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# Emerging modes of ventilation in the intensive care unit

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## Editor's key points

- Novel techniques in pulmonary ventilation are emerging and may offer improved outcome.
- These include airway pressure release ventilation, high-frequency oscillatory ventilation, proportional-assist ventilation, and neutrally adjusted ventilator assist.
- Most techniques are based in applied physiology and observed improvements in comfort, physiological measures, or both.
- None has yet been demonstrated convincingly to improve survival or shorten intensive care unit stay.

**Summary.** Potentially harmful effects of positive pressure mechanical ventilation have been recognized since its inception in the 1950s. Since then, the risk factors for and mechanisms of ventilator-induced lung injury (VILI) have been further characterized. Publication of the ARDSnet tidal volume trial in 2000 demonstrated that a ventilator strategy limiting tidal volumes and plateau pressure in patients with acute respiratory distress syndrome was associated with a 22% reduction in mortality. Since then, a variety of ventilator modes have emerged seeking to improve gas exchange, reduce injurious effects of ventilation, and improve weaning from the ventilator. We review here emerging ventilator modes in the intensive care unit (ICU). Airway pressure release ventilation seeks to optimize alveolar recruitment and maintain spontaneous ventilatory effort. It is associated with improved indices of respiratory and cardiovascular physiology, but data to support outcome benefit are lacking. High-frequency oscillatory ventilation is associated with improvements in gas exchange, but outcome data are conflicting. Extracorporeal modes of ventilation continue to evolve, and extra-corporeal CO<sub>2</sub> removal is a technique that could be used in non-specialist ICUs. Proportional-assist ventilation and neutrally adjusted ventilator assist are modes that vary level of assistance with patient ventilatory effort. They result in greater patient-ventilator synchrony, but at present there is no evidence of a reduction in the duration of mechanical ventilation or outcome benefit. Although the use of many of these modes is likely to increase in intensive care units, further evidence of a beneficial effect is desirable before they are recommended.

**Keywords:** APRV; ECMO; oscillator; ventilation

Mechanical positive pressure ventilation has formed the mainstay of respiratory support in the intensive care unit (ICU) since the 1950s. After the 1952 Copenhagen polio epidemic, Lassen<sup>1</sup> reported the experience of 316 patients with respiratory paralysis and/or bulbar dysfunction who required tracheostomy, ventilation, postural drainage, or a combination of these. At times, up to 200 medical students were used to hand-ventilate up to 70 patients concurrently. In his report, he identified several disadvantages of positive pressure ventilation, including: 'When bag ventilation is administered for weeks there is a risk of emphysema', 'If bag ventilation is not administered correctly venous return may be reduced, leading to lowered cardiac output and a state of shock', and 'The weaning period from positive pressure ventilation is not infrequently difficult'.

As positive pressure ventilation evolved as a treatment strategy for respiratory failure, the harmful effects became further recognized. Barotrauma, such as pneumothorax or surgical emphysema, were, for many years, the major recognized form of ventilator-induced lung injury (VILI), and high inflation pressures an obvious and recognized risk

factor for their development.<sup>2</sup> However, in the 1980s and 1990s, more subtle harmful effects of ventilation were identified. An increase in vascular filtration pressures associated with high tidal volume ventilation leads to disruption of the endothelium, epithelium, and basement membranes, and ensuing leakage of fluid, protein, and blood into pulmonary tissue and air spaces.<sup>3</sup> This establishes an inflammatory process that has effects beyond the lungs.<sup>4</sup> The diffuse alveolar damage that can occur is pathologically indistinguishable from other causes of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).<sup>5</sup> It became apparent from radiological studies<sup>6</sup> that these conditions did not lead to homogeneous lung damage as previously thought, but dependent and patchy oedema and atelectasis resulted in significantly reducing the volume of aerated lung, leading to stretch and over-distension of healthy areas, if traditional tidal volumes (10–15 ml kg<sup>-1</sup>) were applied during mechanical ventilation.

In 2000, the publication of the ARDSnet tidal volume trial,<sup>7</sup> a randomized controlled trial (RCT) including 861 patients, established that patients with ALI or ARDS who received 6 ml kg<sup>-1</sup> tidal volumes with a maximum plateau pressure

of 30 cm H<sub>2</sub>O had a 22% lower mortality than those who received 12 ml kg<sup>-1</sup> and a maximum plateau pressure of 50 cm H<sub>2</sub>O. This established firmly that mechanical ventilation must not only optimize alveolar recruitment and provide adequate oxygenation and carbon dioxide removal, but minimize iatrogenic harm to already damaged lung.

The principles of mechanical ventilation in the ICU are thus to maintain adequate gas exchange, avoid cyclical closure, and reopening of already damaged alveoli and overdistension of healthy alveoli. Advances in ventilator technology have led to an explosion in the variety of ventilators available that utilize these principles to either improve gas exchange in critical hypoxaemia, further reduce the harmful effects of mechanical ventilation, or aid weaning from ventilation. This article will review a selection of emerging ventilator modes.

