The injured lung: conventional and novel respiratory therapy

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The optimum approach to respiratory therapy in the adult respiratory distress syndrome (ARDS) or acute lung injury remains a dilemma. Such therapy is essentially supportive until the basic defect of damage to the alveolar-capillary membrane resolves, alveolar stability is restored, and remodelling of alveolar architecture by alveolar type II cells, characteristic of the reparative phase of acute lung injury, can take place.\(^1\) This cycle of events suggests that effective respiratory support should be provided in an environment appropriate for the resolution of injury and should not contribute to the ongoing pathophysiology of the disease. At the same time, as the supply dependency of tissue oxygen uptake in acute lung injury (to be reviewed separately in this series) is a generally accepted phenomenon that occurs even at very high levels of oxygen delivery,\(^2,3\) it is imperative that any respiratory therapy should not adversely influence either haemodynamics or oxygen delivery.

Several new approaches to supporting the injured lung have been developed with a particular view to minimising the adverse effects associated with conventional modes of mechanical ventilation. The new techniques have theoretical attractions in physiological terms, but often represent a substantial escalation in intervention, are for the most part extremely labour intensive, and may invoke their own complications. When these factors are added to the recognition that acute lung injury has a range of severity from mild pulmonary insult to full blown ARDS,\(^4\) it is difficult to identify any respiratory therapy that may be regarded as appropriate and effective in all forms of lung injury. A second consideration is what is the best approach where the development of acute lung injury after a recognised insult is predicted. Optimisation of respiratory therapy at an early phase may influence the development of lung injury or modulate the severity of the clinical course. Early intervention can influence the disease progression, the duration of ventilatory support required, the incidence of complications, and clinical outcome; and it may have a substantial financial impact on the provision of critical care services in a given institution. So far, however, there is no evidence that any respiratory therapy has a specific prophylactic effect against the development of acute lung injury, and the use of prophylactic positive end expiratory pressure\(^5\) and high frequency jet ventilation\(^6\) have been found disappointing in this respect.

**Pathophysiology of acute lung injury**

The pathological appearance associated with acute lung injury is diffuse alveolar damage, characterised by degeneration of alveolar wall lining, hyaline membrane formation, alveolar wall oedema, and inflammatory infiltrates. Microatelectasis is also seen as a diffuse but focal lesion, such that areas of histologically normal lung are juxtaposed with areas of microatelectasis.\(^7\) Surfactant activity may be substantially reduced, leading to further loss of alveolar volume.\(^7\) The dependent nature of radiological densities in acute lung injury has been clearly shown by computed tomography, which shows preferential obliteration of air spaces in the dependent areas of lung.\(^8\) Although this process is partly due to consolidation and may be influenced by redistribution of oedematous fluid within the lung, it has been suggested that this appearance is also due simply to the compressive effects of the overlying oedematous tissue.\(^9\) Interestingly, despite a considerable increase in lung weight in patients with acute lung injury, the transverse thoracic area as assessed by computed tomography is similar to that in normal subjects, implying that gas volume but not lung volume is decreased. More recently, dynamic breath to breath variation in the degree of this dependent atelectasis has also been demonstrated.\(^10\) The clinical consequences are decreased accessible alveolar volume and a substantial fall in pulmonary compliance (with a total static lung compliance sometimes less than 10 ml/cm H\(_2\)O). This leads to arterial hypoxaemia, secondary to widespread intrapulmonary shunting, and increased work of breathing. After conventional ventilatory support has been started the hypoxaemia is often resistant both to increases in inspired oxygen concentrations and to manipulating the ventilatory pattern. Low compliance necessitates high peak airway pressures and increases the potential for barotrauma. Although pulmonary vascular microemboli undoubtedly contribute to the pathogenesis of acute lung injury, hypercarbia secondary to increased
physiological dead space is rarely encountered during the early phase. Low compliance in established acute lung injury and in patients who proceed to the late fibrotic phase—a condition characterised by poor compliance and an increase in lung collagen—may lead to hypercarbia.

