inherent to all currently used methods of triggering. It may be caused by random noise in the circuit, water in the circuit (which can cause abrupt changes in circuit resistance), leaks and cardiogenic oscillations.[26 29] Autotriggering occurs more
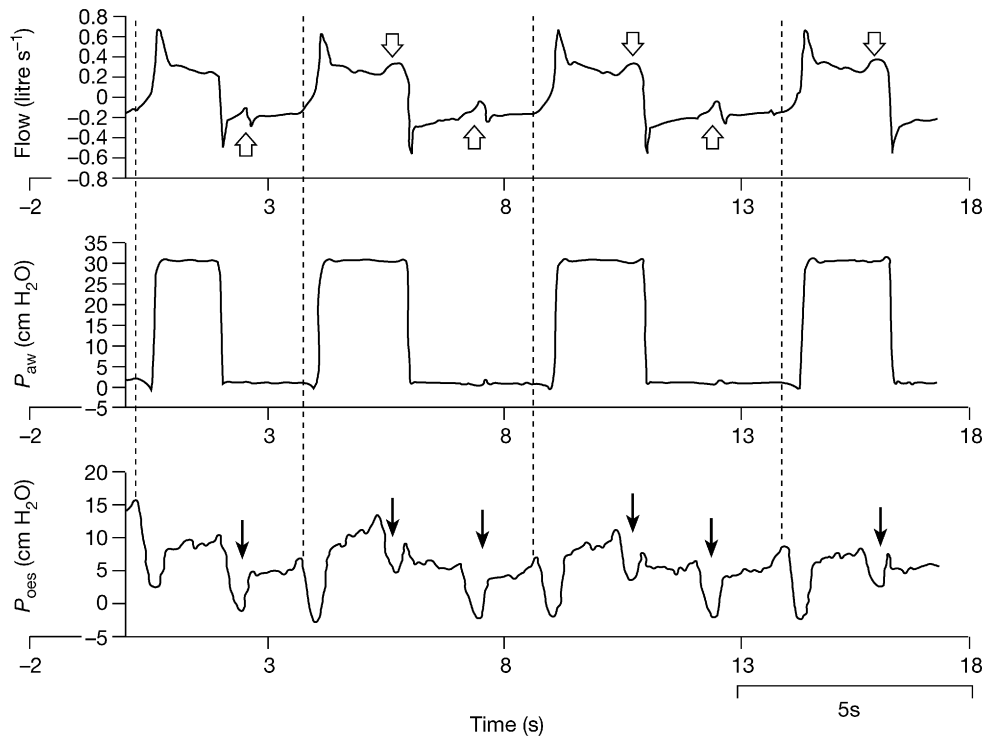
Fig 3 Flow and airway (P_{aw}) and oesophageal (P_{oes}) pressures in a patient with severe chronic obstructive pulmonary disease ventilated with pressure support. Dotted vertical lines indicate the beginning of inspiratory efforts that triggered the ventilator. Closed arrows indicate ineffective efforts. Notice the time delay between the beginning of inspiratory effort and ventilator triggering. Observe also that ineffective efforts occurred during both mechanical inspiration and expiration. These ineffective efforts may be identified easily using the flow tracings; ineffective efforts during mechanical inspiration result in an abrupt increase in inspiratory flow, whereas during expiration they result in an abrupt decrease in expiratory flow (open arrows in flow tracing). The ventilator frequency is 12 bpm and that of the patient is 33 inspiratory efforts min^{-1}.

often with low respiratory drive and breathing frequency and when dynamic hyperinflation is absent. Such factors allow zero flow for some time during expiration before the next inspiration, making the system vulnerable to triggering from changes of airway pressure which are not caused by inspiratory effort. In these circumstances a large stroke volume is important in triggering by cardiac oscillations.[29] The risk of triggering increases with greater sensitivity of the triggering system. Imanaka and colleagues[29] found that decreasing the flow threshold for triggering from 2 to 1 l/min increased the frequency of autotriggering from 15% to 22%. Autotriggering can interfere with patient management, reducing Pa_{CO_2} and thus patient effort. In addition it may affect decision-making. Autotriggering in a brain-dead patient has delayed the declaration of death with serious consequences for organ donation.[60]

The converse of patient–ventilator asynchrony is when the patient's inspiratory effort does not trigger the ventilator.[22 57] Ineffective triggering is very common in ventilator-dependent patients when dynamic hyperinflation is present.[13 47 65] Dynamic hyperinflation is caused by factors such as low elastic recoil, high ventilatory demands, increased expiratory resistance and short expiratory time.[40 47] When dynamic hyperinflation is present,