### Airway pressure release ventilation

Airway pressure release ventilation (APRV) was first described in 1987.<sup>8</sup> It combines relatively high levels of continuous positive airway pressure; typically >20 cm H<sub>2</sub>O in the first instance (termed  $P_{\text{high}}$ ) with time cycled 'releases' at a lower pressure; usually 0 cm H<sub>2</sub>O (termed  $P_{\text{low}}$ ) (Fig. 1). It aims to maintain spontaneous breathing at  $P_{\text{high}}$ , thus maintaining diaphragmatic ventilation<sup>9</sup> of more dependent, better perfused areas of the lung that are not usually well ventilated during mechanical ventilation.<sup>10</sup> In order to aid ventilation and CO<sub>2</sub> elimination,  $P_{\text{high}}$  is briefly released, typically for <1 s. Increasing the duration of release ( $T_{\text{low}}$ ) risks alveolar derecruitment if long enough to allow the loss of intrinsic PEEP. As time at  $P_{\text{high}}$  ( $T_{\text{high}}$ ) normally considerably exceeds  $T_{\text{low}}$  Paw is maintained, yet high plateau pressures are avoided. It is the marked inverse inspiratory:expiratory ratio; typically in the region of 8:1–10:1 that defines APRV compared with other pressure-controlled ventilatory modes.

In ALI and ARDS, alveolar recruitment is both time- and pressure-dependent. The threshold opening pressure and time required for recruitment varies throughout the lung, as it is dependent on radial traction of opening alveoli on each other.<sup>11</sup> A porcine model of ALI suggests that there is a considerable variation in both the inspiratory and expiratory time constants of different areas of the lung. Some lung units may take up to 10 s to recruit, and may de-recruit with as little as 0.8 s of pressure release.<sup>12</sup> APRV therefore offers potential advantages over conventional ventilatory modes in terms of alveolar recruitment. Yoshida and colleagues<sup>13</sup> investigated 18 patients with ARDS who received either pressure support ventilation (PSV) or APRV and had helical computed tomography of their chest twice in 3 days. They found that patients who received APRV had a reduction in atelectatic areas from 41% to 19% ( $P=0.008$ ) and an increase in normally aerated lung from 29% to 43% ( $P=0.008$ ); compared with 39–29% ( $P=0.379$ ) and 39–44% ( $P=0.445$ ) in patients who received PSV.

Putensen and colleagues<sup>14</sup> evaluated the effects of APRV and PSV on the ventilation/perfusion ratio of 24 ARDS

patients. APRV with spontaneous ventilation was found to be associated with decreased intrapulmonary shunt and dead space, and increased  $Pa_{O_2}$  and oxygen delivery. Sydow and colleagues<sup>15</sup> compared APRV with volume-controlled inverse ratio ventilation patients with ALI, and found that APRV was associated with 30% lower peak inspiratory pressures, and significant improvement in alveolar-arterial oxygen tension difference/fractional inspired oxygen tension ( $AaDO_2/F_{I_{O_2}}$ ) and venous admixture.

The relatively high mean airway pressure attained with APRV might be expected to have adverse haemodynamic consequences. However, investigators have demonstrated increased stroke volume, cardiac index,<sup>14</sup> and improved renal blood flow and glomerular filtration rate<sup>16</sup> with APRV compared with conventional ventilatory modes. Others have demonstrated no change in haemodynamic variables.<sup>15</sup> It is possible that maintenance of diaphragmatic ventilation leads to less reduction in intrathoracic venous return than is seen with conventional ventilation (CV).

The maintenance of spontaneous breathing has potential benefits for weaning ventilatory support; however, studies have been conflicting. APRV has been associated with a reduction in sedation requirements, duration of ventilation, length of ICU stay,<sup>17</sup> reduced incidence of ventilator-associated pneumonia, and improved sedation-agitation scores<sup>18</sup> compared with conventional ventilatory modes. However, other studies have not found any difference in these variables.<sup>19–20</sup> Studies comparing APRV with CV have so far all been small and it is not clear whether APRV conveys benefits beyond the improvements in cardiovascular and respiratory physiology reported. Interpreting the evidence is difficult as there are no consensus definition criteria for APRV<sup>21</sup> and some studies reporting to use APRV are using ventilatory modes that would be more conventionally described as biphasic positive airways pressure (BIPAP).<sup>22</sup>