Conventional respiratory support

In the conventional approach to respiratory support in patients with acute lung injury tidal volume preset mandatory positive pressure ventilation is combined with positive end expiratory pressure (PEEP), with a ratio of inspiratory to expiratory (I:E) time of less than 1. The ideal level of PEEP remains controversial. Clinicians commonly titrate levels against oxygenation, taking into account its adverse effects on airway pressures and haemodynamics. Comparisons of static pressure-volume curves and computed tomograms in acute lung injury have suggested that the ideal level of PEEP may be closely related to the lower inflection point or “knee” of the pressure-volume curve (fig 1). On the inspiratory limb this point is thought to represent recruitment of collapsed alveoli and on the expiratory side closure of alveoli that fall below critical closing pressure. Maintaining PEEP at least as high as the expiratory inflection point would thus appear to be a rational aim. The shape of the pressure-volume curve at zero PEEP may also indicate the patients in whom alveolar recruitment is likely with the manipulation of PEEP.

In recent years attention has been focused on the possibility that modes of ventilatory support may contribute to ongoing pathophysiological processes in acute lung injury and that the course of the disease may be influenced by the type of ventilatory support used. Studies on the eventual cause of death in patients with acute lung injury have given conflicting results, but a recent study has suggested that most deaths are due to sepsis, multiorgan failure, or the underlying disease. Fewer than 20% of patients die primarily from respiratory failure. Despite these findings, there remains a strong suspicion that ongoing ventilator induced lung damage may contribute substantially to mortality. The duration of illness is prolonged and hence the potential for complications; new sites of sepsis may emerge within the lung, or inadequate oxygen delivery may persist and lead inexorably to multiorgan failure.

DISADVANTAGES OF CONVENTIONAL PRACTICE

The current practice of tidal volume preset ventilation in the poorly compliant injured lung may predispose to high peak inspiratory pressure. In the most severe cases static compliance may fall to less than 10 ml/cm H2O. The application of PEEP, though it may favourably influence alveolar recruitment, may substantially increase peak inspiratory pressure as the lung volume reaches the upper inflection point of the pressure-volume curve (fig 1). Barotrauma, of which the major risk factor is thought to be a high peak inspiratory pressure, is a complex phenomenon that includes not only gross changes such as pneumothorax and pneumomediastinum but also pulmonary interstitial emphysema and haemorrhage at peripheral alveolar and perivascular levels. A safe peak inspiratory pressure has not yet been identified; in one clinical study no radiological evidence of gross barotrauma occurred at less than 50 cm H2O but other workers have identified pulmonary interstitial emphysema in 12 of 13 patients having 40 cm H2O or more. Overdistension of the lung in the absence of high peak inspiratory pressure may lead to lung microvascular injury and high permeability pulmonary oedema. Pulmonary oedema and severe atelectasis can be induced in sheep ventilated at a peak inspiratory pressure of 50 cm H2O for 48 hours and more recently similar observations have been made at peak inspiratory pressure as low as 30 cm H2O. Currently, most clinicians aim for a peak inspiratory pressure below 50 cm H2O, though this may still be excessive. The concept of alveolar overdistension or “volutrauma” has been proposed as a potential cause of ventilator induced lung damage in acute lung injury and Gattinoni has suggested that when a conventional tidal volume is applied to the small residual component of functional lung tissue in acute lung injury it may result in pronounced regional overdistension of the remaining functional alveoli. Haemodynamic depression may also occur secondary to high intrathoracic pressures and a balance needs to be struck between maximising arterial oxygenation and maintaining cardiac output. Thus, although decreased lung compliance in acute lung injury results in less fractional transmission of airway pressure to the intrapleural space, high PEEP and large tidal volume ventilation may reduce cardiac output, and therefore tissue oxygen availability, even though the arterial oxygen tension (PaO2) may rise.
New strategies in respiratory support

Deficiencies in the conventional approach have stimulated the search for more effective forms of ventilatory support in acute lung injury. For the most part, these attempts to maintain mean airway pressure and lung volume, on which oxygenation depends, while avoiding high peak inspiratory pressure. By the very nature of clinical studies in acute lung injury, the application of these recent developments has been limited to feasibility studies and very few prospective investigations comparing them with conventional techniques have been completed.

CONTINUOUS POSITIVE AIRWAY PRESSURE

Continuous positive airway pressure (CPAP) refers to the maintenance of a predetermined increased airway pressure throughout the spontaneous respiratory cycle, which thus increases lung volume. All CPAP circuits have similar design characteristics and require a high gas flow and efficient pressure release valves to maintain the pressure of the system at the required level while venting excess flow. Mild forms of lung injury may be adequately treated with continuous positive airway pressure alone, often without the need for intubation. The technique is attractive in that the work of breathing is diminished and cyclical distending forces applied at alveolar level are avoided. In some centres even relatively severe forms of acute lung injury are managed either with continuous positive airway pressure alone, applied via a tightly fitting mask, or in conjunction with low frequency mandatory ventilation. The early application of continuous positive airway pressure represents a very simple intervention that may favourably influence pulmonary function and the progress of acute lung injury, but there is no evidence that its prophylactic use prevents the development of acute lung injury in patients exposed to precipitating causes.