end-expiratory lung volume is greater than passive FRC determined by the set external PEEP ($PEEP_e$). Consequently, elastic recoil pressure at end-expiration is higher than $PEEP_e$. This difference in elastic recoil pressure, referred to as intrinsic PEEP ($PEEP_i$), represents an elastic threshold load for the patient. With flow or pressure triggering, the patient must first generate a P_{mus} equivalent to $PEEP_i$ to be able to decrease alveolar pressure below $PEEP_e$ and trigger the ventilator. Therefore, part of P_{mus} is dissipated to counteract $PEEP_i$ (elastic threshold load) and this delays the onset of effective inspiratory effort and the triggering. At times triggering is so delayed that the ventilator cycles are almost completely out of phase with the patient, defeating the purpose of assisted ventilatory support (Fig. 3). In some circumstances (high $PEEP_i$ or low P_{mus}) the patient cannot decrease the P_{aw} below PEEP and the inspiratory effort is ineffective (Fig. 3). When asynchrony occurs, the relationship between the patient's spontaneous breathing and the machine frequency is easily affected by changes in ventilator settings or in the patient's respiratory output (Fig. 4). Although ineffective triggering is usually associated with obstructive lung disease, it may also occur in patients with normal or restrictive lung disease, particularly when assistance is great. In addition, the
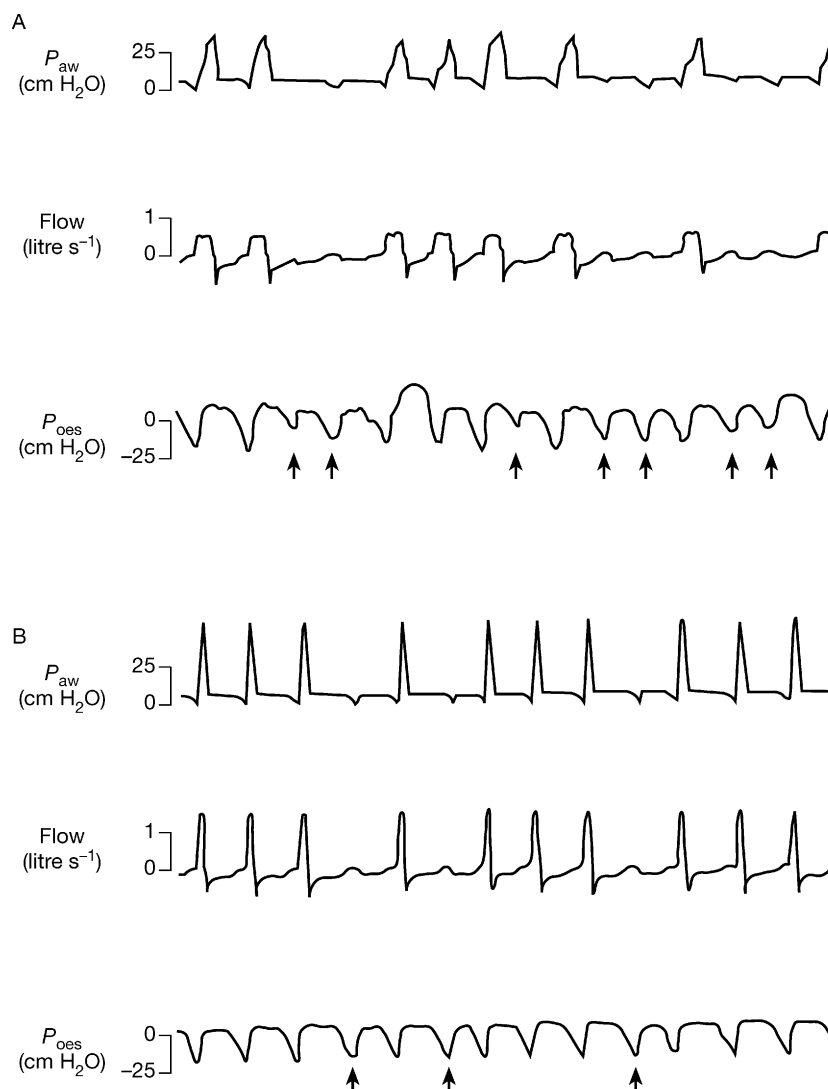
Fig 4 Airway pressure (P_{aw}), flow and oesophageal pressure (P_{oes}) in a patient with chronic obstructive lung disease ventilated with assist volume control with two inspiratory flow rates ($\dot{V}_I$), 30 litres min^{-1} (A) and 90 litres min^{-1} (B). With both flow rates tidal volume (V_T) was kept constant (0.55 litre). Ineffective efforts are indicated by arrows. By increasing the time available for expiration (increase in inspiratory flow at constant V_T; panel B), dynamic hyperinflation was decreased and as a result the number of ineffective efforts was reduced and the rate of the ventilator increased.

expiratory circuit of the ventilator may impose significant resistance on expiratory flow. This can prevent the respiratory system reaching equilibrium at the end of expiration, even in patients with normal respiratory mechanics.

With modern ventilators, the incidence of ineffective triggering does not differ between the flow- and pressure-triggering systems.[50] However, compared with flow triggering, the flow waveform method of triggering (Fig. 2A) is associated with significantly less ineffective efforts.[43] This is because flow waveform triggering does not require patients to fully counterbalance $PEEP_i$ to trigger the ventilator. Distortion of expiratory flow is sufficient to trigger the ventilator (Fig. 2A). However, even the flow waveform method of triggering may not be activated in patients with severe airway obstruction and dynamic hyperinflation. These patients have a high expiratory

resistance associated with flow limitation, so that after an initial peak the expiratory flow may decrease to relatively low values (<0.25 litre s^{-1}). In these circumstances the flow signal is positive throughout the remaining expiration and the crossing point occurs only when the flow has an inspiratory direction (Fig. 2B).

Apart from asynchrony between the patient and ventilator and wasted effort, ineffective triggering may have serious consequences for inspiratory muscle function. Ineffective triggering often occurs during exhalation of the previous mechanical breath, and the inspiratory muscles are activated to contract when they would normally be lengthening as lung volume decreases. This type of muscle contraction is referred to as pliometric contraction and causes ultrastructural damage to muscle fibres and reduced strength.[10][28] After a single maximal pliometric contraction of skeletal
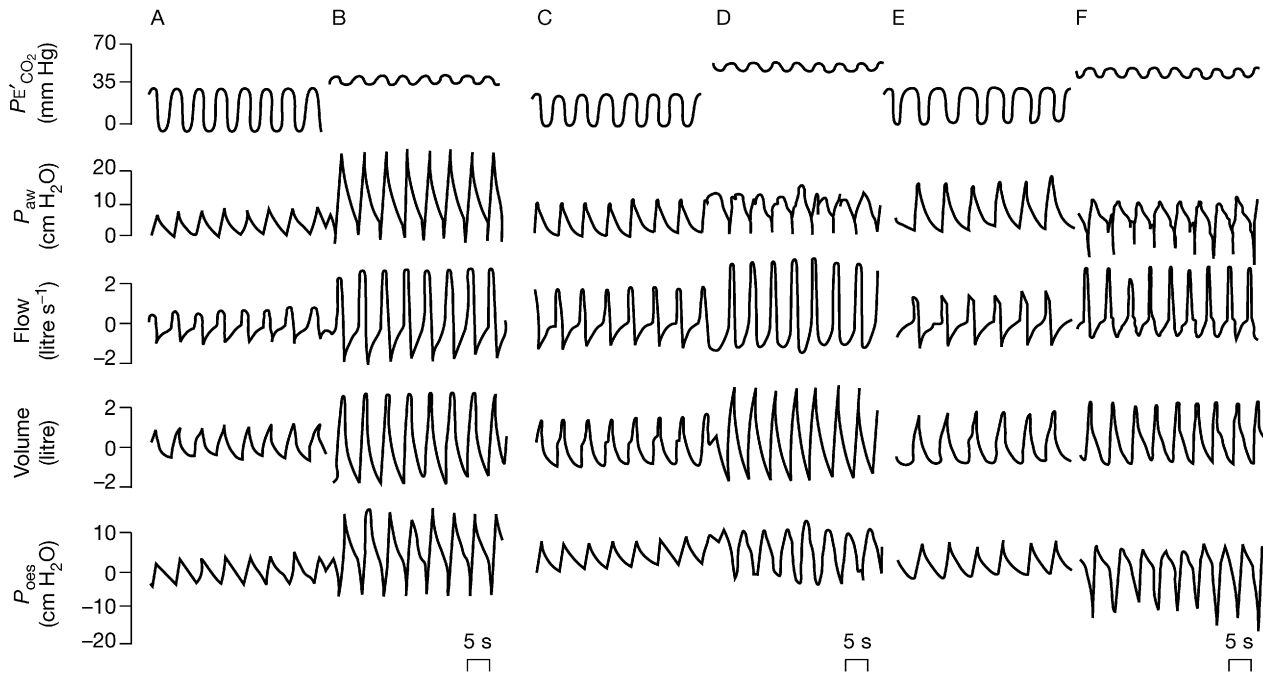
Fig 5 End-tidal carbon dioxide tension ($P_{E'CO_2}$), airway pressure (P_{aw}), flow (inspiration up), volume (inspiration up) and oesophageal (P_{oes}) pressure in a representative subject during proportional assist ventilation (A, B), pressure support (C, D) and assist volume control (E, F) without (A, C, E) and with (B, D, F) carbon dioxide challenge. Observe the different response of P_{aw} with carbon dioxide stimulation between the three modes of support. From reference 38.

muscle the injury to the muscle fibres causes a marked force deficit, which may exceed 50%.[28] Ineffective triggering during mechanical expiration could injure the inspiratory muscles and cause inspiratory muscle weakness and weaning failure. No study of mechanically ventilated patients has studied this possibility.

