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. 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 ($P_{\text{mus}}$). According to the equation of motion for the respiratory system, $P_{\text{mus}}$ is dissipated to overcome the resistance ($R_{rs}$) and elastance ($E_{rs}$) of the respiratory system (inertia is assumed to be negligible), as follows:

$$P_{\text{mus}} = (R_{rs} \times V) + (E_{rs} \times V)$$

where $V$ is volume relative to passive functional residual capacity (FRC) and $V$ 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 $P_{\text{mus}}$ 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 ($P_{aO_2}$, $P_{aCO_2}$). 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. In mechanically ventilated patients the driving pressure for inspiratory flow ($P_T$) is the sum of $P_{\text{mus}}$ and $P_{aw}$. 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:

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

(2)

The change in volume affects the pattern of $P_{\text{mus}}$ 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. $P_{\text{mus}}$) and (ii) the response of the patient to ventilator delivered breath (Fig. 1).

**Response of the ventilator to patient effort**

This depends on factors related to the ventilator and the patient. 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 $P_{\text{mus}}$ waveform.

**Ventilator-related factors**

For given mechanical properties of the respiratory system and $P_{\text{mus}}$ 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. 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. With pressure triggering, the inspiratory muscles contract isometrically, and with flow...
triggering contraction is isotonic. It is generally believed that triggering of the ventilator is better with flow than with pressure. 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. 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.

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 inspiratory 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. 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.

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. Autotriggering occurs more
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.\textsuperscript{29} The risk of triggering increases with greater sensitivity of the triggering system. Imanaka and colleagues\textsuperscript{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 $P_{\text{aCO}_2}$ 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.\textsuperscript{60}

The converse of patient–ventilator asynchrony is when the patient’s inspiratory effort does not trigger the ventilator.\textsuperscript{22, 57} Ineffective triggering is very common in ventilator-dependent patients when dynamic hyperinflation is present.\textsuperscript{13, 47, 65} Dynamic hyperinflation is caused by factors such as low elastic recoil, high ventilatory demands, increased expiratory resistance and short expiratory time.\textsuperscript{40, 47} When dynamic hyperinflation is present, end-expiratory lung volume is greater than passive FRC determined by the set external PEEP ($\text{PEEP}_e$). Consequently, elastic recoil pressure at end-expiration is higher than $\text{PEEP}_e$. This difference in elastic recoil pressure, referred to as intrinsic PEEP ($\text{PEEP}_i$), represents an elastic threshold load for the patient. With flow or pressure triggering, the patient must first generate a $P_{\text{mus}}$ equivalent to $\text{PEEP}_i$ to be able to decrease alveolar pressure below $\text{PEEP}_e$ and trigger the ventilator. Therefore, part of $P_{\text{mus}}$ is dissipated to counteract $\text{PEEP}_i$ (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 $\text{PEEP}_i$ or low $P_{\text{mus}}$) 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

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{flow_and_airway_pressures.png}
\caption{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$^{-1}$.}
\end{figure}
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. However, compared with flow triggering, the flow waveform method of triggering (Fig. 2A) is associated with significantly less ineffective efforts. This is because flow waveform triggering does not require patients to fully counterbalance PEEP 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.

After a single maximal pliometric contraction of skeletal

---

**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 ($V_I$), 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.
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 $P_{\text{mus}}$. 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 $P_{\text{aw}}$ and $P_{\text{mus}}$ in PAV mode with some important aspects of patient–ventilator interaction.

The features of each ventilator mode determine the relationship between $P_{\text{aw}}$ and $P_{\text{mus}}$. 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, $P_{\text{aw}}$ 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 $P_{\text{aw}}$ remains relatively constant. With PS there is no relationship between $P_{\text{mus}}$ and $P_{\text{aw}}$. 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 $P_{\text{mus}}$ and $P_{\text{aw}}$. 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 5** End-tidal carbon dioxide tension ($P_{E\text{CO}_2}$), airway pressure ($P_{\text{aw}}$), flow (inspiration up), volume (inspiration up) and oesophageal ($P_{\text{oes}}$) 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 $P_{\text{aw}}$ with carbon dioxide stimulation between the three modes of support. From reference 38.
Patient—ventilator interaction

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-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-
Abnormal mechanics of the respiratory system often cause asynchrony between $P_{\text{mus}}$ and $P_{\text{aw}}$, mainly because of dynamic hyperinflation. It can occur with all modes of mechanical ventilation.\textsuperscript{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, even when patient effort is constant.\textsuperscript{27} This dynamic instability increases if the time constant of the respiratory system is increased and causes asynchrony that varies significantly between breaths.\textsuperscript{27} Increased arousals during PS, but not volume-cycled ventilation, could be caused partly by dynamic patient–ventilator asynchrony.\textsuperscript{42}

**Characteristics of the $P_{\text{mus}}$ waveform**

The pattern of $P_{\text{mus}}$ waveform affects $P_{\text{aw}}$ 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 $P_{\text{mus}}$ can affect ventilator function.\textsuperscript{21}

The initial rate of $P_{\text{mus}}$ increase interacts with the trigger function of the ventilator. If $P_{\text{mus}}$ increases slowly, for example when respiratory drive is small (i.e. low $P_{\text{aCO}_2}$, 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).\textsuperscript{33} If dynamic hyperinflation is also present, the prolonged triggering time, particularly if the neural inspiratory time is short and peak $P_{\text{mus}}$ is small, can cause ineffective efforts. If inspiratory effort is great, for example with increased metabolic rate, high $P_{\text{aCO}_2}$, reduced sedation or reduced ventilation assistance, then both the rate of increase of $P_{\text{mus}}$ and peak $P_{\text{mus}}$ will increase. This will reduce the time delay and allow patient–ventilator synchrony (Fig. 7).\textsuperscript{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 $P_{\text{mus}}$ 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 $P_{\text{mus}}$.\textsuperscript{68} For a given neural activation of the inspiratory muscles, $P_{\text{mus}}$ will be less when lung volume and flow are greater. Thus, for a given degree of muscle activation, $P_{\text{mus}}$ 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.\textsuperscript{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, $P_{\text{mus}}$ may underestimate the neural output to respiratory muscles: during hypercapnic hyperventilation mechanical feedback can reduce peak $P_{\text{mus}}$ by up to 15%.\textsuperscript{20}