INVERSE RATIO VENTILATION

Inverse ratio ventilation is a variation on conventional ventilatory treatment, in which the I:E ratio is lengthened by prolonging inspiratory time to more than half of the respiratory cycle (fig 2). Inverse ratio ventilation is both uncomfortable for patients and incompatible with patient initiated (triggered) ventilation; thus heavy sedation and even neuromuscular blockade may be necessary.

VOLUME CONTROLLED INVERSE RATIO VENTILATION

Initial studies of inverse ratio ventilation used a volume controlled mode (VC-IRV), in which a predetermined tidal volume was delivered with each breath for up to 80% of the respiratory cycle. This provides a constant inspiratory flow rate throughout inspiration and the peak inspiratory pressure is reached at the end of inspiration. A pause time, during which the lung volume is maintained at end inspiratory levels and no further inward flow occurs, is then added, peak pressure falls to what is termed the "plateau pressure," and both the inspiratory and the expiratory valves remain closed (fig 2A). Inspiration is terminated by the opening of the expiratory valve at a preset time late in the expiratory cycle. Such a technique is prone to produce high peak inspiratory pressure by "stacking" of mandatory tidal breaths on an already increased lung volume. This may occur when incomplete exhalation, due to an insufficiently short expiratory time, precedes the delivery of an ensuing breath. The first investigators of VC-IRV used I:E ratios as high as 4:1 and, although arterial oxygenation was improved, the potential of the method for affecting oxygen delivery adversely because of haemodynamic depression was also identified. VC-IRV is still used, though generally in combination with pressure limitation (a safety facility available on recently developed ventilators), which prevents further inspiratory flow when a preset upper pressure limit is reached. The influence of VC-IRV with pressure limitation on clearance of carbon dioxide must be considered because, although lung volume is maintained and oxygenation improved, it may substantially decrease minute volume and result in hypercarbia.

PRESSURE CONTROLLED INVERSE RATIO VENTILATION

More recently, pressure controlled inverse ratio ventilation (PC-IRV) has been used in acute lung injury and has been the subject of two published retrospective studies. In this mode pressure generation is used to deliver a breath for which the tidal volume is not preset. A preset inspiratory pressure is applied to the airway at the beginning of inspiration such that inspiratory flow, a product of the pressure gradient between alveolus and ventilator, is maximal at the beginning of inspiration and decreases rapidly as inspiration continues. This preset inspiratory pressure also acts as a pressure limit above which no further inspiratory flow occurs. The rise to maximum airway pressure early in inspiration effects a similar change in lung volume, whereas in VC-IRV airway pressure and lung volume rise more slowly throughout inspiration to a maximum at end inspiration (fig 2B). PC-IRV therefore maintains lung volume more efficiently than VC-IRV with or without pressure limitation, and by its very mechanism eliminates the

Figure 2 Inverse ratio ventilation: the patterns of airway pressure seen with (A) volume controlled inverse ratio ventilation (note that an inspiratory pause following delivery of the preset tidal volume is included in the cycle) and (B) pressure controlled inverse ratio ventilation (note that the airway pressure rapidly rises to equal the pressure control level). From Kogel et al"; reproduced by courtesy of the "British Journal of Hospital Medicine."
potential problem of stacking. As in VC-IRV with pressure limitation, carbon dioxide removal may be unsatisfactory in circumstances where PEEP is high or compliance very low, in which lung volume is maintained but effective tidal and minute volumes may be inadequate to achieve normocarbia. Despite raised mean airway pressure haemodynamic tolerance is reported as satisfactory. The application of PC-IRV in acute lung injury has several theoretical advantages over conventional techniques and is being widely applied in such patients, despite a lack of prospective comparative data showing a definite advantage and in the face of disappointing statistics—only 23% of such patients surviving. An attempt is being made to investigate this issue further and PC-IRV is now being compared with conventional ventilation in a prospective trial in patients with acute lung injury. Failure of PC-IRV to prompt progression to low flow extracorporeal removal of carbon dioxide (see below). Only preliminary data are available from this trial.