### High-frequency oscillatory ventilation

Interest in high-frequency ventilation arose in 1915 when Henderson and colleagues<sup>23</sup> observed that effective ventilation occurs in panting dogs, even with tidal volumes lower than anatomical dead space. However, it was the 1970s before systems were designed that could effectively achieve oscillatory ventilation in animal models.<sup>24–25</sup> This led to the development of high-frequency oscillatory ventilators that are now commercially available for adults and children. High-frequency oscillatory ventilation (HFOV) uses an oscillating piston pump and a bias gas (flow rate) of 20–40 litre min<sup>-1</sup> to generate a ventilatory frequency typically between 180 and 900 bpm and a tidal volume typically 1–2 ml kg<sup>-1</sup> which is usually less than anatomical dead space (Fig. 2). The mean pressure ( $P_{\text{aw}}$ ) and  $F_{I_{O_2}}$  are adjusted to maintain oxygenation, and the oscillatory pressure amplitude ( $\Delta P$ ) and frequency are adjusted to optimize CO<sub>2</sub> removal. The value of  $\Delta P$  determines tidal volume, but the pressure changes measured in the circuit are greatly attenuated in the tracheal tube and large airways such that the pressure changes in the alveoli are considerably

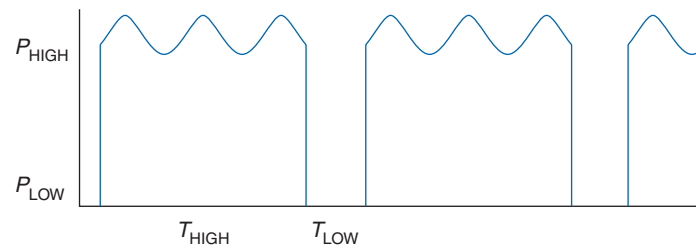


Fig 1 APRV waveforms.

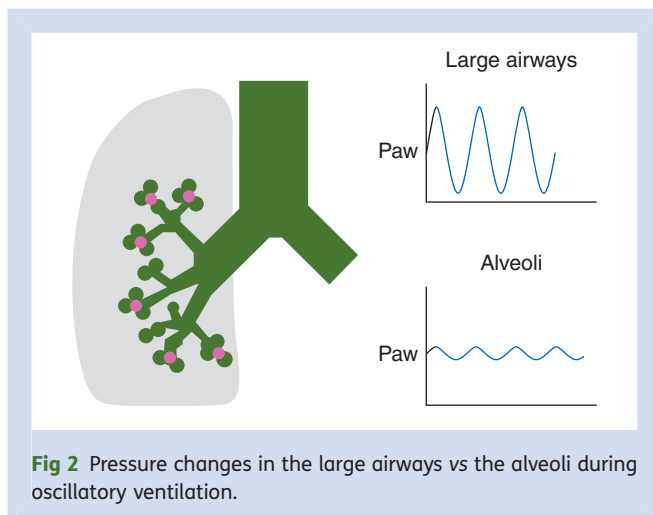


Fig 2 Pressure changes in the large airways vs the alveoli during oscillatory ventilation.

lower. Alveolar ventilation occurs predominantly through acceleration of molecular diffusion, although other mechanisms including Pendelluft, Taylor dispersion (mixing related to laminar gas flow), and cardiogenic mixing (oscillations related to transmitted cardiac pulse) are thought to contribute.<sup>26</sup> The overall effect is that the mean pressure ( $P_{aw}$ ) delivered is higher than with conventional modes of ventilation, maintaining alveolar recruitment, but plateau pressure can be maintained below 30 cm H<sub>2</sub>O and  $FI_{O_2}$  often reduced. As  $\Delta P$  is greatly attenuated in the alveoli, cyclical collapse and over-distension is avoided, thus theoretically reducing ventilator-induced lung injury (VILI). However, whether attenuation of  $\Delta P$  applies equally to normal, compliant airways and rigid consolidated airways is not known.

Animal studies<sup>27, 28</sup> have demonstrated reduced inflammatory mediators such as platelet activating factor, thromboxane B<sub>2</sub>, and tumour necrosis factor  $\alpha$  with HFOV compared with CV. Others have demonstrated a reduction in pathological features such as hyaline membrane formation, polymorphonuclear leucocyte infiltration, and improved indices of gas exchange in animal models of ALI.<sup>29, 30</sup>

Potential disadvantages of HFOV include increased requirement for sedation and neuromuscular block, noise (which leads to difficulty with clinical examination), haemodynamic instability (as a result of increased  $P_{aw}$  reducing

intrathoracic venous return) and a lack of portable equipment. It is also necessary to wean patients using conventional ventilator modes before extubation. I.V. fluid loading may be required before commencement of HFOV in order to prevent haemodynamic compromise. Adjusting ventilatory support in response to changes in gas exchange is less intuitive than with conventional modes, for example, hypercapnia is often managed by reducing ventilatory frequency.

