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# Acute respiratory distress syndrome

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The acute respiratory distress syndrome (ARDS), also known by many pseudonyms such as 'DaNang lung', was first described in 1967 by Ashbaugh and colleagues as the 'acute onset of tachypnea, hypoxemia and loss of compliance after a variety of stimuli'.[1] Continued research examining the underlying mechanisms and management strategies is now translating into improved outcome.

## DEFINITIONS

The ARDS Definition Task Force (the Berlin definition[2]) has recently revised the long-standing 1994 American-European Consensus Conference (AECC) definition (Table 33.1).[3] ARDS is now classified as mild, moderate and severe based on the $Pa_{O_2}/Fi_{O_2}$ ratio (see Table 33.1). The broad term 'acute lung injury' (ALI), which referred to cases with a $Pa_{O_2}/Fi_{O_2}$ ratio less than 300, has been replaced and many concerns addressed. A minimum positive end-expiratory pressure (PEEP) of 5 cm $H_2O$ is specified, and chest radiograph criteria and exclusion of hydrostatic oedema clarified, including examples. The lung injury score (LIS),[4] which uses a four-point score attributed to ranges of $Pa_{O_2}/Fi_{O_2}$ ratio, PEEP, respiratory system compliance and the number of quadrants involved on chest radiograph, has also been used to quantify severity of ARDS; however, as neither lung compliance nor dead space improved the predictive ability of the Berlin definition, the LIS may become less pertinent.

## CHEST RADIOGRAPH AND CHEST COMPUTED TOMOGRAPHY IN ACUTE RESPIRATORY DISTRESS SYNDROME

The intent of chest imaging is to exclude opacities due to pleural effusion, nodules, masses, collapse and pleural thickening; the infiltrate must be bilateral and consistent with pulmonary oedema.[2] Autopsy and chest radiographs of ARDS show a uniform process affecting both lungs. However, chest computed tomography (CT)[5] has demonstrated marked heterogeneity of lung inflation in ARDS with a dorsal, dependent increase in lung density, and relatively normal inflation of ventral lung. In addition, CT frequently reveals previously undiagnosed pneumothorax, pneumomediastinum and pleural effusion. After the second week of mechanical ventilation, CT scans may demonstrate altered lung architecture and emphysematous cysts or pneumatoceles.

CT numbers or Hounsfield units can be assigned to each voxel (~2000 alveoli in a standard 10-mm slice).[5] These data can then be used to assess what proportion of a region of interest is non-aerated, poorly aerated, normally aerated, or hyperinflated. Whole-lung CT allows (a) reconstruction of the upper and lower lobes (the middle lobe is difficult to separate), (b) the same section of lung to be studied at different levels of inflation or PEEP (the lung also moves in a cepahalocaudad direction with respiration), and (c) a broader picture of the lung to be obtained (lung damage is heterogeneous in ARDS). However, whole-lung CT demands considerable exposure to ionising radiation, and different information, perhaps more pertinent to mechanical ventilation, is obtained from dynamic CT.

Clinical assessment of chest CT is discussed in Chapter 39, and CT findings in ARDS as discussed under Clinical management.

## EPIDEMIOLOGY

Estimates of the incidence and outcome from ARDS vary widely due to differences in the definitions used, case-mix and local factors. Using the AECC definition, the Australian incidence was 34 per 100,000 for ALI and 28 per 100,000 for ARDS[6]; while US estimates were 79 and 59 per 100,000, respectively[7] – both much greater than many previous estimates. Recent data from 50 countries reports period prevalence of mild ARDS as 30.0%, moderate ARDS as 46.6%, and severe ARDS as 23.4%, respectively. ARDS represented 10.4% of intensive care unit (ICU) admissions and 23.4% of patients requiring mechanical ventilation. Clinical recognition of ARDS ranged from 51.3% in mild to 78.5% in severe ARDS.[8] However, the incidence of ARDS appears to be decreasing likely due to improvements in health care such as use of protective ventilation strategies, reduced transfusion-related acute lung injury ALI (TRALI) and better management of sepsis.[9]

For many years the mortality for ARDS was reported to be ~60%; data from 459 ICUs from 50 countries reports hospital mortality as 34.9% for those

## ABSTRACT

Acute respiratory distress syndrome (ARDS) is an acute diffuse, inflammatory lung injury leading to increased pulmonary permeability, increased lung weight, loss of aerated lung tissue, hypoxaemia and bilateral radiographic opacities, associated with increased physiological dead space and decreased lung compliance which is not fully explained by cardiac failure or fluid overload. Patients with ARDS have a high rate of morbidity and mortality. Lung protective invasive mechanical ventilation with adequate positive end-expiratory pressure remains the cornerstone of management, although new therapies are being developed as underlying mechanisms and pathophysiology are better understood.

## KEYWORDS

Acute respiratory distress syndrome
mechanical ventilation
positive end-expiratory pressure
fluid balance
ventilation-induced lung injury

Table 33.1 Criteria and classification of acute respiratory distress syndrome

| | AECC DEFINITION* | BERLIN DEFINITION† |
|---|---|---|
| Onset | Acute (not defined) onset<br>No risk factor formally defined | Within 7 days of a known risk factor<br>(See Box 33.1) |
| Chest imaging | Bilateral opacities on chest radiograph | Bilateral opacities consistent with pulmonary oedema on either chest radiograph or CT |
| Pulmonary oedema | PAOP ≤18 mm Hg when measured or no clinical evidence of raised left atrial pressure | Non-hydrostatic oedema; not fully explained by heart failure or fluid overload<br>Echocardiography or another objective measure may be required |
| Classification | ALI $Pa_{O_2}/Fi_{O_2} \leq -300$<br>ARDS $Pa_{O_2}/Fi_{O_2} \leq -200$ | Mild $200 < Pa_{O_2}/Fi_{O_2} \leq 300$<br>Moderate $100 < Pa_{O_2}/Fi_{O_2} \leq 200$<br>Severe $Pa_{O_2}/Fi_{O_2} \leq 100$ |

*No minimum ventilatory setting defined for $Pa_{O_2}/Fi_{O_2}$ data.