AIRWAY PRESSURE RELEASE VENTILATION
This variation of inverse ratio ventilation was originally described in 1987. The system is essentially continuous positive airway pressure with two or more levels of CPAP applied intermittently, over which the patient may superimpose spontaneous respiration. A release valve discharges airway pressure from higher to lower levels of CPAP, enhancing clearance of carbon dioxide. The system is attractive in that lung volume is maintained and high peak inspiratory pressures (PIPs) are avoided, and it retains the favourable characteristics of spontaneous respiration, enhances carbon dioxide clearance, and should decrease respiratory work in patients with poor respiratory compliance. Preliminary data suggested that airway pressure release ventilation could maintain gas exchange with substantially lowered PIPs in mild acute lung injury, an impression confirmed subsequently in a multicentre study comparing airway pressure release ventilation with conventional ventilation. The survival figures (71%) for this study are difficult to interpret, as the patients were described as having mild to moderate acute lung injury. Little specific information on severity of illness was provided and airway pressure release ventilation cannot be recommended in severe acute lung injury on the basis of this trial alone. If this system is to make a tangible impact on outcome, it is most likely to do so in patients with mild degrees of lung injury, in whom appropriate respiratory support applied early in the development of the disease may prevent the further deterioration of pulmonary function.

HIGH FREQUENCY VENTILATION
High frequency ventilation, defined as incorporating frequencies above the normal physiological range, was first described by Storaard in 1967 and has been applied in acute lung injury in various forms for more than 15 years. The only practical technique currently being used in adults is high frequency jet ventilation, which was developed in 1977. Gas is delivered into the airway via some form of high pressure nozzle at frequencies of 1–10 Hz and expiration is passive. High frequency oscillation, described by Lunkenheimer in 1972, uses an active expiratory phase, allowing the use of much higher frequencies. High frequency oscillation has found application in the infant distress syndrome, but has not yet been applied successfully in adults with acute lung injury.

High frequency ventilation was most aggressively applied in acute lung injury in the early 1980s, at which time Lachmann and Jonson suggested that the ideal alveolar environment was a still, quiet, open structure subjected to minimal cyclical distending forces and that the most feasible way of achieving this was through high frequency ventilation. A prospective randomised trial of high frequency jet ventilation versus conventional ventilation in acute lung injury reported in 1983 showed high frequency jet ventilation to be effective, but not to have any significant benefit over conventional techniques. Research in which high frequency ventilation was used in the infant respiratory distress syndrome has influenced attitudes towards lung volume recruitment and maintenance, but difficulties in the assessment of high frequency ventilation persist; the variety of machinery available and the lack of recognition that small changes in design may cause substantial changes in performance have invalidated comparisons between apparently similar techniques.

Interest in high frequency techniques in acute lung injury currently revolves around the maintenance of lung volume and the use of frequencies at or near the resonant frequency of the lung (about 5 Hz)—termed ultrahigh frequency ventilation. Potential advantages of this approach include enhanced alveolar gas kinetics and minimal barotrauma while recruitment and maintenance of alveolar volume are achieved. An important advantage of this approach is that mean airway pressure is maintained to recruit and stabilise alveoli. Major difficulties, such as appropriate monitoring of ventilator-patient interaction and adequate humidification, have now been addressed satisfactorily. A multicentre feasibility study using a prototype ultrahigh frequency ventilation ventilator in patients with acute lung injury deemed not to be helped by conventional treatment is currently in progress. The predicted improvements in gas exchange and airway pressure have been observed in the context of haemodynamic stability and survival has been encouraging. Despite very low levels of static compliance, clearance of carbon dioxide (a problem associated with early high frequency ventilation technology) is very effective. The most striking preliminary information from this trial is that survival is substantially improved (76% compared with no survival of 45% in 107 patients) in patients with severe acute lung injury who are identified and switched to ultrahigh frequency ventilation within 48 hours of the start of
mechanical ventilation. A suggested explanation for this observation is that alveolar volume and compliance are improved and ventilator induced lung damage is limited by reducing cyclical alveolar distension to a minimum, while adequate oxygen delivery can be achieved without adverse effects. As with the other techniques, prospective randomised studies with ultrahigh frequency ventilation have started, but it will be some time before results from large studies are available.