The first case series of HFOV use in adults was by Fort and colleagues<sup>31</sup> in 1997 where they described their experience of 17 adults with severe ARDS, failing on conventional ventilatory strategies, in whom HFOV was used. The age range was 16–82 yr and severity of illness was high, with a mean APACHE II score of 23.3 (7.5),  $Pa_{O_2}/FI_{O_2}$  ratio of 66.13 mm Hg, and oxygenation index (OI)  $[(P_{aw} \times FI_{O_2} \times 100)/Pa_{O_2}]$  of 48.56 cm H<sub>2</sub>O kPa<sup>-1</sup>. The peak inspiratory pressure and PEEP before commencing HFOV was 54 and 18 cm H<sub>2</sub>O, respectively. They demonstrated a significant improvement in both  $Pa_{O_2}/FI_{O_2}$  ratio and OI over the 48 h of the study and an overall survival of 53% in a group in whom HFOV was being used as a rescue strategy. They did not demonstrate any significant change in cardiac output, oxygen delivery, heart rate, or arterial pressure with HFOV. Mehta and colleagues<sup>32</sup> also demonstrated a significant improvement in  $Pa_{O_2}/FI_{O_2}$  ratio within 8 h of commencing HFOV in 24 patients failing on conventional ventilatory strategies. They demonstrated a significant decrease in cardiac output and an increase in central venous pressure and pulmonary artery occlusion pressure; but no significant changes in heart rate, arterial pressure, or vasopressor requirements.

The Multicentre Oscillatory Ventilation for Acute Respiratory Distress Syndrome (MOAT) trial<sup>33</sup> was the first RCT comparing HFOV with conventional ventilatory strategies in adults. One hundred and forty-eight patients with ARDS and receiving CV were randomized to either continue with CV or receive HFOV. The primary outcome was survival without the need for mechanical ventilation at 30 days. The HFOV group had a significant improvement of  $Pa_{O_2}/FI_{O_2}$  ratio initially, although this did not persist beyond the first 24 h. There was no significant difference between haemodynamic variables. The percentage of patients alive without mechanical ventilation at day 30 was 36% and 31% in the HFOV and CV groups, respectively ( $P=0.686$ ). In the HFOV

group, 30 day mortality was 37% and 52% in the CV group ( $P=0.102$ ). However, this study was powered to demonstrate equivalence rather than mortality. In addition, the study was performed before the publication of the ARDSnet tidal volume trial,<sup>7</sup> and the CV group did not receive a lung protective ventilatory strategy that would now be considered preferable for such patients.

Bollen and colleagues<sup>34</sup> have also published an RCT of HFOV vs CV, although their trial was stopped early due to poor recruitment. They failed to demonstrate a significant difference in mortality between the HFOV- and CV-treated groups (43% vs 33%,  $P=0.59$ ), or in indices of gas exchange. The results of this trial are difficult to interpret due to its small size (61 patients) and difference in baseline OI (HFOV=25, CV=18).

The results of these two trials and six others are included in the meta-analysis conducted by Sud and colleagues.<sup>35</sup> This includes two trials recruiting exclusively children. In the 365 patients for whom mortality data were available, they found that patients assigned to HFOV had a significantly lower mortality (risk ratio 0.77,  $P=0.03$ ) compared with those assigned to CV. They also found that HFOV was associated with significantly lower treatment failure (hypoxaemia, refractory hypercapnia, hypotension, barotrauma), resulting in discontinuation of the assigned therapy (risk ratio 0.67,  $P=0.04$ ). The applicability of these findings is limited by the heterogeneity of the trials, and the lack of lung protective ventilation used in the control groups of most of the trials included.

HFOV has an established role in the management of refractory hypoxaemia in neonates, although its role in adults is not yet clear. Data from extracorporeal membrane oxygenation (ECMO) studies suggest that HFOV is presently in widespread use as a rescue strategy in patients with refractory hypoxaemia.<sup>36 37</sup> The effects of frequency and Paw on degree of VILI seen with HFOV are not known, and parallels with CV are probably misleading. Two large multi-centre randomized trials are currently being conducted, OSCAR based in the UK (ISRCTN10416500) and OSCILLATE based in Canada (ISRCTN87124254), which each aim to recruit more than 1000 patients with early ARDS using low tidal volume ventilatory strategies as a control. Until these studies report the beneficial effects of HFOV for adults in the post-ARDSnet era remain uncertain.