**Chemical feedback**

Chemical feedback involves the response of the respiratory system to $P_{\text{aO}_2}$, $P_{\text{aCO}_2}$ and pH. It acts to reduce changes in blood gas tensions that would otherwise occur from changes in metabolic rate or gas exchange.\textsuperscript{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 $P_{\text{mus}}$? (ii) Is the effectiveness of chemical drive modified by mechanical ventilation?

**Contribution of chemical feedback to $P_{\text{mus}}$ during mechanical ventilation**

An important reason for using mechanical ventilation is to unload the respiratory muscles. 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. 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. Thus, at first glance it seems that the contribution of chemical feedback in determining $P_{\text{mus}}$ 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 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. Leung and colleagues 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. This study showed that neuromuscular 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. 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 $P_{\text{mus}}$ 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. As in spontaneous breathing, increases in $P_{aCO_2}$ caused increased respiratory effort ($P_{\text{mus}}$) with initially no change in respiratory rate. Respiratory rate increased if $P_{aCO_2}$ 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.

The above studies used carbon dioxide as a changing chemical stimulus but similar principles should apply if other chemical stimuli ($P_{aO_2}$, pH) are altered. The steady-state ventilatory response to these stimuli is qualitatively similar, affecting the intensity of respiratory effort. We studied the effectiveness of chemical feedback in normal humans mechanically ventilated with the three main modes of support: PAV, AVC and PS. The subjects were ventilated with the maximum tolerable level of assist, which was 80% reduction of patient resistance and elastance with PAV, 10 cm H2O 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
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 $P_{\text{CO}_2}$ ($P_{\text{E}}{\text{CO}_2}$), 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 $P_{\text{CO}_2}$ respiratory loop gain to carbon dioxide ($\dot{V}E/ P_{\text{E}}{\text{CO}_2}$) was less with PAV than with PS and AVC (Fig. 9). The respiratory loop gain to carbon dioxide is the product of respiratory controller gain (PTP minute/$P_{\text{E}}{\text{CO}_2}$) and respiratory controlled gain ($\dot{V}E/\text{PTP minute}$). 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 $P_{\text{E}}{\text{CO}_2}$, the sensitivity of the respiratory muscles to carbon dioxide was not appreciably affected by the mode of support (Fig. 9). 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 $P_{\text{aCO}_2}$. 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
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 \( P_{aCO_2} \) 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. Similar results occurred in patients with brain damage. This hypoventilation suggests deficient or reduced short-term poststimulus potentiation, which is a brainstem mechanism promoting ventilatory stability. 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 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. 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 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 \( P_{aCO_2} \) is increased. Under these circumstances, a decrease in \( P_{aCO_2} \) 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 hypoxaeemia, which is important in the critically ill. By reducing assist, breathing will become stable and this may improve oxygenation and sleep quality. Periodic breathing occurs with PS and AVC. Unstable breathing was not seen with PAV despite ventilation at the highest level of assist (90%). These results are predictable: with PAV, the patient can keep \( V_T \) constant with different degrees of assist by appropriate adjustment of \( P_{mus} \). 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

![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 FICO2) and with carbon dioxide challenge (final FICO2 ~7%); PTP\(_{\text{minute}}\)=pressure time product of respiratory muscles per minute; Pt\(\text{CO}_2\)=partial pressure of end tidal \( P_{\text{CO}_2} \); \( V_t\)=minute ventilation. *P<0.05 compared with the corresponding value with PAV; *P<0.05 compared with the corresponding values at initial FICO2. From reference 38.
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 $P_{\text{aCO}_2}$, which reduced respiratory drive but did not affect respiratory timing. 61

Reflux 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 69 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 $P_{\text{mus}}$ 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 $P_{\text{mus}}$ 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 $P_{\text{mus}}$ 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 $P_{\text{mus}}$ 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 58 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

![Fig 10 Changes in flow, airway pressure ($P_{aw}$), volume ($\Delta V$) and transdiaphragmatic pressure ($\Delta P_{di}$) 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.](image-url)
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 VT 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 VT is increased. Assume that, in another patient ventilated on AVC, an increase in flow rate is applied with a constant VT, 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. 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 VT by 0.7 litre s⁻¹ or PS by 11 cm H₂O resulted in an acute increase (within one breath) of 31% and 15% respectively in the pressure–time product of the inspiratory muscles. 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. Increased dyspnoea may cause rapid shallow breathing and disturb patient–ventilator synchrony. Jubran and colleagues 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. 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 \( P_{\text{mus}} \) to \( P_{\text{aw}} \)**

The final response of respiratory efforts to ventilatory assistance is complex and influenced by several factors. \( P_{\text{mus}} \) can depend on (i) flow and volume, (ii) \( P_{\text{aO₂}}, P_{\text{aCO₂}} \) 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. \( P_{\text{aw}} \), controlled by the physician, and the patient’s own respiratory muscle pump (\( P_{\text{mus}} \), 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.
References


48 Sassoon CS. Mechanical ventilator design and function: the trigger variable. Respir Care 1992; 37: 1056–69
64 Younes M. Patient–ventilator interaction with pressure-assisted modalities of ventilator support. Semin Respir Med 1993; 14: 299–322