†Based on oxygenation measured on a minimum of 5 cm $H_2O$ PEEP. For the mild classification only, oxygenation can also be assessed during non-invasive ventilation. For the moderate and severe classification, the patient must be receiving intubated ventilatory assistance.

with mild, 40.3% for moderate, and 46.1% for severe ARDS.[8] Particular diagnostic groups such as multiple trauma have a lower mortality rate than other causes of ARDS, and patients with ARDS who have chronic liver disease, non-pulmonary organ dysfunction, sepsis or age greater than 70 years (hazard ratio, 2.5) have a higher risk of death. Clinical trial outcomes report low mortality rates in the control arm in part due to the exclusion of patients with limited life expectancy; consequently, many factors need to be considered when assessing outcome prediction.

## PULMONARY FUNCTION IN SURVIVORS

Respiratory function continues to improve after discontinuation of mechanical ventilation, and usually returns towards normal by 6–12 months.[10,11] Although a variety of abnormal pulmonary function tests may be found, impaired diffusing capacity is the most common. This is rarely symptomatic, but occasional patients have severe restrictive disease, and this is correlated with their cumulative LIS.[11]

## QUALITY OF LIFE IN SURVIVORS

Compared with disease-matched ICU patients who do not develop ARDS, patients with ARDS have a more severe reduction in both pulmonary and general health-related quality of life.[12] Many patients have reduction in exercise tolerance that may be attributable to associated critical illness neuropathy and myopathy; nerve entrapment syndromes, contractures, postural hypotension, and heterotopic calcification may play a role in a minority.[10] When followed for 5 years in a young and severe cohort (median age 45 years) with relatively few prior co-morbidities, there was persistent functional impairment with little improvement after 12 months.[13] Depression, anxiety and post-traumatic stress disorder are also common (20%–50% of survivors). Finally, most survivors have cognitive impairments such as slowed mental processing, or impaired memory or concentration, and these correlate with the duration of ventilation, hyperglycaemia and variability in blood glucose, and the period and severity of desaturation less than 90%.[14,15] In an analysis of survivors of the ARDS Network Fluid and Catheter Trial (FACTT),[16] Mikkelsen and co-workers[17] found that over half the subjects suffered from cognitive dysfunction and from psychological disability, and that these parameters were associated with lower $Pa_{O_2}$, enrolment in the restrictive fluid arm, and hypoglycaemia. Taken together these data caution against permissive hypoxaemia as a strategy to reduce ventilator-induced lung injury (VILI), and suggest that quality of survival is an important additional outcome for clinical trials.

# PATIENTS AT RISK FOR ACUTE RESPIRATORY DISTRESS SYNDROME

About one-third of critically ill patients exposed to either a direct or indirect risk factor (Box 33.1) develop ARDS, most within 6–48 hours. Multiple risk factors such as low pH, chronic alcohol abuse or chronic lung disease substantially increase the incidence of ARDS in at-risk patients. Diabetes reduces the risk of developing ARDS.[18]

## FAT EMBOLISM SYNDROME

Fat embolism syndrome (FES) is most commonly associated with long bone and pelvic fractures, and is more frequent in closed fractures than open fractures. Patients with a single long bone fracture have a 1%–3% chance of developing FES, which increases with the number of fractures. Fat emboli usually result from fat

Box 33.1 Clinical risk factors for acute respiratory distress syndrome

| DIRECT | INDIRECT |
|---|---|
| Pneumonia | Non-pulmonary sepsis |
| Aspiration of gastric contents | Multiple trauma |
| Lung contusion | Massive transfusion |
| Fat embolism | Pancreatitis |
| Near drowning | Cardiopulmonary bypass |
| Inhalational injury | |
| Reperfusion injury | |

globules entering the bloodstream or via production of the toxic intermediaries of plasma-derived fat.

FES typically manifests 24–72 hours after the initial insult.[19] Affected patients develop a classic triad – hypoxaemia, neurological abnormalities and a petechial rash. Neurological abnormalities such as confusional state followed by an altered level of consciousness develop in the majority of patients. The characteristic petechial rash may be the last component of the triad to develop. It occurs in only 20%–50% of cases and is found most often on the head, neck, anterior thorax, axillae, and subconjunctiva.[20] The rash resolves in 5–7 days

Early immobilization of fractures reduces the incidence of FES, otherwise treatment is the same as for ARDS.

## PATHOGENESIS

Although it is well accepted that diffuse alveolar damage with: (a) pulmonary oedema due to damage of the alveolocapillary barrier, (b) a complex inflammatory infiltrate and (c) surfactant dysfunction,[21] are essential components of ARDS, the sequence of events is uncertain and probably depends upon the precipitating insult and host response. For example, in endotoxin-induced lung injury, hypoxaemia and reduced lung compliance occur well before recruitment of neutrophils or an increase in lung weight due to an increase in permeability.[22] In addition, typical of early ARDS, surfactant turnover is dramatically increased prior to these changes. Furthermore, epithelial lining fluid sampled immediately following intubation in patients with ARDS has markedly increased concentrations of type III procollagen peptide,[23] suggestive of fibrosing alveolitis extremely early in the course of lung damage.

### THE ALVEOLOCAPILLARY BARRIER

The normal lung consists of 300 million alveoli with alveolar gas separated from the pulmonary microcirculation by the extremely thin alveolocapillary barrier (0.1–0.2 μm thick). Since the endothelial pore size is 6.5–7.5 nm, and the epithelial pore size is almost one-tenth that at 0.5–0.9 nm, the epithelium is the major barrier to protein flux.[24] The surface area of the alveoli is estimated to be 50–100 $m^2$, which is made up predominantly of alveolar type I cells, with the metabolically active type II cells accounting for ~10% of the surface area. In turn, these cells are covered by the epithelial lining fluid with an estimated volume of 20 mL, ~10% of which is surfactant, the rest being filtered plasma water and low-molecular-weight proteins and a small number of cells, mainly alveolar macrophages and lymphocytes.

In ARDS the alveolocapillary barrier is damaged with bidirectional leakage of fluid and protein into the alveolus and leakage of surfactant proteins (SP) and alveolar cytokines into the plasma. Total protein content in bronchoalveolar lavage (BAL) fluid is 20–100 times that found in both healthy subjects and ventilated subjects without cardiorespiratory disease.[25,26] There is also disruption of the epithelial barrier, surfactant dysfunction and proliferation of alveolar type II cells as the progenitor of type I cells. Indirect causes of ARDS result in pulmonary endothelial injury, followed by recruitment of inflammatory cells and then epithelial damage, whereas direct causes of ARDS result in epithelial injury and secondary recruitment of inflammatory cells. The outcome of these processes must reflect a balance between repair and fibrosing alveolitis.