Ineffective inspiration and autotriggering affect the assessment of ventilatory output during mechanical ventilation. If ineffective efforts or autotriggering are present, ventilator frequency does not indicate the patient's spontaneous breathing rate. Both features can alter patient respiratory effort by changes in neural feedback (Fig. 1).

Factors that alter pressure delivery

There are several modes of assisted mechanical ventilation.[54 67] Depending on the variable that controls the delivered pressure, they can be classified into three categories: (i) assist volume control (AVC), in which the ventilator, once triggered, delivers a preset tidal volume with a preset flow–time profile; (ii) pressure support (PS), in which the ventilator delivers a preset pressure;[54] and (iii) proportional assist ventilation (PAV),[67] in which the ventilator delivers pressure which is proportional (the proportionality is preset) to instantaneous flow and volume and, thus, to P_{mus}. With AVC the mechanical inflation time is determined by the ventilator, whereas with PS it is influenced both by the patient and ventilator,[54] and with PAV mechanical inflation time is controlled mainly by the patient.[67] Modern ventilators can combine various modes and ventilate the patient simultaneously with more than one

mode. Currently, PAV is under investigation and it is not universally available. We consider here the relationship of P_{aw} and P_{mus} in PAV mode with some important aspects of patient–ventilator interaction.

The features of each ventilator mode determine the relationship between P_{aw} and P_{mus}. Figure 5 shows the response of the ventilator to respiratory effort of a patient ventilated with different modes of support.[38] A carbon dioxide challenge was used to alter patient effort. With volume control, P_{aw} decreased to almost zero with a greater patient inspiratory effort caused by hypercapnia and a set tidal volume. It follows that with this mode the ventilator overcomes patient effort. With PS, tidal volume and inspiratory flows are increased with increasing carbon dioxide, while P_{aw} remains relatively constant. With PS there is no relationship between P_{mus} and P_{aw}. With PAV carbon dioxide stimulation causes an increase both in patient effort and pressure provided by the ventilator. Here there is a positive relationship (the gain is preset) between P_{mus} and P_{aw}. It is obvious from Fig. 5 that during mechanical ventilation the ventilatory output cannot be interpreted properly if the mode of support is not taken into account, as changes in ventilatory output may not reflect corresponding changes in patient effort.[38]

Cycling off variable

Ideally, during assisted modes of support the end of mechanical inspiration should coincide with the end of neural inspiration. However, this happens rarely, if ever. Usually ventilator flow stops either before or after the
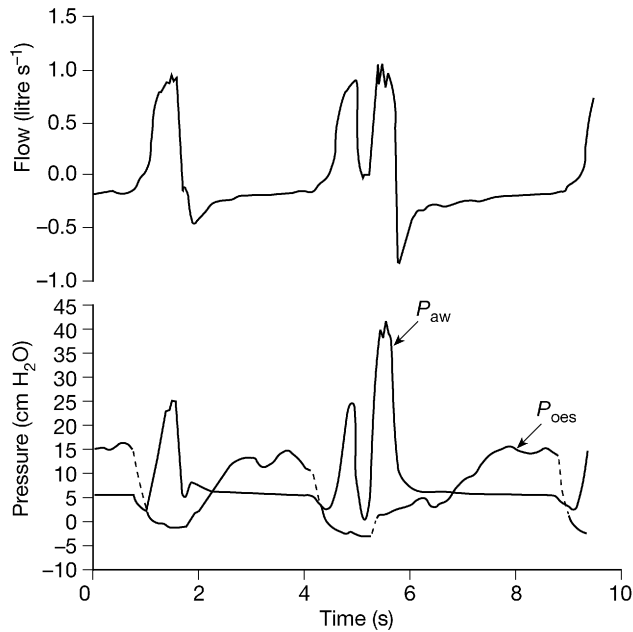
Fig 6 Flow and airway (P_{aw}) and oesophageal (P_{oes}) pressures in a patient recovering from acute lung injury and ventilated with assist volume control with constant inspiratory flow. In the second breath, tidal volume (volume not shown) was decreased at the same inspiratory flow. As a result there was a premature end to mechanical inspiration, and because inspiratory muscles continued to contract they developed pressure which overcame the elastic recoil at the end of inspiration. As a result P_{aw} decreased below the triggering threshold and the ventilator therefore delivered a new mechanical breath. The ventilator was triggered three times by the two inspiratory efforts. Observe the high P_{aw} of the third mechanical breath because lung volume was greater (the volume of the third breath was added to that of the second). Notice also that total breath duration of the second respiratory effort of the patient was considerably longer than that of the first, owing to activation of the Hering–Breuer reflex by the high volume.

patient stops his or her inspiratory effort: expiratory asynchrony.[57] This is because the algorithms used to cycle off the ventilator are far from ideal. With assist volume mode, inspiratory flow is usually preset and the ventilator controls the duration of inspiration to achieve a preset tidal volume. In these circumstances inspiratory time does not differ between breaths and is not affected by the patient. Because neural respiratory timing varies, any synchrony between the end of mechanical and neural inspiration is by chance. Mechanical inspiratory time can be shorter or longer than the neural inspiratory time.[58] During PS ventilation most ventilators stop inspiration when inspiratory flow decreases to less than an absolute value or a percentage of peak inspiratory flow.[4] During PS, P_{mus} can affect inspiratory flow and thus inspiratory time, but these controls were designed to promote expiratory synchrony. Mathematical models and clinical studies show that, as with assist volume mode, expiratory asynchrony is the rule with PS.[62] Models show that the end of mechanical inspiration can be affected by several factors, such as the assist level, the maximum P_{mus} and the ratio of the time constant of the respiratory system to mechanical inspiratory time.[62] For a

given neural inspiratory time, mechanical inspiratory time may change if there is a change in the mechanics of the respiratory system, the pressure level or the respiratory drive. The recently introduced flow waveform method (using either the flow shape or spontaneous expiratory threshold method) to terminate the PS (Fig. 2) did not improve expiratory synchrony between the patient and ventilator.[43] With the flow waveform method of cycling off, we found that the relationship between the end of neural and mechanical inspiration did not differ from that observed when a criterion of 25% peak flow cycling was used. Thus, expiratory asynchrony is common with the flow waveform method of breath termination.[43] On the other hand, PAV may solve the problem of expiratory asynchrony because with this mode the ventilator inspiratory flow is driven by the inspiratory effort, so theoretically the end of neural inspiration should coincide with the end of inspiratory flow. Nevertheless, considerable asynchrony has been found with PAV, attributed to delay between the ventilator control system's input and output.[12] This delay is also influenced by the mechanical properties of the respiratory system. Generally, expiratory asynchrony is common during all modes of assisted mechanical ventilation.