## Extracorporeal ventilation

ECMO was first utilized in the management of respiratory failure in the 1970s.<sup>38</sup> Since then the Extracorporeal Life Support Organisation has a registry of more than 27 000 neonates, 9000 children, and 2500 adults who have been treated with ECMO.<sup>39</sup> The first RCT investigating the role of ECMO in adults with severe acute respiratory failure in the era of lung protective ventilatory strategies (the CESAR trial)<sup>36</sup> suggests a significant reduction in death or severe disability in those allocated to an ECMO-based management protocol compared with CV (relative risk=0.69). This trial has proved

controversial, since only 75% of patients allocated to the ECMO arm of the study actually received it and the benefit seen may have been related to transfer to a tertiary centre experienced in managing patients with severe acute respiratory failure; while the control patients were managed in the referring hospitals. ECMO has been used extensively as rescue therapy in adults failing with conventional ventilatory strategies, particularly during and following the 2009 H1N1 influenza pandemic. Observational data from Australasian patients<sup>37</sup> with confirmed or suspected H1N1 pneumonitis treated with ECMO reported 21% mortality at the end of the study period, compared with a >90% mortality seen in both groups in the first RCT.<sup>40</sup>

ECMO is an invasive procedure requiring specific skills and personnel, as wide-bore cannulae are required (typically 21–23 FG in adults) to gain the flow rate necessary to achieve adequate oxygenation (typically 3.5–5 litre  $\text{min}^{-1}$ ). Thus, it is likely that ECMO in this form will continue to be provided in specialist centres and remain outside the remit of the majority of ICUs. As is the case with the normal lung, high blood flow rates are required because oxygen is carried predominantly bound to haemoglobin (total concentration in blood being  $\sim 200$  ml  $\text{litre}^{-1}$ ). Transfer of oxygen across the membrane is saturation-dependent (mixed venous and membrane inlet being around 65–70%); there is an upper limit of oxygen carriage because saturation cannot exceed 100%. In contrast,  $\text{CO}_2$  is predominantly carried dissolved in blood, as bicarbonate (normal being around 500 ml  $\text{litre}^{-1}$ ); and in this case, there is (theoretically) no maximum. Transfer of  $\text{CO}_2$  across the membrane is partial pressure-dependent.<sup>41</sup> Given that human  $\text{CO}_2$  production is  $\sim 250$  ml  $\text{min}^{-1}$ , it is conceivable that an efficient system could achieve  $\text{CO}_2$  clearance at considerably lower flows than conventional ECMO, thus utilizing a system involving flows and cannulae comparable with renal replacement therapy.

The use of extracorporeal  $\text{CO}_2$  removal (ECCO<sub>2</sub>R) in humans was first reported in the 1980s.<sup>42 43</sup> Gattinoni and colleagues reported a case series of 43 patients with severe acute respiratory failure of parenchymal origin. They instituted veno-venous extracorporeal  $\text{CO}_2$  removal with combinations of femoral–jugular, dual-lumen femoral, and saphenous–saphenous cannulation. The circuit incorporated two membrane lungs with a total area of 9 m<sup>2</sup> which were ventilated with a humidified mixture of 15 litre  $\text{min}^{-1}$  each of oxygen and air. Patients' lungs were ventilated with low frequency, positive pressure ventilation at a rate of 3–5 bpm, with PEEP of 15–25 cm H<sub>2</sub>O and peak inspiratory pressure of 35–45 cm H<sub>2</sub>O. Mortality was 51.2% in a group of patients who fulfilled exactly the same entry criteria as a previous study which had a mortality of >90%.<sup>40</sup> They concluded that low flow positive pressure ventilation made possible because  $\text{CO}_2$  was removed using ECCO<sub>2</sub>R was likely to be less harmful than conventional positive pressure ventilation, and that this accounted for the apparent improvement in mortality. In 1994, Morris and colleagues<sup>44</sup> published the results of an RCT in which 40 patients with