### CELL TYPES INVOLVED

The large surface area of pulmonary epithelium and endothelium including the associated microcirculation, myofibroblasts, and both alveolar macrophages and recruited neutrophils are all important components of ALI. BAL fluid has a marked increase in cell count; alveolar macrophage numbers are increased about twofold, but as a fraction of the cell count falls from around 90% to 20%–40% of the cell count due to a greater increase in neutrophils from around 1% to 50%–80% of the cell count. In addition, microparticles, tiny vesicles potentially derived from most of these cell types, are found in both BAL fluid and blood and may play an important role in both lung damage and repair.[27] A temporal trend towards more normal neutrophil and alveolar macrophage ratios in BAL fluid is associated with survival.

#### *NEUTROPHILS*

Neutrophils are the most abundant cell type found in both the epithelial lining fluid (e.g. BAL fluid), and alveoli in histological specimens from early in the course of ARDS. Although neutrophil migration across the endothelium and then the epithelium does not cause injury, when activated, neutrophils are pro-inflammatory and pro-apoptotic, and release reactive oxygen species, cytokines, eicosanoids and a variety of proteases that may make an important contribution to basement membrane damage, increased permeability and direct cell damage. Following bone marrow

demargination, activated neutrophils adhere to the endothelium on their passage to the alveolus, and this may be accompanied by an early, transient leucopenia. Although neutrophils have an important role in host defence due to their bactericidal activity, there is a marked (50–1000-fold) increase in the release of cytotoxic compounds when they are activated by adherence to the endothelium, epithelium or contact with interstitial extracellular matrix proteins.[28] The factors involved in adhesion of neutrophils are complex and involve the integrin family of proteins, selectins and a number of adhesion molecules.

In models of ARDS, antibodies to adhesion molecules (e.g. CD11b/CD18 antibodies) ameliorate lung injury, suggesting a crucial and central role of this cell type. However, ARDS occurs in neutropenic patients, and was not more common when granulocyte colony-stimulating factor was administered to patients with pneumonia.[29] Clearly, other cell types play an important role, and neutrophil chemoattractants such as interleukin (IL)-8 must be present in the lung prior to neutrophil accumulation.

### *ALVEOLAR MACROPHAGES*

Alveolar macrophages are the most common cell type normally found in BAL fluid, and together with interstitial macrophages play an important role in host defence and modulation of fibrosis. They are capable of releasing IL-6 and a host of mediators similar to the activated neutrophil, including tumor necrosis factor (TNF)-α and IL-8 in response to stretch,[30] and may amplify lung injury. Macrophages also release factors such as transforming growth factor (TGF)-α and platelet-derived growth factor (PDGF) that stimulate fibroblast proliferation, deposition of collagen and glycosaminoglycans, angiogenesis and lung fibrosis.

A study using different cell markers found that there appear to be different pools of alveolar macrophages termed the M1 and M2 phenotype.[31] The M1 phenotype is characterised as a resident alveolar macrophage that is pro-inflammatory, and the M2 phenotype appears to represent recruited monocytes and be central to lung repair and fibrosis depending upon timing, local milieu and cross talk with other cell types. This may account for the observation that ARDS survivors progressively increase alveolar macrophage number; however, any conclusion awaits further work examining alveolar macrophage phenotypes and clinical outcomes.

### *EPITHELIUM*

Alveolar epithelial type II cells are extremely metabolically active; they manufacture and release surfactant, along with type I cells control alveolar water clearance through epithelial Na channels and $Na^+/K^+$ ATP-ase, express cytokines, which in turn interact with surfactant production, and are the progenitor of type I cells following injury. In response to both stretch and endotoxin, type II cells express IL-8 and TNF-α, with the latter cytokine augmenting $Na^+$, and hence water, egress from the alveolus.[32] Damage to the epithelium leads to dysfunctional surfactant release and impaired resolution of alveolar oedema which both reduces vectorial transport of $Na^+$ in part through down-regulation of ion transport genes, and up-regulates gene expression of Il-8, TNF-α, and IL-β.[33] Similarly, TGF-β acutely reduces transepithelial sodium transport by inducing endocytosis of epithelial sodium channel (ENaC) and plays a central role in lung fluid balance.[34]

Epithelial biomarkers include surfactant protein B (SP-B), which is predictive of ARDS,[35] and SP-D, and the receptor for advanced glycation end-products (RAGE), both of which have been associated with severity and outcome of ARDS.

### *ENDOTHELIUM*

Pulmonary endothelial cells express a variety of adhesion molecules and cyclooxygenase (COX)-2, secrete endothelin and cytokines including IL-8,[36] stimulate procoagulant activity and 'cross talk' with the alveolar macrophages and type II cells. In addition to generalised endothelial activation, the endothelium is subject to mechanical stress both secondary to vascular pressure, and its association with the alveolus. Plasma levels of von Willebrand factor antigen are both predictive of and associated with outcomes from ARDS[37]; however, as it is synthesised by all vascular endothelial cells it is a non-specific biomarker. Similarly, plasma Angiopoietin-2 both predicts the onset of ALI in critically ill patients and has prognostic and pathogenetic significance.[38,39]

Microvascular thrombosis is common in ARDS, associated with inflammation, and contributes to pulmonary hypertension and wasted ventilation. Platelet aggregation contributes through release of thromboxane $A_2$, serotonin, lysosomal enzymes, and platelet-activating factor. Impaired fibrinolysis also contributes to these changes, and abnormal plasma levels of protein C and plasminogen activator inhibitor-1 are associated with outcome and organ failure in ARDS. Lung injury also leads to expression of the coagulation factor X on pulmonary epithelium, which appears to be a direct link between coagulation and pulmonary fibrosis.[40]

## CHEMOKINES IN ACUTE RESPIRATORY DISTRESS SYNDROME

The expression and secretion of chemokines (chemoattractant cytokines) at sites of inflammation is a key proximal step in initiating the inflammatory cascade. IL-8-induced chemotaxis and activation of neutrophils are elevated in ARDS BAL fluid both within hours of the initiating insult and before recruitment of neutrophils, and in a manner that reflects subsequent morbidity and mortality. IL-8 antibodies prevent recruitment of neutrophils and protect the lung. Indeed, the recruitment and retention of neutrophils requires the

generation and maintenance of a localised chemotactic/haptotactic gradient.[41]