The effects of asynchrony depend on the type of asynchrony present.[21] If mechanical inspiration ends before neural inspiration, then ventilator assistance will cease while the inspiratory muscles continue to contract. This asynchrony may cause double triggering and overestimation of patient breathing frequency (Fig. 6). At the end of mechanical inspiration, P_{mus} continues to increase and, because inspiratory flow is zero or is reversed, the muscle tension is applied to overcome the elastic recoil of the respiratory system. If the respiratory system volume decreases rapidly, P_{mus} may be greater than elastic recoil. Airway pressure could decrease below PEEP and this will trigger the ventilator (Fig. 6). A short mechanical inflation time and low elastic recoil at end-inspiration can promote retriggering. When neural inspiration ends before the end of mechanical inspiration, ineffective triggering may occur because the ventilator delivers gas flow during neural expiration. This can reduce the time available for neural expiratory time (Figs 3 and 4), and the ventilator frequency underestimates the patient's breathing frequency. In addition to ineffective or double triggering, expiratory asynchrony may cause discomfort to patients and unnecessary inspiratory and expiratory work. It may also activate various receptors (reflex feedback) and change the pattern of respiratory muscle activation (see below).

Patient-related factors

Mechanics of the respiratory system
The mechanical properties of the respiratory system (and ventilator tubing) can affect the pressure delivered by the ventilator (P_{aw}) independently of P_{mus} and cause asyn-
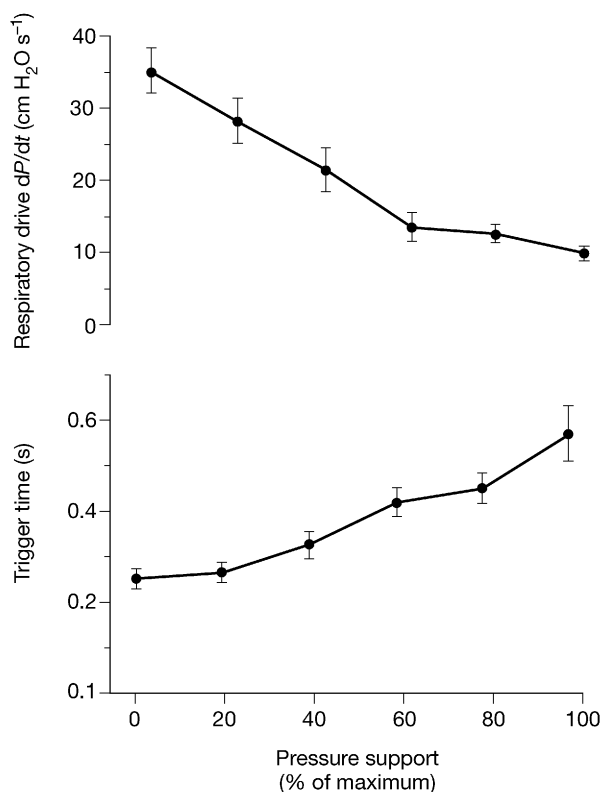
Fig 7 Graded increases in pressure support cause a decrease in respiratory drive (dP/dt), associated with considerable increase in the triggering time. Adapted from reference 33.

chrony. Abnormal mechanics of the respiratory system often cause asynchrony between P_{mus} and P_{aw}, mainly because of dynamic hyperinflation. It can occur with all modes of mechanical ventilation.[13 47 64] Ineffective triggering, excessive triggering delay and prolonged inflation time are frequent in patients with obstructive lung disease. Mathematical models predict that PS ventilation in the presence of airflow obstruction is associated with variations in tidal volume and $PEEP_i$ even when patient effort is constant.[27] This dynamic instability increases if the time constant of the respiratory system is increased and causes asynchrony that varies significantly between breaths.[27] Increased arousals during PS, but not volume-cycled ventilation, could be caused partly by dynamic patient–ventilator asynchrony.[42]

Characteristics of the P_{mus} waveform
The pattern of P_{mus} waveform affects P_{aw} in several ways, depending on factors related to both patient and ventilator. An extensive review of these factors is beyond the scope of this article, but some examples can explain how P_{mus} can affect ventilator function.[21]

The initial rate of P_{mus} increase interacts with the trigger function of the ventilator. If P_{mus} increases slowly, for example when respiratory drive is small (i.e. low Pa_{CO_2}, sedation, sleep, high level of assist), the time between onset of the patient's inspiratory effort and ventilator triggering increases, causing asynchrony (see *Trigger variable* above) (Fig. 7).[33] If dynamic hyperinflation is also present, the prolonged triggering time, particularly if the neural inspiratory time is short and peak P_{mus} is small, can cause ineffective efforts. If inspiratory effort is great, for example with increased metabolic rate, high Pa_{CO_2}, reduced sedation or reduced ventilation assistance, then both the rate of increase of P_{mus} and peak P_{mus} will increase. This will reduce the time delay and allow patient–ventilator synchrony (Fig. 7).[33] 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 inspiratory effort (Fig. 6). Changes in ventilation caused by such interactions may modify patient effort secondarily, through feedback loops (Fig. 1).

Response of patient effort to ventilator-delivered breath

The waveform of P_{mus} during mechanical ventilation is affected by mechanical, chemical, reflex and behavioural feedback (Fig. 1).

Mechanical feedback
Mechanical feedback is related to the length (related to lung volume) and velocity of contraction (related to flow) of the respiratory muscles, and to the way chest wall geometry can influence P_{mus}.[68] For a given neural activation of the inspiratory muscles, P_{mus} will be less when lung volume and flow are greater. Thus, for a given degree of muscle activation, P_{mus} will be less during mechanical ventilation than during spontaneous breathing if the 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 are relatively small because the values of operating volume and flow are small.[68] Nevertheless, mechanical feedback should be taken into account if pressure measurements are used to infer changes in respiratory muscle activation. At high ventilatory demands, P_{mus} may underestimate the neural output to respiratory muscles: during hypercapnic hyperventilation mechanical feedback can reduce peak P_{mus} by up to 15%.[20]

Chemical feedback
Chemical feedback involves the response of the respiratory system to Pa_{O_2}, Pa_{CO_2} and pH. It acts to reduce changes in blood gas tensions that would otherwise occur from changes in metabolic rate or gas exchange.[2 69] In spontaneously breathing normal subjects chemical feedback determines respiratory motor output both during wakefulness and during sleep. In mechanically ventilated patients, there are

two important questions: (i) Does mechanical ventilation affect the chemical drive to P_{mus}? (ii) Is the effectiveness of chemical drive modified by mechanical ventilation?