POSTURE MANIPULATION

The use of the prone position in ventilated patients, first suggested in 1974, has been shown to be effective in improving gas exchange in acute lung injury. The therapeutic benefits associated with this manoeuvre have been examined critically byGattinoni and colleagues, who used computed tomography to observe redistribution of atelectasis and oedema after patients with moderate to severe acute lung injury had been put in the prone position. Eight of 13 patients responded in terms of improved oxygenation, which persisted after reversion to the supine position. In several patients changes in lung density associated with the prone position could be identified. This study suggests that the prone position should always be considered in the absence of contraindications and that it should be particularly beneficial in combination with a ventilatory technique capable of alveolar recruitment and maintenance, such as PC-IRV or ultrahigh frequency ventilation. The potential benefits of regular postural changes and the ideal periodicity of such changes remain unclear. An interesting variation of this concept, known as kinetic therapy, has been described recently. Patients are nursed in a bed that constantly rotates through 67° each side of horizontal. Although data are preliminary and the technique would substantially increase the nursing care of these patients, this represents a novel attempt to influence ventilation-perfusion relationships favourably by postural manipulation.

PERMISSIVE HYPERCAPNIA

Pressure limited, low tidal volume, synchronised intermittent mandatory ventilation with permitted hypercapnia has been advocated recently, on the basis of the results of a five year retrospective study of 50 patients with severe acute lung injury in whom peak inspiratory pressure was limited to 30 cm H₂O, often necessitating the use of tidal volumes as low as 5 ml/kg. Arterial carbon dioxide tension (Paco₂) was allowed to rise, generally to around 10 kPa but as high as 18 kPa in one patient. PEEP was manipulated as necessary to achieve adequate oxygenation with inspired oxygen concentrations of less than 0-6. The survival rate for this group was 84%. Although this was a retrospective, uncontrolled study, the results are compelling and have prompted many clinicians to reassess their goals for arterial blood gas tensions in favour of limiting the stress applied to the pulmonary system.

<table>
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<th>Terms used in extracorporeal membrane oxygenation*</th>
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<td>ECGE</td>
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*Reproduced from Evans and Keogh.

EXTRACORPOREAL GAS EXCHANGE

Techniques for extracorporeal gas exchange (ECGE) (table) are limited to a few centres and are extremely labour intensive. A detailed analysis of various forms and applications of ECGE is beyond the scope of this review but has been the subject of a recent editorial. Since the United States venoarterial extracorporeal membrane oxygenation (ECMO) study in acute lung injury published in 1979, which found only a 4% survival in both the extracorporeal gas exchange group and the conventional treatment group, interest has switched to the alternative veno-venous approach, commonly known as ECCO₂R, which refers to either partial or total removal of carbon dioxide. Such techniques require some degree of ongoing ventilatory support, such as continuous positive airway pressure or low frequency positive pressure ventilation. Nevertheless, complications still represent a major difficulty with these techniques; the most serious being haemorrhage, coagulopathy, and sepsis. Technical advances include percutaneous cannulation and heparin bonded circuits that decrease the requirement for anticoagulation. Despite the drawbacks, ECCO₂R has been pursued enthusiastically as a treatment for acute lung injury in a few centres. The published results from eight centres worldwide with more than 10 patients who had had ECCO₂R up to the end of 1990 showed that the total of 264 patients had a 47% survival rate. Most data on ECGE are from uncontrolled trials, but a prospective comparative study using strict computer assisted protocols to determine the superiority of conventional or non-conventional treatment (pressure controlled inverse ratio ventilation followed by ECCO₂R) is currently under way. Early data from this study have suggested an increase in overall survival rate (45%) to that previously reported, but as yet no significant differences in outcome between the two groups of patients have been found. Falke and colleagues have published recently a series of 38 patients with severe acute lung injury, of whom 20 responded to ventilatory modification. Eighteen did not and proceeded to ECGE; 12 survived. The overall survival of 84%, with a 66% survival in the ECGE group, represents an impressive
outcome from the rational application of available supportive treatment.\textsuperscript{55}

The position of ECGE therefore remains uncertain. If the survival rate remains at about 50\%, no benefit is likely to be shown over conventional techniques. If the technical difficulties can be overcome, however, and potential responders be more reliably identified, ECGE may become a more widespread and vital option in acute lung injury.