## ION CHANNELS IN ACUTE RESPIRATORY DISTRESS SYNDROME

The transient receptor potential (TRP) ion channel superfamily is involved in sensing and transmission of a broad variety of external or internal stimuli, including mechanical stress.[42] TRP vanilloid (TRPV) 4 is expressed on the pulmonary endothelium, epithelium and macrophages. Activation of TRPV4 channels by shear forces,[43] stretch,[44] overinflation,[45] hypothermia,[44] increased hydrostatic pressure,[46] sudden increases in circulatory forces,[47,48] high intracapillary pressure,[44,46] and hypotonicity[49] leads to the rapid intracellular influx of calcium ions and leads to increased permeability of the alveolocapillary barrier through perturbations in cell morphology and disruption to the alveolar septal barrier[50] possibly via activation of matrix metalloproteinases[51] and calcium-activated K channels,[52] manifesting as lung injury.

## MEDIATORS IN ACUTE RESPIRATORY DISTRESS SYNDROME[53]

Inflammation is usually a redundant process so that numerous mediators, including cytokines, chemokines, complement, reactive oxygen species, eicosanoids, platelet-activating factor, nitric oxide, proteases, growth factors and lysosomal enzymes, derived from a number of different cell types, play important roles in the pathophysiology of ARDS. As the alveolocapillary barrier becomes injured, these are no longer compartmentalised in the alveolus, and many of these proteins have been measured in blood as well as in the epithelial lining fluid. Care must be taken when interpreting these data, as immunological levels may not reflect biological activity, inhibitors or binding proteins may complex with the active protein or epitope and interfere with immunological detection, and the ultimate biological effect will depend upon a balance of pro-inflammatory and anti-inflammatory effects.

Of the pro-inflammatory mediators, TNF-α, IL-1β, IL–6, and IL-8 are the most important. However, even greater increases are found in their cognate receptors or antagonists such as the counter-regulatory cytokine IL-10, so that their biological impact is markedly reduced.[54] Blood or epithelial lining fluid levels are associated with mortality, but are rarely used clinically.

## RESOLUTION OF ACUTE RESPIRATORY DISTRESS SYNDROME AND THE DEVELOPMENT OF FIBROSING ALVEOLITIS

Although histological evidence of fibrosing alveolitis (mesenchymal cells and new vessels in alveoli) is not usually found until at least 5 days following the onset of ARDS, elevated levels of type III procollagen peptide are found in the epithelial lining fluid soon after diagnosis[21]; both oedema fluid and plasma levels are associated with mortality.

Clinical resolution of ARDS usually occurs provided that both the underlying cause is promptly and effectively treated, and that appropriate supportive care is provided. Alveolar oedema resolves with active transport of $Na^+$ by the type II cells followed by passive clearance of water through transcellular aquaporin channels; repair of the alveolocapillary barrier is associated with improved outcome. Type II cells proliferate and cover the denuded epithelium before differentiating into type I cells.

Both host response and the clinical course of ARDS influence lung remodelling in ARDS. Cross-talk between type II cells and alveolar macrophages, probably the M2 phenotype, along with epithelial mesenchymal transition – a process where reactive oxygen species, hypoxia, TGF-β and mechanical stress lead to altered epithelial transcription – are central to interstitial responses. Epithelial cells assume characteristics of mesenchymal cells with loss of polarity, increased resistance to apoptosis, and increased migration (into the interstitium) where they lay down a fibrotic matrix.[55]

# CLINICAL MANAGEMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME

The factors leading to ARDS must be promptly and appropriately treated. This includes diagnosis and treatment of infection with drainage of collections and appropriate antimicrobial agents, recognition and rapid resuscitation from shock, splinting of fractures, and careful supportive care. Prevention of deep venous thrombosis, stress ulceration, nosocomial infection, and malnutrition, often with enteral nutrition, must all be considered.

Early mobilisation of mechanically ventilated patients accompanied by appropriate levels of analgesia and sedation is feasible and safe, and offers shorter duration of ventilation, reduced delirium, ICU and hospital length of stay, and improved mortality and functional outcomes.[56–58] However, two other randomised controlled trials[59,60] have not shown benefit, and care must be taken not to exacerbate lung injury with premature spontaneous effort which may result in unintended increases in both transpulmonary airway and transmural hydrostatic pressure,[61] and asynchrony. For example, use of neuromuscular blockers in the first 48 hours of mechanical ventilation in ARDS reduced mortality,[62] possibly through prevention or reduction of these factors.

## MECHANICAL VENTILATION

Acute hypoxaemic respiratory failure,[63] and an increase in the work of breathing, usually mandates mechanical

Table 33.2 Pathophysiology of acute lung injury and adult respiratory distress syndrome

| FEATURE | CAUSE(S) |
|---|---|
| Hypoxaemia | True shunt (perfusion of non-ventilated airspaces)<br>Impaired hypoxic pulmonary vasoconstriction<br>*V/Q* mismatch is a minor component |
| ↑Dependent densities (CT) | Surfactant dysfunction alveolar instability |
| (Collapse/consolidation) | Exaggeration of normal compression of dependent lung due to ↑weight (↑lung water, inflammation) |
| ↑Elastance (↓compliance) | Surfactant dysfunction (↑specific elastance)<br>↓Lung volume ('baby lung')<br>↑Chest wall elastance<br>Fibrosing alveolitis (late) |
| ↑Minute volume requirement | ↑Alveolar dead space ($VD_{phys}$ $V_t$ often 0.4–0.7)<br>↑ $V_{CO_2}$ |
| ↑Work of breathing | ↑Elastance<br>↑Minute volume requirement |
| Pulmonary hypertension | Pulmonary vasoconstriction (thromboxane $A_2$, endothelin)<br>Pulmonary microvascular thrombosis<br>Fibrosing alveolitis<br>Positive end-expiratory pressure |

*CT*, Computed tomography.

ventilation (Table 33.2). The role of non-invasive ventilation in ARDS is contentious; there are no large definitive studies, and although some groups report encouraging results, these are usually in patients with mild ARDS.[64] Failure of non invasive ventilation (NIV) is common, associated with greater complication rates and mortality, perhaps due to delayed intubation.[65–67] If non-invasive ventilation is considered in ARDS, it requires particular care (see Chapter 37).