Contribution of chemical feedback to P_{mus} during mechanical ventilation

An important reason for using mechanical ventilation is to unload the respiratory muscles.[57] Theoretically, the respiratory control system can respond to unloading in three ways. First, respiratory muscle activation is reduced and ventilation remains the same as before the unloading. Secondly, respiratory muscle activation remains the same and ventilation will increase as assistance increases. Thirdly, there may be an intermediate response, whereby ventilation is greater and respiratory muscle activity is reduced, indicating incomplete downregulation of respiratory muscle activity. It is generally believed that the respiratory system follows the third pathway. Several studies have shown that, with unloading, ventilation is increased and respiratory motor output is less.[11 67 68] These results were interpreted as indicating that non-chemical feedback related to the load itself plays a role in determining the level of respiratory muscle activation.[11 67 68] Thus, at first glance it seems that the contribution of chemical feedback in determining P_{mus} is reduced by mechanical ventilation. However, most of the studies of this type used an open loop system and chemical feedback was not rigorously controlled. The observed downregulation of respiratory muscle output could have been related to a reduction of chemical feedback because of the increased ventilation.

Milic-Emili and Tyler[37] studied the ventilatory response to carbon dioxide in normal subjects breathing with different resistive loads. For a given P_{CO_2}, the work output of the inspiratory muscles did not change appreciably with the load. In patients with constant-flow synchronized intermittent mandatory ventilation (SIMV), with constant assistance, inspiratory effort was the same for spontaneous and mandatory breaths.[30 33 35] Leung and colleagues[33] compared the respiratory effort of patients ventilated with SIMV and patients ventilated with a combination of SIMV and PS. When PS was added, the inspiratory pressure–time product (an index of patient effort) was decreased both in mandatory and intervening breaths. This additional reduction during mandatory breaths was proportional to the decrease in respiratory drive (estimated using the change in oesophageal pressure before triggering, dP/dt) during intervening breaths. This suggests that inspiratory activity was preprogrammed and did not respond to the breath-by-breath changes in load seen during SIMV. Chemical feedback could be important. This is supported by a study in which the chemical stimulus was rigorously controlled. Unloading of the respiratory muscles by mechanical ventilation did not reduce respiratory muscle activation. For a given carbon dioxide stimulus, the waveforms of transdiaphragmatic pressure and total pressure of respiratory muscles were not affected by unloading.[20] This study showed that neuromus-

cular output was tightly linked to carbon dioxide (i.e. to the chemical stimulus) and not to load reduction. In a study of patients with acute respiratory distress syndrome (ARDS) receiving PS, respiratory motor output was measured when changes in the level of support were applied for two breaths, which is unlikely to affect chemical stimuli.[61] The respiratory drive was not affected by the change in support, although there was a small change in breathing frequency. The altered frequency meant that no change occurred in the pressure–time product per minute, which is an important index of respiratory effort. However if the changes in PS were applied for a longer period, respiratory drive and the pressure–time product were affected, which was presumably mediated by chemical stimuli.

Such studies suggest that mechanical ventilation does not significantly affect how chemical feedback controls respiratory muscle activity. As during spontaneous breathing, chemical feedback remains an important determinant of P_{mus} during mechanical ventilation.

Effectiveness of chemical feedback during mechanical ventilation

Although mechanical ventilation does not affect chemical feedback, the ability of this feedback to change the chemical stimuli may be altered. This issue is fundamental in understanding patient–ventilator interaction. The effectiveness of chemical feedback may differ substantially between wakefulness and sleep or sedation, so these two aspects will be discussed separately.

Wakefulness

Several studies have examined the ventilatory response to carbon dioxide in mechanically ventilated normal conscious subjects.[18 20 38] As in spontaneous breathing, increases in Pa_{CO_2} caused increased respiratory effort (P_{mus}) with initially no change in respiratory rate. Respiratory rate increased if Pa_{CO_2} increased considerably. This response was found with the three modes of support, with no fundamental difference in response to carbon dioxide for these modes of ventilatory support.[38]

The above studies used carbon dioxide as a changing chemical stimulus but similar principles should apply if other chemical stimuli (Pa_{O_2}, pH) are altered. The steady-state ventilatory response to these stimuli is qualitatively similar, affecting the intensity of respiratory effort.[2 45] We studied the effectiveness of chemical feedback in normal humans mechanically ventilated with the three main modes of support: PAV, AVC and PS.[38] The subjects were ventilated with the maximum tolerable level of assist, which was 80% reduction of patient resistance and elastance with PAV, 10 cm H_2O pressure with PS and 1.2 l tidal volume with AVC. The response of the respiratory system to carbon dioxide challenge was observed. Compared with spontaneous breathing, before carbon dioxide challenge, hypocapnia was caused by AVC and PS but not by PAV. However, the intensity of respiratory effort, expressed by the pressure–time product of respiratory muscles (PTP), was
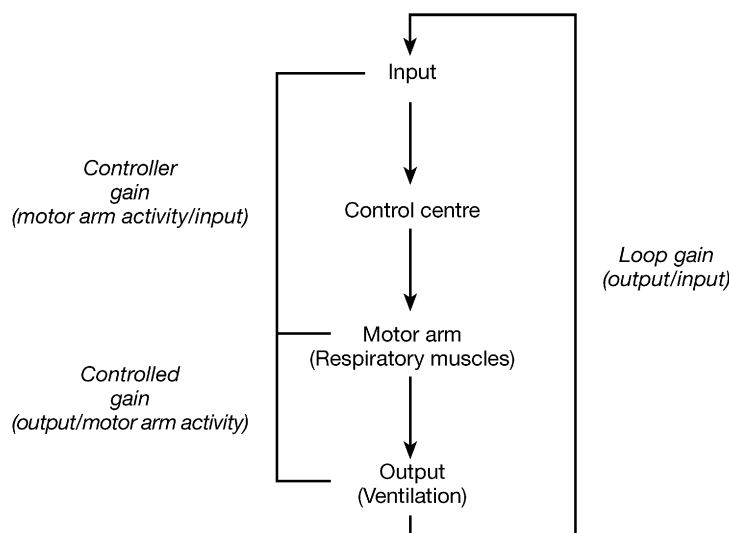
Loop gain=Controller gain×Controlled gain
and
Loop gain=(motor arm activity/input)×(output/motor arm activity)=output/input