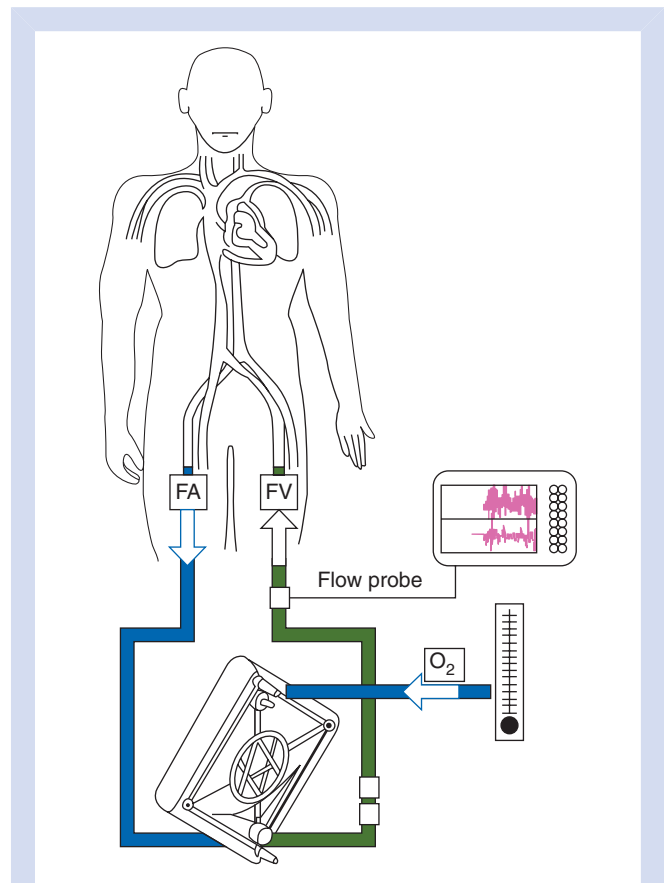


severe ARDS were randomized to either CV or ECCO<sub>2</sub>R and pressure-controlled inverse ratio ventilation. There was no significant difference in 30 day mortality, although this was a small study in real terms.

More recently a pumpless extracorporeal device (interventional Lung Assist; iLA, Fig. 3) has been developed which utilizes cannulae in the femoral artery and vein, with a very low resistance, high efficiency membrane for gas exchange. It utilizes relatively small cannulae (13–15 FG arterial, 15–17 FG venous) and the driving pressure is the arterio-venous pressure difference. Preliminary experience of 90 patients with ARDS demonstrated an improvement in mean  $P_{aO_2}/F_{IO_2}$  ratio from 58 mm Hg before institution to 82 mm Hg after 2 h and 101 mm Hg after 24 h.<sup>45</sup> Hypercapnia was promptly and rapidly reversed, with mean  $P_{aCO_2}$  after 2 h decreasing from 60 to 36 mm Hg. This allowed a significant reduction in peak inspiratory pressure,  $F_{IO_2}$ , and minute ventilation over the first 24 h. A further study from the same group demonstrated significant reductions in plateau pressure, tidal volume, and  $P_{aCO_2}$  and increase in  $P_{aO_2}/F_{IO_2}$  ratio and pH within 2 h of commencing iLA.<sup>46</sup> This system utilizes percutaneous cannulae and single-use, pump-free circuits that could be used in any ICU. Flow required for adequate CO<sub>2</sub> removal can be as low as 1–1.5 litre min<sup>-1</sup>. iLA has been used to facilitate the transfer of patients by air or road from hospitals to a specialized ECMO unit when the patient's condition dictated conventional transfer was not possible.<sup>47</sup> One possible concern with iLA is vascular complications; in the initial study,<sup>44</sup> there was a serious complication rate of 24%, the most common of which was limb ischaemia, and although most patients recovered after removal of the arterial cannulae one required an amputation. The serious complication rate was lower in the further study at 11.9%,<sup>46</sup> which the authors believe was related to ultrasound assessment of vessels before cannulation and selection of smaller cannulae where appropriate.

Although the iLA system conveys the advantage of pumpless technology, an alternative system has been developed which utilizes a dual-lumen 14 FG femoral venous cannula that can effectively reduce  $P_{aCO_2}$  at flow rates of around 350 ml min<sup>-1</sup>. It utilizes a membrane surface area of just 0.33 m<sup>2</sup>. As part of a management strategy which incorporates reduction in tidal volume to <6 ml kg<sup>-1</sup> in patients with persistent ARDS, Terragni and colleagues<sup>48</sup> have demonstrated an improvement in CT morphological features of lung injury and a reduction of inflammatory cytokines in bronchoalveolar lavage fluid.

If CO<sub>2</sub> removal can be adequately achieved with an extracorporeal circuit which has an equivalent cannula and circuit to haemofiltration, it has the potential to be accessible to the majority of ICUs. If CO<sub>2</sub> removal is no longer a necessary requirement of lung ventilation, it has the potential to significantly reduce plateau pressure, tidal volume, and cyclical alveolar collapse and distension and thus the injurious features of mechanical ventilation. Whether this translates to an outcome benefit remains unanswered.



**Fig 3** The iLA-system. A passive femoro-femoral shunt flow generated by the arterial pressure passes a lung assist device (in the box), in which an oxygen flow is inserted. Reproduced with permission from Zimmerman and colleagues.<sup>47</sup> © The Board of Management and Trustees of the *British Journal of Anaesthesia* 2005. All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org.

## Proportional-assist ventilation

Proportional-assist ventilation (PAV) seeks to optimize the degree of ventilatory support delivered according to the patient's ventilatory drive. It utilizes the rate and volume of gas flow in the inspiratory limb of the ventilator circuit and user-determined gain factors (to account for the elastic and resistive opposing forces) to deliver pressure support in proportion to patient effort.<sup>49</sup> This is according to the 'equation of motion', which states that the pressure applied in the respiratory muscles must overcome elastic forces; proportional to volume and the resistive forces; proportional to flow rate (Fig. 4). The ventilatory support delivered to the patient can be varied both in terms of volume assist (VA) and flow assist (FA). The support delivered can change on a breath-to-breath basis, introducing patient-controlled variability to the breathing pattern rather than having one imposed by the settings of the ventilator.<sup>49</sup> If the patient generates more respiratory effort, more support will be delivered.