The method and delivery of ventilatory support must take into account both the pathophysiology of ARDS and VILI. The ARDS Network randomised 861 ALI patients from 75 ICUs to receive either a tidal volume ($V_T$) of 12 or 6 mL/kg predicted body weight.[68] Mortality was reduced by 22%, from 40% to 31%, in the lower $V_T$ group. There was a strict PEEP and $Fi_{O_2}$ protocol, and patients were ventilated with assist-control ventilation to avoid excessive spontaneous $V_T$. Similar data with improved long-term survival are found in routine clinical practice[69]; however, it is the concept of lung protection rather than an exact $V_T$ formula that is important.[70] As Hager and colleagues[71] found that lower $V_T$ ventilation was protective across all quartiles of plateau pressure ($P_{plat}$) in the ARDS Network trial, with no safe upper limit of $P_{plat}$, it appears that the key variable is lower $V_T$ rather than control of static airway pressure.

## AVOIDANCE OF OVERSTRETCH AND INADEQUATE RECRUITMENT

The increase in dependent lung density found on chest CT, due to non-aerated and poorly aerated lung, reduces the volume of aerated lung available for tidal inflation (baby lung). Both PEEP and tidal recruitment will increase aeration of some of these air spaces, but a $V_T$ that is not reduced in proportion to the reduction in aerated lung may lead to overstretch of aerated lung parenchyma and further diffuse alveolar damage. This is termed volutrauma, as increased airway pressure ($P_{aw}$) despite low $V_T$, due to decreased chest wall compliance, causes minimal damage compared with high $V_T$, high $P_{aw}$ ventilation.[72] Atelectrauma refers to injury due to repeated opening and closing of air spaces during tidal inflation. Both volutrauma and atelectrauma result in alveolar inflammation and elevated alveolar cytokines (biotrauma), which may 'spill' into the systemic circulation.[73] However, as CT scans performed during ARDS Network protective ventilation show that tidal inflation occurs primarily in either normally aerated or overinflated compartments, with little tidal recruitment,[74] and PET-CT scans suggest that overinflation but not tidal recruitment is inflammatory,[75] overstretch appears to be the dominant mechanism causing VILI.

### *OVERSTRETCH*

The normal lung is fully inflated at a transpulmonary pressure of ~25–30 cm $H_2O$. Consequently, a maximum $P_{plat}$, an estimate of the elastic distending pressure, of 30 cm $H_2O$ has been recommended.[68] However, overinflation may occur at much lower elastic distending pressures (18–26 cm $H_2O$).[72,76]

The transpulmonary pressure may be lower than expected for a given $P_{plat}$ in patients with a high chest

wall elastance (e.g. obesity, abdominal compartment syndrome, after abdominal or thoracic surgery). While placement of an oesophageal balloon (see Chapter 38) allows measurement of the transpulmonary pressure and may allow better titration of PEEP,[77] it must be correctly placed, have an adequate occlusion pressure ratio, and measurements are preferably performed in a semi-sitting position in order to lift the mediastinum off the oesophagus.

Finally, inspiratory muscle contraction through reduction of intrapleural pressure lowers $P_{plat}$, potentially avoiding simple detection of an excessive transpulmonary pressure. This is particularly common when pressure support ventilation is used as a primary mode of ventilatory support; $V_T$ that would produce an unacceptably high $P_{plat}$ during mechanical ventilation will produce the same volutrauma during a spontaneous or supported mode of ventilation, and should be avoided. Provided the same $V_T$ is generated, spontaneous ventilation does not reduce VILI compared to controlled ventilation,[78] and may exacerbate it.[61]

Static or dynamic volume-pressure curves or quantitative chest CT can be used to infer overinflation, though chest CT cannot determine overstretch.[5] Consequently, unless particular expertise is available, $V_T$ limitation is currently the most practical approach.

## ADEQUATE PEEP

PEEP improves $Pa_{O_2}$ by recruiting alveoli and increasing end-expiratory lung volume. Because PEEP may reduce cardiac output by impairing venous return, Suter and co-workers suggested that at best PEEP the oxygen delivery (oxygen content × flow) was highest, and that this coincided with greatest compliance.[79] PEEP is commonly titrated to a particular $Pa_{O_2}/Fi_{O_2}$ ratio such as the ARDS Network protocol.[68] However, the amount of lung available for recruitment is extremely variable,[80] and does not differ comparing pulmonary with extrapulmonary ARDS.[81] Factors such as the duration, late ARDS being less recruitable, and phenotype influence whether PEEP leads to alveolar recruitment, overinflation or a balance of both. Based on chest imaging, ARDS can be subdivided into focal, intermediate and diffuse phenotypes, with progressive increase in the amount of recruitable lung.[82,83] Applying ARDS Network ventilation to focal ARDS (about ⅓ of most cohorts) leads to high lung stress, with increased cytokine release, which can be ameliorated by using lower levels of PEEP.[84]

The lower inflection point of a volume-pressure curve has been used to set PEEP; early studies suggested that this reflected recruitment of collapsed alveoli. However, in patients with ARDS, recruitment occurs well above the lower inflection point, often along the entire volume-pressure curve and above the upper inflection point.[85,86] Concurrently, there is frequently evidence of overstretching and hyperinflation on CT scans[41,87] or dynamic volume-pressure analysis.[76]

Meta-analysis of major clinical trials using protective $V_T$ and comparing higher and lower PEEP scales[88] did not find an overall improvement in outcome with higher PEEP, although rescue therapies were required less often. However, patients with mild ARDS tended to have worse outcomes with higher PEEP, and those with moderate to severe ARDS had better outcomes.

These data suggest individual patients may benefit from a tailored approach. Although routine CT analysis has been advocated by some, it is cumbersome and has not been shown to influence outcome; non-invasive bedside alternatives are under investigation. Consequently, PEEP titration is often a compromise aiming to minimise both atelectrauma and volutrauma.[89] Reasonable approaches to PEEP titration include: (a) the use of a scale similar to the ARDS Network protocol, (b) titration of PEEP to $Pa_{O_2}$ aiming for a PEEP of ~15 cm $H_2O$, or (c) measuring elastic mechanics at the bedside. Consistent with Suter's early observation,[79] both nadir elastance after a recruitment manoeuvre,[90] or minimal change in driving pressure[76] (see also Chapter 38), offer bedside methods to individualise PEEP.