\section*{INTRAVASCULAR GAS EXCHANGE}

A potentially important recent advance has been the development of an intravascular oxygenation device (IVOX, Cardiopulmonics, Salt Lake City, USA), which is essentially a scaled down hollow fibre oxygenator inserted surgically into the vena cava. Oxygen is drawn (at subatmospheric pressure to prevent possible air embolism) through the device, which is capable, through a non-thrombogenic gas-exchanging membrane up to 0.5 m\(^2\) in area, of exchanging up to 150 ml/min of oxygen and carbon dioxide. The role of this device in the treatment of acute lung injury remains to be defined, but it may have substantial benefit in decreasing the ventilatory requirement in such patients. Although the device has generated much interest, published data have so far been limited to case reports.\textsuperscript{53}

\section*{NITRIC OXIDE AND INTRAVENOUS VASODILATORS}

An exciting further development in support for the acutely injured lung in the last four years has been the identification of nitric oxide as an endothelium derived relaxing factor\textsuperscript{44} and the recognition of a potential role for this agent in matching ventilation and perfusion in acute lung injury. Nitric oxide is an endogenous vasodilator produced in the vascular endothelial cell that produces smooth muscle relaxation. Inhaled nitric oxide is toxic but has a very short half life, and it is avidly bound by haemoglobin; toxicological investigations in animals do not suggest that it is harmful in low doses.\textsuperscript{55} Nitric oxide has been shown to abolish pulmonary vasoconstriction\textsuperscript{56} and to cause pulmonary vasodilatation in patients with primary pulmonary hypertension.\textsuperscript{57} Its attraction in acute lung injury is the potential for selective dilatation of those pulmonary vessels supplying ventilated alveoli, thus preferentially directing tidal flow towards these alveoli and thereby decreasing intrapulmonary shunt. Falke and colleagues have reported preliminary data on seven patients with acute lung injury given nitric oxide in whom such improvements were seen.\textsuperscript{57} Other potential effects include a decrease in pulmonary vascular resistance and an increase in the right ventricular ejection fraction.\textsuperscript{58} The effects of intravenous vasodilators have been investigated in acute lung injury, with indifferent results. Specifically, a controlled trial of infusions of prostaglandin (PG) E\(_1\) established no strong indication for its use.\textsuperscript{59} Although some authors have observed an encouraging response to PGI\(_2\) (prostacyclin),\textsuperscript{60} its use may be complicated by an increase in intrapulmonary shunt and systemic hypotension. Theoretically, nitric oxide should offer selective pulmonary effects, decreasing shunt and perhaps pulmonary artery pressure, and be free of unwanted systemic vasodilatory properties; but few clinical data are so far available.

\section*{Long term outcome in acute lung injury}

Survivors of acute lung injury are usually considered unlikely to suffer symptoms of respiratory impairment after resolution of the disease.\textsuperscript{61} This view has been examined critically by several authors and, although patients are relatively symptom free, impairment of respiratory function at one year was common (66\%) in one series of 27 patients.\textsuperscript{62} These and other workers have found that severity in terms of physiological indices, such static compliance, PIP, maximum PEEP, mean pulmonary artery pressure, and venous admixture, was correlated with residual impairment,\textsuperscript{63} particularly if these abnormalities were persistent or associated with sepsis.\textsuperscript{64} With ventilatory and other treatments for acute lung injury improve and patients with the most catastrophic forms of lung injury can be salvaged, will we begin to see a population of patients with residual severe abnormalities in lung function? The possible role of corticosteroid treatment in the refractory forms of acute lung injury has again been highlighted in case reports.\textsuperscript{59,66} In our own institution one patient who progressed to a severely fibrotic phase of acute lung injury, and required a PIP of 100 cm H\(_2\)O to achieve adequate gas exchange, eventually required extracorporeal support and subsequently underwent successful heart-lung transplantation.\textsuperscript{67} Although transplantation may prove to be an option for patients with acute lung injury, most are rarely suitable in the acute phase because of the high incidence of persistent sepsis. Furthermore, the transplantation "window" is short and often passed owing to the limited and unpredictable availability of organs.

\section*{Summary}

Several alternatives to conventional ventilation in acute lung injury are now available and have been investigated to a varying degree. The assessment of all such techniques is limited by difficulties in designing proper comparative studies and by the time needed to recruit a large number of appropriate patients with acute lung injury. A common theme of lung volume maintenance combined with strategies designed to limit the extent of ventilator induced lung damage has emerged and should encourage reassessment of the conventional approach. The results of several large prospective comparative studies are eagerly awaited. Meanwhile we may reasonably suggest that improvements in respiratory support, together with advances in microbiological and pharmacological treatment, have the potential for improving the persistently disappointing survival rate in acute lung injury.
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51. Pepke-Zaba J, Higenbottom TW, Tuan Dinh-Xuan A,