In initial physiological trials, PAV has been found to successfully unload respiratory muscles, and decrease sensation of breathlessness in acute respiratory failure.<sup>50 51</sup> PAV

$$P_{\text{mus}} = V \times E + V' \times R$$

With PAV:  $P_{\text{mus}} = V \times (E - VA) + V' \times (R - FA)$

$P_{\text{mus}}$  = pressure in respiratory muscles  
 $V$  = volume displacement       $R$  = resistive forces  
 $V'$  = flow rate                       $VA$  = volume assist  
 $E$  = elastic forces                       $FA$  = flow assist

**Fig 4** The equation of motion.

successfully allows patients to adapt their breathing pattern after a hypercapnic stimulus in a manner closer to normal physiology than those on PSV; minute ventilation is enhanced in PAV by increasing tidal volume rather than rate.<sup>51</sup> PAV has also been shown to adapt to artificial increase in respiratory work better than PSV; minute ventilation was maintained by increasing the delivered pressure rather than by increased rate and was associated with less increase in respiratory muscle work and dyspnoea.<sup>52</sup> The other apparent advantage of PAV over PSV is an improvement in patient-ventilatory synchrony by reducing the occurrence of missed efforts, where the patient makes effort to attempt to take a breath but fails to trigger the ventilator.<sup>53 54</sup>

One limitation of PAV is a requirement to quantify the elastic and restrictive properties of the lung in each patient before ventilator settings can be determined. If this is not carried out and the gain factors over correct these properties, then a phenomenon called 'run away' can develop where the ventilator enters a positive feedback loop where the pressure delivered by the ventilator generates sufficient flow and volume delivery to trigger further increase in pressure.<sup>50 53</sup> As lung mechanics are not static it has been suggested that for PAV to be effective, continuous monitoring is necessary in order to ensure run away is avoided.<sup>50 52</sup>

The addition of automated techniques to measure elastance<sup>55</sup> and resistance<sup>56</sup> without interruption of ventilation has been termed PAV+.<sup>57</sup> In this mode, the gain factors are continuously adjusted to account for a user-determined fraction of measured elastance and resistance which should prevent over- or under-assist in the context of changing lung dynamics. PAV+ has been demonstrated to be safe and feasible in patients, both awake<sup>56</sup> and asleep<sup>57</sup> and require fewer adjustments to ventilator settings and sedation than PSV.<sup>58 59</sup> As yet, outcome data for PAV+ are limited, but it has been shown to reduce patient ventilator dyssynchrony<sup>59 60</sup> and to be associated with a lower failure rate in ventilator weaning than PSV.<sup>58 59</sup> Until more studies comparing outcome on PAV+ with conventional ventilator modes, its best use or superiority cannot be determined.

## Neurally adjusted ventilatory assist

If a pressure or flow change within the ventilator circuit is used to initiate a ventilator-supported breath, there is inevitably some delay between the initiation of effort by the respiratory muscles and the delivery of support. Neurally adjusted ventilatory assist (NAVA) aims to avoid this delay

by using the neural stimulus to those respiratory muscles to trigger the ventilator simultaneously with muscular effort.<sup>61</sup>

This triggering is achieved through detection of the electrical activity of the diaphragm (EAdi) as it is stimulated by the respiratory centre via the phrenic nerve by means of an array of bipolar electrodes mounted on a nasogastric tube. Signals from each electrode are amplified and filtered to remove noise and interference from other electrical activity such as that generated by the heart or oesophageal peristalsis. Analysis of signals recorded from pairs of electrodes allows determination of the position of the electrically activated diaphragm and tracking of this position, as it moves along the array during respiratory movements. This results in reliable isolation and recording of EAdi throughout inspiration.<sup>61 62</sup> This signal can then be passed to a connected ventilator triggering it to deliver support. In the event of loss of EAdi signal, the ventilator defaults to conventionally delivered breaths.

In addition to triggering the ventilator, EAdi is used to determine the level of pressure support provided. As EAdi is recorded and passed to the ventilator in real time, and since it varies both through a single inspiration and between inspirations, the amount of support provided can be continuously adjusted in direct proportion to the activation of the diaphragm. The ventilator is set to deliver support by applying a gain factor, or NAVA level (in  $\text{cm H}_2\text{O } \mu\text{V}^{-1}$ ), to the recorded EAdi. Thus, the pressure delivered increases with EAdi through a breath until the cycling-off criteria are reached, typically a defined percentage decrease in EAdi. Since EAdi is centrally controlled by the patient's respiratory centre via the phrenic nerve, the ventilator is essentially coupled to this system and is also under the control of the patient.<sup>61</sup>