In patients at risk for ARDS, prophylactic PEEP (8 cm $H_2O$) was not protective.[91]

### Driving pressure

This is defined as the difference between the end-inspiratory plateau pressure and the total PEEP. In a meta-analysis of nine randomised controlled trials of protective ventilation strategies (lower $V_T$, lower $P$plat, and higher PEEP), Amato and colleagues identified the driving pressure as the variable most robustly associated with improved outcome.[92] Although the driving pressure is an appealing and intuitive way of thinking about minimising lung stress, protocols examining this method need to be prospectively tested using patient-centred outcomes to exclude indirect association as the basis for these findings.

### Recruitment manoeuvres and open lung ventilation

Open lung ventilation refers to an approach where the lung is maximally recruited, usually through application of higher PEEP, recruitment manoeuvres, and efforts to minimise derecruitment. In theory, increased lung volume will result in less tidal overinflation and improved outcome. However, despite alveolar recruitment with open lung ventilation, overinflation may occur in previously normally aerated lung.[93] The recruitment manoeuvre may be followed by a marked improvement in oxygenation; however, this is not a consistent finding, and hypotension may occur due to reduced venous return if there is inadequate fluid loading.

During a typical recruitment manoeuvre, a high level of continuous positive airway pressure (CPAP) (30–40 cm $H_2O$) is applied for 30–40 seconds in an apnoeic patient, followed by return to a lower level of PEEP and controlled ventilation. This may be

suboptimal; an alternative, for example, is a staircase recruitment manoeuvre where airway pressure is sequentially increased every 2 minutes, and then decreased until oxygenation deteriorates.[94] A number of small trials have shown improvement in oxygenation following recruitment manoeuvres; however, the largest clinical trial[95] failed to show an effect. Grasso and colleagues[96] found that recruitment manoeuvres were effective only early in ARDS and with lower levels of baseline PEEP, which probably explains the variable responses reported.

In addition to physical recruitment of alveoli, lung stretch above resting $V_T$ is the most powerful physiological stimulus for release of pulmonary surfactant from type II cells. This is associated with a decrease in lung elastance and improved $Pa_{O_2}$ in the isolated perfused lung,[97] and is a possible explanation for the improvement in oxygenation, recruited lung volume and elastance reported with addition of three sigh breaths in patients with ARDS.[98] Similarly, in models of lung injury, biologically variable or fractal $V_T$ is associated with less lung damage with lower alveolar levels of IL-8,[99] improved oxygenation and lung elastance, and greater surfactant release.[100] These data caution against monotonous low $V_T$ ventilation, and suggest that intermittent or variable lung stretch may reduce lung injury.

## MODE OF VENTILATION

Non-invasive ventilation should not be routinely used in ARDS (see Chapter 37) and most patients require intubated mechanical ventilation. Following intubation, controlled ventilation allows immediate reduction in the work of breathing, and application of PEEP and a controlled $Fi_{O_2}$. Later in the clinical course, assisted or supported modes of ventilation may allow better patient-ventilator interaction (see Chapter 31), and possibly improved oxygenation through better $\dot{V}/\dot{Q}$ mismatch as a result of diaphragmatic contraction.[101] Withdrawal or weaning from mechanical ventilation is discussed in Chapter 31.

An advantage of assist-control ventilation (as used in the ARDS Network study) is that spontaneous effort generates a controlled $V_T$. However, the fall in airway pressure during triggered ventilation (e.g. assist control or supported ventilation) can result in worse lung injury than controlled ventilation in early ARDS, although a beneficial effect can be seen when the underlying lung injury is less severe.[102] This may be due to greater transpulmonary and transmural pressure changes, and heterogeneity of lung inflation. Care should also be taken with synchronised intermittent mandatory ventilation (SIMV), particularly if pressure support is added to SIMV, as excessive $V_T$ may occur during supported breaths.

There is an increasing tendency to use pressure-controlled ventilation (PC) or pressure-regulated volume control (PRVC), as $P_{pk}$ is lower than volume-controlled (VC) ventilation with a constant inspiratory flow pattern. However, the decelerating flow pattern of PC or PRVC means that most of the resistive pressure ($P_{res}$) during inspiration is dissipated by end inspiration, which is in contrast to VC with a constant inspiratory flow pattern where $P_{res}$ is dissipated at end inspiration (see Fig. 31.2). Consequently, with PC and PRVC $P_{pk} \approx P_{plat}$ which is the same as $P_{plat}$ during VC.[103] Both oxygenation, haemodynamic stability and mean airway pressure are no different between PC and VC, and a moderate-sized randomised study found no difference in outcome.[104] However, there may be differences in lung stress due to greater viscoelastic build-up with VC.[105]

Inverse ratio ventilation, often together with PC, has been used in ARDS. However, when $PEEP_i$ and total PEEP are taken into account, apart from a small decrease in $PaCO_2$, there are no advantages with inverse ratio ventilation. Mean airway pressure is higher with a greater risk of both haemodynamic consequences, and regional hyperinflation.[103] Consequently, an inspiratory to expiratory ratio greater than 1:1 is recommended.

A number of other modes of ventilation (see Chapter 31) including airway pressure release ventilation (APRV) and high-frequency oscillation (HFO) have been proposed for use in ARDS. Randomised clinical trials have not shown improved outcomes with APRV,[106] despite potential physiological benefits. The small $V_T$ used with HFO, although appealing, may increase hospital mortality when compared with a ventilation strategy of low tidal volume and high PEEP.[107]

Use of venovenous extracorporeal membrane oxygenation (ECMO) has been investigated in patients with ARDS and shown to both increase survival and minimise severe disability, and to be cost effective.[108] However, caution must be taken in extrapolating these results, as almost a quarter of those considered for ECMO group did not receive it, and control patients were not transferred to the trial hospital. Further trials are underway and vv-ECMO is sometimes used as a rescue therapy (see Chapter 41).