Fig 8 Schematic representation of the respiratory system in terms of respiratory system loop, controller and controlled gains. An input to the control centre of the respiratory system (located in the brainstem) will change the activity of respiratory muscles (motor arm) depending on (i) the sensitivity of the control centre to the input change, (ii) the integrity of the pathway that connects the control centre to respiratory muscles (bulbospinal neural tract, lower motor neurones, peripheral nerves and neuromuscular junction) and (iii) the ability of respiratory muscles to develop pressure. The change in respiratory muscle activity for a given change in the input stimulus defines the respiratory controller gain. Depending on (i) the modes of mechanical ventilation, (ii) the assist level and (iii) the mechanics of respiratory system, the activity of respiratory muscles will determine the ventilation that is the final output. The change in ventilation for a given change in respiratory muscle activity defines the respiratory system-controlled gain. The change in output (ventilation) for a given change in the input defines the respiratory system loop gain and is the product of controller and controlled gain factors.

reduced by all modes of support. The reduction was greater with AVC and PS than with PAV, and tidal volume with these two modes was considerably greater. Breathing frequency was very similar with all modes; the subjects continued to trigger the ventilator despite being hypocapnic. We can explain these results by considering the respiratory system in terms of respiratory loop gain (change in ventilation for a given change in carbon dioxide stimulus), respiratory controller gain (change in respiratory effort for a given change in carbon dioxide stimulus) and controlled system gain (change in ventilation for a given change in respiratory effort) (Fig. 8). End-tidal P_{CO_2} ($P_{E'CO_2}$), PTP per minute (PTP_{minute}) and ventilation ($\dot{V}_E$) were used, respectively, as indices of carbon dioxide stimulus (input), respiratory efforts (motor arm activity) and output. At zero $F_{I_{CO_2}}$ respiratory loop gain to carbon dioxide ($\dot{V}_E/P_{E'CO_2}$) was less with PAV than with PS and AVC (Fig. 9).[38] The respiratory loop gain to carbon dioxide is the product of respiratory controller gain ($PTP_{minute}/P_{E'CO_2}$) and respiratory controlled gain ($\dot{V}_E/PTP_{minute}$). Thus, the reduced respiratory loop gain with PAV could be caused by either a small respiratory controller gain or a small controlled system gain. The respiratory controller gain did not differ between the various modes of support, indicating that, at least at low $P_{E'CO_2}$, the sensitivity of the respiratory muscles to carbon dioxide was not appreciably affected by the mode

of support (Fig. 9).[38] On the other hand, with PAV, the controlled system gain was 5- to 6-fold less than with AVC and PS, approaching the value observed during spontaneous breathing (Fig. 9). Therefore, neuroventilatory coupling was preserved with PAV, but not with PS and AVC. This suggests that, before carbon dioxide was given, the ventilatory mode effect on controlled system gain was the main determinant of hypocapnia. For a similar respiratory controller gain, controlled system gain was less with PAV (Fig. 9). The low controlled system gain forced the respiratory loop gain to be reduced, thus preventing a reduction in $P_{a_{CO_2}}$. The mode of ventilatory support affected the response of the respiratory loop gain to carbon dioxide. With PAV, the respiratory loop gain increased as carbon dioxide increased, whereas loop gain remained constant with PS and decreased with AVC (Fig. 9). The increase in respiratory loop gain with carbon dioxide challenge observed with PAV came entirely from the increase in respiratory controller gain, and the controlled system gain remained constant (Fig. 9). On the other hand, with PS and AVC there was a significant decrease in controlled system gain, while respiratory controller gain responded as it did with PAV, increasing with increasing carbon dioxide stimulus (Fig. 9). Therefore, with PS and AVC there was a negative feedback between respiratory effort and controlled system gain; controlled system gain
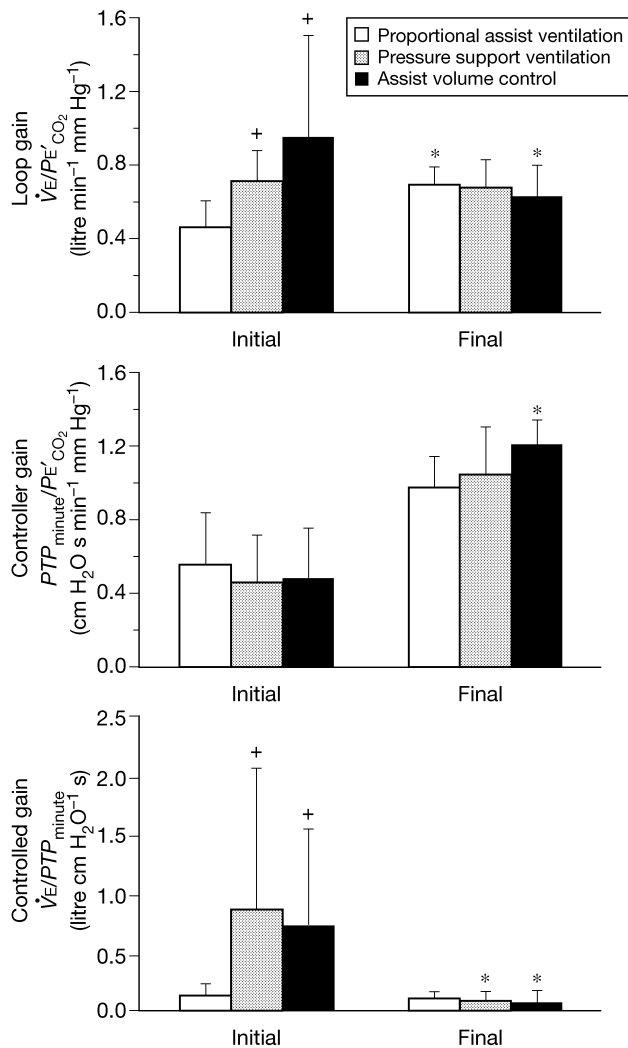
Fig 9 Respiratory system loop, controller and controlled gains in normal subjects ventilated with assist volume control (cross-hatched bars), proportional assist ventilation (open bars) and pressure support (hatched bars) without (initial, zero $F_{I_{CO_2}}$) and with carbon dioxide challenge (final $F_{I_{CO_2}}$ ~7%); PTP_{minute}=pressure time product of respiratory muscles per minute; PE'_{CO_2}=partial pressure of end tidal PCO_2; $\dot{V}E$=minute ventilation. $^{+}P<0.05$ compared with the corresponding value with PAV; $^{*}P<0.05$ compared with the corresponding values at initial $F_{I_{CO_2}}$. From reference 38.

decreased with increasing respiratory effort. In contrast, with PAV the controlled system gain was independent of respiratory effort; neuroventilatory coupling remained even at high drive. Figure 9 clearly shows that the capacity of chemical feedback to compensate for changes in chemical stimuli depends on the effect of ventilator mode on controlled system gain.