Neurally adjusted ventilatory assist has been successfully used in a range of patients and situations, including neonatal and paediatric populations,<sup>63–66</sup> adults with ARDS,<sup>67</sup> or acute respiratory failure of postoperative<sup>68</sup> or mixed causes<sup>69–73</sup> and also in conjunction with other means of respiratory support such as ECMO.<sup>74–76</sup> It has also been demonstrated to effectively offload respiratory muscle work, both in healthy subjects<sup>77</sup> and the critically ill.<sup>72</sup> Of particular importance for the safe use of this technology is the finding that at the highest NAVA levels, where the inspiratory muscles are almost completely offloaded, there is a reduction in electrical activity in the diaphragm and therefore a limitation to the pressure delivered.<sup>77</sup> This feedback has potential advantages in the patient ventilated with NAVA in avoiding injurious tidal volumes.

One benefit of NAVA appears to be improvement in patient-ventilator synchrony when compared with commonly used PSV.<sup>64 69–71</sup> Patients ventilated with NAVA do not experience the increased tidal volumes and reduced ventilatory frequency seen at higher levels of PSV.<sup>67 69–71</sup> As such, NAVA should prevent dynamic hyperinflation which has been implicated as the major factory in asynchrony,<sup>67</sup> and since asynchrony has been associated with longer ICU

stays,<sup>78</sup> it may be expected, although has yet to be demonstrated, that the use of NAVA may shorten patient stay in ICU. As expected, NAVA is also associated with shorter trigger delays between the onset of inspiratory effort and the delivery of support,<sup>67 70 71</sup> and it has been reported that NAVA eliminates 'wasted efforts' where a patient makes inspiratory effort but fails to trigger the ventilator.<sup>70 71</sup> This contributes to NAVA, reducing the work of breathing by ensuring the respiratory muscles are supported throughout inspiration and energy is not wasted in failed attempts to initiate support.

Karagiannidis and colleagues<sup>74</sup> have investigated the role of NAVA on patients requiring ECMO. The alternative source of oxygenation and elimination of carbon dioxide allows ventilatory drive, and hence EAdi, to decrease. Patients appear to automatically adopt a lung-protective pattern of ventilation, with low tidal volumes and respiratory frequency, while retaining the ability to vary that pattern and hence retain control of CO<sub>2</sub> and acid–base homeostasis that may otherwise become deranged when such a pattern is imposed.

The pattern of breathing of patients on NAVA is inherently variable as opposed to the uniform breaths of fixed rate and volume or pressure of normal ventilation.<sup>72</sup> This is of particular significance for ventilator weaning where increased variability following removal of ventilator support has been associated with greater success of maintained separation from the ventilator.<sup>79</sup>

Another reported benefit of NAVA is that successful ventilation with NAVA demonstrates the presence of an intact neuromuscular connection between the respiratory centre and diaphragm<sup>65</sup> while failure may assist in the diagnosis of severe diaphragmatic dysfunction.<sup>67</sup> Interestingly, NAVA has been successfully used in a patient with left hemidiaphragm paralysis,<sup>65</sup> although it is obviously unsuitable for patients with complete loss of diaphragmatic breathing. One group have also reported an improvement in oxygenation after 24 h of NAVA,<sup>67</sup> an effect which was not seen in other studies,<sup>64 69 71</sup> although these used NAVA for considerably shorter periods of time.

As yet, studies of NAVA have been mainly physiological or focused on comparison of synchrony with other ventilator modes. Although NAVA is available at present, it is not yet in widespread use and the patient groups most likely to benefit are yet to be defined. Further studies are required, to establish the most appropriate situations in which to deploy this technology and to determine whether the improvements in patient-ventilator synchrony outlined translate into a benefit in terms of duration of ventilation or outcome.

## The future?

We have now progressed from the negative pressure cuirass ventilators to the sophisticated microprocessor-controlled ventilators we use today. Progress from here may include even more automated ventilators which would be able to sense changes in the physiological variables of the patient and make automatic compensations. These physiological

variables could include pulmonary resistance, elastance, and compliance but perhaps the ventilator will be able to automatically compensate for gas exchange disturbances also. On another track, it may be that with developments in gas exchange membrane technology connecting a patient to a mechanical ventilator may be a thing of the past. In the future, we would ask for the patient to be connected to the gas exchange membrane in much the same way that we use continuous haemofiltration circuits at present.

## Conclusions

The modalities available for mechanical ventilation in the ICU continue to expand and evolve. While there is evidence that many of these modes confer benefit in terms of gas exchange,<sup>14 15 31–33</sup> we know from previous trials that an improvement in gas exchange does not necessarily correlate with an improvement in outcome.<sup>7 80</sup> Until we have evidence of outcome benefit from RCTs, these strategies will remain unproven.

## Conflict of interest

None declared.

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