## TARGET BLOOD GASES

As discussed earlier, there are many variables that need to be considered when choosing target blood gases in ARDS. For example, if a patient also has a traumatic brain injury, it may be inappropriate to accept hypercapnia.

### Oxygenation targets and $Fi_{O_2}$

There must be a compromise between the major determinants of oxygenation, including the extent of poorly or non-aerated lung, hypoxic pulmonary vasoconstriction and mixed venous oxygen saturation, and the target $Pa_{O_2}$. The association between cognitive impairment and arterial saturation ($Sa_{O_2}$) less than 90%[14] suggests that a $Sa_{O_2} \geq 90\%$, usually a $Pa_{O_2} > 60$ mm Hg, is a reasonable target. A recent trial reported lower ICU

mortality with target $Pa_{O_2}$ values of 70–100 mm Hg versus values up to 150 mm Hg.[109] Because positive-pressure ventilation may reduce cardiac output, it is also important to consider tissue oxygenation.

In addition to PEEP, increased $Fi_{O_2}$ is used to improve $Sa_{O_2}$. However, high $Fi_{O_2}$ may also cause tissue injury, including diffuse alveolar damage. The balance between increased airway pressure and $Fi_{O_2}$ is unknown, but high $Fi_{O_2}$ is generally regarded as being less damaging.[110] In part this is because diffuse alveolar damage itself protects the lung against hyperoxia, perhaps through prior induction of scavengers for reactive oxygen species.[111] A reasonable compromise is to start ventilation at a $Fi_{O_2}$ of 1 and to titrate down, aiming for a $Fi_{O_2} \leq 0.6$. In patients with extreme hypoxaemia, additional measures such as inhaled nitric oxide (iNO) and prone positioning may be tried, along with a lower $Sa_{O_2}$ target.

### Carbon dioxide target

Low $V_T$ strategies will result in elevations in $PaCO_2$ unless minute ventilation is augmented by an increase in respiratory rate. The ARDS Network protocol aimed at normocapnia, with a maximum respiratory rate of 35, to minimise respiratory acidosis.[68] This exposes the lung to more repeated tidal stretch, and may result in dynamic hyperinflation due to a shortened expiratory time.[112] In addition, allowing the $PaCO_2$ to rise above normal may not be harmful in many patients.

If hypercapnic acidosis occurs slowly, intracellular acidosis is well compensated, and the associated increase in sympathetic tone may augment cardiac output and blood pressure. Although the respiratory acidosis may worsen pulmonary hypertension and induce myocardial arrhythmias, these effects are often small, particularly if there has been time for metabolic compensation. In addition, in an ischaemia-reperfusion model of ARDS, therapeutic hypercapnia reduced lung injury and apoptosis,[113] but was harmful in prolonged untreated pneumonia.[114]

Extracorporeal $CO_2$ removal technologies may facilitate further lowering of ventilator stretch, allowing dissection of the contribution of $CO_2$ and tidal stretch to lung injury or protection in ARDS. However, clinical studies of permissive hypercapnia and extracorporeal $CO_2$ removal technologies must be undertaken before they can be considered. Hypercapnia should be avoided in patients with or at risk from raised intracranial pressure.

## NON-VENTILATOR MANAGEMENT

### PRONE POSTURE

In patients with severe ARDS, early application of prolonged prone-positioning sessions significantly decreased 28- and 90-day mortality.[115] Notably, the study entry $Pa_{O_2}/Fi_{O_2}$ ratio was less than 150, enrolment was within 36 hours of commencing mechanical ventilation, and the ICUs had more than 5 years of experience in managing ARDS patients with prone positioning. The mechanisms involved include recruitment of dorsal lung, with concurrent ventral collapse; however, perfusion is more evenly distributed leading to better $\dot{V}/\dot{Q}$ matching. While this study is supported by a meta-analysis,[116] a number of prior studies did not find clear evidence of benefit.[117,118] Moreover, the study did not control for lung heterogeneity (ARDS phenotype), or co-interventions (did not control or report fluid balance, or cumulative dose of catecholamines), and had baseline imbalances of neuromuscular blockers and a high rate of cardiac arrest. Consequently, the uptake of prone positioning remains sporadic; more studies are needed.

### MANIPULATION OF THE PULMONARY CIRCULATION

iNO and aerosolised prostacyclin ($PGI_2$) may be used to reduce pulmonary shunt and right ventricular afterload by reducing pulmonary artery impedance. When hypoxic pulmonary vasoconstriction is active, there is redistribution of pulmonary blood flow away from the poorly ventilated dependent areas to more normally ventilated lung leading to an increase in $Pa_{O_2}$. Both iNO and $PGI_2$ are delivered to well-ventilated lung; both vasodilate the local pulmonary circulation and augment the effects of hypoxic pulmonary vasoconstriction. Intravenous almitrine is a selective pulmonary vasoconstrictor that reinforces hypoxic pulmonary vasoconstriction and, although this may improve oxygenation alone, there is a synergistic effect with iNO.

Inhaled NO or $PGI_2$ may also be used to reduce right ventricular afterload; however, a consequent increase in cardiac output is rare in ARDS. Intravenous $PGI_2$ will improve cardiac output in ARDS, though there is non-specific pulmonary vasodilation with increased blood flow through poorly ventilated lung zones, resulting in deterioration in oxygenation.

### Inhaled nitric oxide

Nitric oxide is an endothelium-derived smooth muscle relaxant. It also has other important physiological roles including neurotransmission, host defence, platelet aggregation leucocyte adhesion and bronchodilation. Doses as low as 60 parts per billion iNO may improve oxygenation; however, commonly used doses in ARDS are 1–60 parts per million, with the higher doses required for reduction in pulmonary artery pressure. A rise in $Pa_{O_2}$ exceeding 20% is generally regarded as a positive response; iNO should be continued at the minimum effective dose.