These observations may be altered by disease. The exact effects are not known, but we give some examples. In conscious patients with sleep apnoea syndrome, when Pa_{CO_2} is reduced by a brief period of hypoxia (40 s), which causes hyperventilation, this is followed by hypoventilation and in some cases periodic breathing. This response is not seen in normal subjects.[16] Similar results occurred in patients with brain damage.[19] This hypoventilation suggests deficient or reduced short-term poststimulus potentiation, which is a brainstem mechanism promoting ventilatory stability.[15] In these conditions, a level of assist that causes hypocapnia may promote unstable breathing, which is similar to the response observed during sleep (see *Sleep and sedation* below). Ranieri and colleagues[44] studied the effects of additional deadspace in patients with abnormal respiratory system mechanics (high resistance and elastance) during ventilation with either PS or PAV. During PAV, this carbon dioxide challenge increased tidal volume (V_T) with no change in breathing frequency. A similar response was observed in normal subjects. During PS the carbon dioxide challenge caused an increase in rate with little change in V_T, and the patients experienced more discomfort. In patients with abnormal respiratory system mechanics, the response to increased mechanical load was studied in patients ventilated with PS and PAV.[25] Minute ventilation was preserved with both modes. The form of compensation for the added load differed between the modes. With PS, ventilation was maintained by a 58% increase in breathing frequency; this compensated for a 29% reduction in V_T. With PAV the changes were less: V_T decreased by 10% and breathing frequency increased by 14% (Fig. 10). Such studies suggest that, when an awake patient has a limited ability to increase V_T in response to a chemical challenge either applied directly (increase in dead space) or indirectly (increase in impedance), the only response is an increase in breathing rate. In these studies the patients were awake and the greater respiratory distress observed with PS[25 44] could cause tachypnoea by a behavioural pathway. Studies of sedated patients are needed to resolve this issue.

Sleep and sedation
When the drive to breathe from wakefulness is reduced during sleep or sedation, the dependence of the respiratory rhythm on Pa_{CO_2} is increased.[53 63] Under these circumstances, a decrease in Pa_{CO_2} by 3–4 mm Hg causes apnoea. This has major consequences during mechanical ventilation. Any assist that increases V_T will increase the likelihood of apnoea and may trigger periodic breathing, indicating excessive assist. Periodic breathing could cause hypoxaemia, which is important in the critically ill. By reducing assist, breathing will become stable and this may improve oxygenation and sleep quality.[42] Periodic breathing occurs with PS and AVC.[9 39 53] Unstable breathing was not seen with PAV despite ventilation at the highest level of assist (90%).[36] These results are predictable: with PAV, the patient can keep V_T constant with different degrees of assist by appropriate adjustment of P_{mus}.[25 36 38 44] It follows that a form of ventilatory support that decreases V_T in response to a decrease in P_{mus} will promote ventilatory stability. However, if there is lung disease, such as pneumonia or ARDS, other inputs to the respiratory controller may prevent chemical feedback from decreasing a tendency to
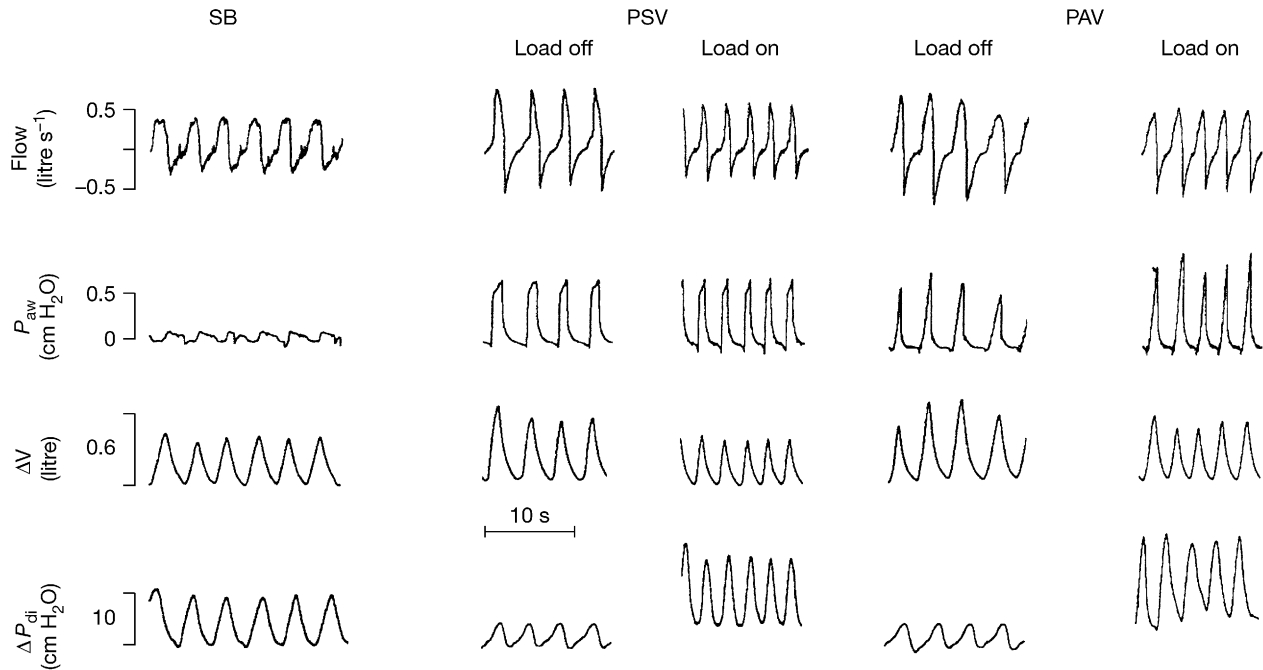
Fig 10 Changes in flow, airway pressure (P_{aw}), volume (ΔV) and transdiaphragmatic pressure (ΔPdi) in a patient during spontaneous breathing (SB) and during pressure support (PSV) and proportional assist ventilation (PAV) without (load off) and with chest and abdominal binding (load on). Observe the difference in breathing pattern response to load application between pressure support and proportional assist ventilation. From reference 25.

respiratory alkalosis during sleep or sedation. In sedated patients with ARDS ventilated with PS, an increase in the assist level led to a decrease in Pa_{CO_2}, which reduced respiratory drive but did not affect respiratory timing.[61]

Reflex feedback

Other reflexes are important in controlling breathing.[2 69] These reflexes are related to lung volume or flow and mediated by receptors located in the respiratory tract, lung and chest wall.[2 6 52 69] Mechanical ventilation may stimulate these receptors by altering flow and volume in comparison with spontaneous breathing.[21] Changes in volume and flow may also elicit P_{mus} responses caused by other reflexes.[21 65] Such reflex responses have been largely ignored in mechanically ventilated patients, but under certain circumstances they may be important in patient management.

We studied mechanically ventilated patients with ARDS and measured the reflex response of P_{mus} to a ventilator breath when the ventilator setting was changed.[32] We altered (i) V_T at constant inspiratory flow, (ii) PS level, and (iii) inspiratory flow at constant V_T for two breaths, and measured the response of the P_{mus} waveform. Because the patients were sedated and the changes were applied for two breaths only, behavioural and chemical influences were small, and any changes in P_{mus} would be caused by other reflex feedback. Changing ventilator settings altered the neural respiratory timing immediately (in one breath), whereas respiratory drive remained constant. By decreasing

V_T and PS and increasing inspiratory flow, breathing frequency was increased. Depending on the ventilation, the changes in breathing frequency were caused by changes in either the inspiratory or the expiratory direction. If inspiratory flow was increased, breathing frequency changed mainly by decreasing the neural inspiratory time. Decreasing V_T and PS increased frequency by decreasing the neural expiratory time.[32] This reflex response is qualitatively similar to responses in normal humans during wakefulness and sleep.[8 14 17 56] It is interesting to note that neural expiratory time strongly depended on the time that mechanical inflation extended into neural expiration; neural expiratory time increased in proportion to the increase in the delay between ventilator cycling off and the end of neural inspiratory time (Fig. 11).[32] This shows that expiratory asynchrony causes a reflex timing response, and the dependency of neural expiratory time on expiratory asynchrony was subsequently confirmed.[66] The response seems to be relatively weak in patients with obstructive lung disease. The most obvious reflex mechanism is the Hering–Breuer reflex.

Although the final response may be unpredictable, depending on factors such as the magnitude and type of lung volume change, the level of consciousness and the relative strengths of the reflexes involved, reflex feedback should be taken into account. Consider the following examples. Assume that a patient is receiving PS and the PS level is decreased to allow weaning. A reduced V_T and inspiratory flow will cause reflex feedback to increase
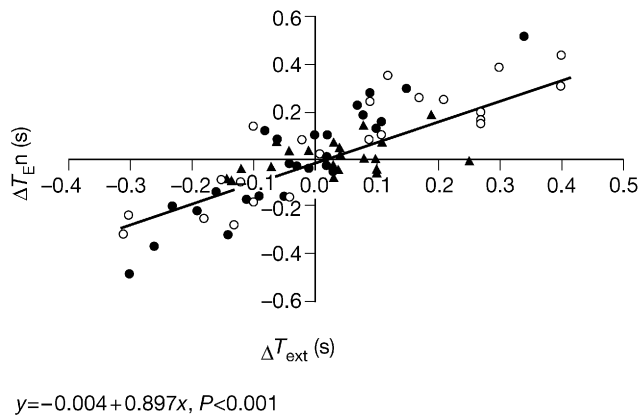
$y = -0.004 + 0.897x$, $P < 0.001$

Fig 11 Relationship between the changes in the time that mechanical inspiration extended into neural expiration (ΔText, changes in expiratory asynchrony) and in neural expiratory time ($\Delta T_E n$) of mechanically ventilated patients with ARDS. The solid line is the regression line. Closed circles=ΔText induced by changes in volume (at constant flow); open circles=flow (at constant volume); open triangles=pressure support. From reference 32.

neural inspiratory time and decrease neural expiratory time to a greater extent, resulting in an increase in breathing frequency. This increase in breathing frequency should not be misinterpreted to indicate poor tolerance of the reduction in PS. Consider another patient with obstructive lung disease, ventilated with AVC, in whom the tidal volume is decreased at constant inspiratory flow in order to reduce the magnitude of dynamic hyperinflation (less volume is exhaled in a longer period). The lower V_T usually reduces the delay in breath termination compared with the end of neural inspiration (decrease in expiratory asynchrony). By vagal reflex feedback this will decrease neural expiratory time, which will limit the ability of this strategy to reduce dynamic hyperinflation. The reverse will occur when V_T is increased. Assume that, in another patient ventilated on AVC, an increase in flow rate is applied with a constant V_T, intended to reduce inflation time and provide more time for expiration and reduce dynamic hyperinflation. This causes a reflex decrease in neural inspiratory time and an increase in breathing frequency. Expiratory time may change in either direction, depending mainly on the relation between neural and mechanical inspiratory time. In patients ventilated with AVC mode, expiratory time had a variable response to changes in flow rate. Some patients had a shorter expiratory time when inspiratory flow rate was increased. This prevented the desired effect of reducing dynamic hyperinflation.[7] Consider finally a patient in whom inspiratory flow decreases during PS or assist volume. This reflexly increases neural inspiratory time, and inspiratory activity will continue to increase to a greater value without alteration in the respiratory drive, and inspiratory effort will increase. Reducing inspiratory flow at constant V_T by 0.7 litre s^{-1} or PS by 11 cm H_2O resulted in an acute increase (within one breath) of 31% and 15% respectively in the pressure–time

product of the inspiratory muscles.[32] This increase would increase inspiratory muscle activity, which could cause fatigue with serious clinical consequences.

Behavioural feedback

Behavioural influences on breathing in mechanically ventilated patients are unpredictable, depending on the individual patient and the environment. Changing the ventilator settings to achieve a particular goal (e.g. reduction of dynamic hyperinflation) could be ineffective in awake patients because of behavioural feedback. In normal subjects ventilated with AVC mode, if inspiratory flow is more or less than the spontaneous value, then breathing discomfort, estimated using a visual analogue scale, is increased.[34] Increased dyspnoea may cause rapid shallow breathing and disturb patient–ventilator synchrony. Jubran and colleagues[31] observed active expiratory effort in patients with chronic obstructive pulmonary disease (COPD) when PS was increased. In patients with flow limitation, active expiratory efforts cause breathing discomfort.[41] Thus, increasing assistance for patients with COPD may cause behavioural feedback that makes them fight with the ventilator. Behavioural efforts are affected by changes in sedation, the sleep–wake state and other aspects of the patient environment.

Composite response of P_{mus} to P_{aw}

The final response of respiratory efforts to ventilatory assistance is complex and influenced by several factors. P_{mus} can depend on (i) flow and volume, (ii) Pa_{O_2}, Pa_{CO_2} and pH, (iii) sensitivity to these stimuli, (iv) the disease state, (v) the level of consciousness, and (vi) the type and strength of different reflexes. Unpredictable behavioural effects further complicate the situation. All these factors can influence the ventilatory outcome intended when the ventilator settings are changed.

Conclusion

In conclusion, during assisted mechanical ventilation there is an important interaction between the patient and ventilator. During mechanical ventilation the respiratory system is affected by two pumps, the ventilator (i.e. P_{aw}), controlled by the physician, and the patient's own respiratory muscle pump (P_{mus}), controlled by the patient. Patient–ventilator interaction is mainly an expression of the function of these two controllers, which should be in harmony if the result is to be appropriate for the patient. Harmony depends on the physician, who should realize that the respiratory system is not passive but reacts, sometimes vigorously, to pressure from the ventilator, depending on factors related both to the ventilator and the patient.

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