Inhaled NO may be delivered continuously or using intermittent inspiratory injection. Delivery is usually in the form of medical grade $NO/N_2$, and this should be adequately mixed to avoid delivery of variable NO concentrations. It is recommended that inspiratory NO

and $NO_2$ concentrations are measured, either by an electrochemical method or by chemiluminescence. The electrochemical method is accurate to 1 ppm, which is adequate for clinical use, and is less expensive. Local environmental levels of NO and $NO_2$ are low and predominantly influenced by atmospheric concentrations; however, it is still common practice to scavenge expired gas. Binding to haemoglobin in the pulmonary circulation rapidly inactivates NO, and systemic effects are reported only following high concentrations of iNO. Systemic methaemoglobin levels may be monitored, and are generally less than 5% during clinical use of iNO, but they should be compared with a baseline level. Nitric oxide may cause lung toxicity through combination with oxygen free radicals, and through metabolism of NO to $NO_2$; however, these do not appear to be major clinical problems. However, there are concerns about delayed resolution of pulmonary oedema with its usage.[119]

Only 40%–70% of patients with ARDS have improved oxygenation with iNO (responders), and this is likely due to active hypoxic pulmonary vasoconstriction in the remainder. Addition of IV almitrine can have an additive effect on oxygenation, and may improve the number of responders. Clinical trials[120] have shown no improvement in mortality or reversal of ARDS, and an increased risk of renal impairment. However, iNO transiently improves oxygenation (as compared with placebo or no iNO), which has been sustained beyond 12–24 hours in some trials. As constant dosing of iNO leads to both increased sensitivity and apparent tachyphylaxis,[121] subsequent investigation needs to consider different dose regimens. Currently iNO cannot be recommended for routine use in ARDS; however, in some patients with severe hypoxaemia, perhaps in combination with almitrine, iNO will provide temporary rescue.

### *Inhaled prostacyclin*

$PGI_2$ (up to 50 ng/kg per minute) improves oxygenation as effectively as iNO in ARDS patients,[122] and may reduce pulmonary hypertension. It is continuously jet nebulised due to its short half-life (2–3 minutes). Potential advantages include increased surfactant release from stretched type II cells, avoidance of the potential complications of iNO, and minimal toxicity. However, $PGI_2$ is dissolved in an alkaline glycine buffer, which alone can result in airway inflammation, and the sticky nature of the aerosol can result in expiratory valve obstruction. Iloprost is a derivative of $PGI_2$ with similar activity, a longer duration of action, without an alkaline buffer. Neither agent has been shown to improve outcome in ARDS patients.

## CONSERVATIVE FLUID BALANCE

Conservative fluid balance has been shown to decrease the length of mechanical ventilation when compared with liberal fluid balance in patients with ARDS,[16] although in a small number of patients who were followed up (30% of eligible survivors) it was associated with adverse neurocognitive outcome.[17] An intermittent approach between conservative and liberal fluid balance offers[123] solutions but has to be examined in larger prospective trials. A positive sodium balance is associated with respiratory dysfunction independent of fluid balance,[124] and future trials need to control for sodium balance in addition to fluid balance in patients with ARDS.

## HIGH FLOW OXYGEN

Use of high flow humidified oxygen through nasal cannula (HFNC) has become common in patients with acute hypoxaemic respiratory failure. As the gas flow rate (15–60 L/min) is close to the subject's inspiratory flow rate, there is little dilution of the inspired oxygen fraction. Additional mechanisms include flow dependent continuous positive airway pressure with increased end-expiratory lung volume, and washout of upper airway carbon dioxide leading to decreased physiological dead space, with both contributing to reduce the work of breathing. Compared to standard oxygen or NIV, HFNC reduced intubation in patients with hypoxic respiratory failure.[125] However, as the rate of intubation was high (38%), caution should be used. The role in of HFNC in ARDS is uncertain and endotracheal intubation and lung protective ventilation should not be delayed.[126]

## NEUROMUSCULAR BLOCKER

The ACURASYS trial in 2010 examined neuromuscular blockade in patients with severe, early ARDS and found that both the adjusted 90-day survival rate and time off the ventilator were greater in the cisatracurium group as compared with the placebo group.[62] This was despite the fact that variables commonly used to assess the propensity for VILI (e.g. plateau pressures and tidal volumes) did not differ significantly between the cisatracurium group and the placebo group, although reduced asynchrony and adverse effects attributable to triggering ventilation cannot be excluded.[61,127] These results have to be repeated, the possible mechanisms understood,[128] and concerns about long-term muscle weakness and the optimal duration of neuromuscular blocker also need to be addressed before it becomes a routine in the care of ARDS patients.

## SURFACTANT REPLACEMENT THERAPY

Surfactant dysfunction is an important and early abnormality contributing to lung damage in ARDS.[21,129] Pulmonary surfactant reduces surface tension promoting alveolar stability, reducing work of breathing and lung water. In addition, surfactant has important roles in lung host defence. Reactive oxygen species, phospholipases and increased protein permeability lead to inhibition of surfactant function. In addition, composition is abnormal, and turnover markedly increased.

VILI is difficult to demonstrate without surfactant dysfunction.[129] Consequently, there has been considerable interest in exogenous surfactant replacement therapy.

Exogenous surfactant therapy has an established role in neonatal respiratory distress syndrome. In paediatric ARDS, particularly that due to direct lung injury, clinical trials have been promising. However, in adults results have been disappointing; subgroup analysis of recombinant SP-C-based surfactant administered intratracheally improved oxygenation in direct ARDS without an improvement in mortality.[130] However, subsequent research in this cohort failed to confirm these data, perhaps owing to inactivation of the surfactant during administration.[131]

### GLUCOCORTICOIDS

Glucocorticoids may have a role in ARDS through their reduction of the intense inflammatory response and their potential to reduce fibroproliferation and collagen deposition, by faster degradation of fibroblast procollagen mRNA. Preventative steroids increase the incidence of ARDS and, although there may be a greater number of ventilator-free days and the possibility of a reduction in mortality,[132,133] neuromuscular complications, immunosuppression, superadded infection and higher blood glucose levels and increased mortality when steroids are administered more than 13 days after the onset of ARDS,[134] argue against their routine use.

### OTHER PHARMACOLOGICAL THERAPIES

Numerous other therapies including cytokine antagonism, non-steroidal anti-inflammatory drugs, scavengers of reactive oxygen species, and lisofylline[135] have been trialled without success. The complex balance of inflammation and repair in ARDS, and the critical additional damage secondary to VILI, may explain these results. However, studies in less heterogeneous groups with minimisation of VILI using standardised ventilation protocols, together with a growing understanding of ARDS, offer potential pharmacological therapies. Many promising therapeutic options such as TRPV4 antagonism, hyperosmolar therapy recombinant human angiotensin converting enzyme 2 and stem cell therapy are under trials.

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