Sequele of the adult respiratory distress syndrome

The adult respiratory distress syndrome (ARDS) is characterised by hypoxaemia, bilateral pulmonary infiltrates due to increased permeability, pulmonary oedema and, in most but not all instances, reduced lung compliance. The yearly incidence of ARDS is approximately six per 100,000.

ARDS may occur in response to various direct or indirect insults to the lung. Gastric aspiration, bacterial or pneumonia, major trauma, transfusion, and sepsis are among the most common causes (table). A generally standardised approach to the acute, supportive care of these patients has evolved which uses mechanical ventilation and positive end expiratory pressure (PEEP) but, despite increased experience in caring for these critically ill patients, the mortality of patients with ARDS remains at about 50%. Death is often due to non-pulmonary causes, multiple organ system failure, or sepsis.

Patients who survive an episode of ARDS may be asymptomatic and have normal pulmonary function, or they may have marked dyspnoea and severe physiological abnormalities. This editorial will review (1) the functional and physiological abnormalities seen in survivors of ARDS, (2) the predictors of pulmonary dysfunction in this population, and (3) those aspects of acute patient care which might adversely affect outcome.

Functional and physiological abnormalities

SYMPTOMS

Although many series report that the majority of survivors of ARDS are symptom free, in most instances symptoms were not aggressively sought and documented. The larger of these series also appear biased in that they included patients with mild illness. Douglas and Downs identified 54 patients with acute respiratory failure who required mechanical ventilation and PEEP of whom 43 (80%) survived; all survivors were asymptomatic at the time of hospital discharge. Of 15 patients evaluated for 1–30 months after ARDS by Yahav and colleagues none had symptoms, although only 10 of the 15 (66%) required mechanical ventilation, and only seven of these (47%) needed PEEP to maintain oxygenation.

Data from more recent series using a more rigorous definition of ARDS and including a more severely affected patient population suggest that symptom free recovery is somewhat less likely (66% and 50% in the studies by Peters et al and Haley et al respectively). Interpretation of the study by Haley et al, as well as that by Lakshminarayan et al in which 40% of the group was asymptomatic, is complicated by the high incidence of smoking in the two study populations, although only 11% of the patients had symptoms that could be related to smoking before ARDS.

Causes of adult respiratory distress syndrome

- Sepsis
- Multiple trauma
- Hypertransfusion
- Multiple fractures
- Pneumonia
- Aspiration
- Pancreatitis
- Near drowning
- Drug overdose
- Inhalation injury

SPIROMETRY

Spirometric abnormalities are to be expected early in the post ARDS period (fig 1). In most patients parallel reduc-
tions in forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) with a preserved FEV₁/FVC value consistent with a restrictive defect are the predominant findings. These abnormalities may occasionally be severe. Forced expiratory volumes tend to improve over time so that normal or near normal values are generally seen by one year.

A subset of ARDS survivors (ranging from 14% to 50%) are left with at least mild airflow limitation (FEV₁/FVC < 65%), forced expiratory flow 25–75% of the vital capacity < 50% predicted) measured up to at least one year after the acute episode. Although in the study by Lakshminarayan and colleagues, four of the five patients with airflow limitation were smokers, Elliott et al. found a reduced FEV₁/FVC value in four of 16 non-smokers (25%) one year after their episode of ARDS.

Increased airway resistance is characteristic of the acute phase of ARDS. During recovery, however, increased resistance is uncommon. Although this may, in part, be due to resolution of the airway inflammation, it probably results from the increase in total lung capacity (TLC) that occurs as ARDS resolves. A chronic increase in bronchial reactivity has been observed in response to methacholine or exercise in patients studied more than one year after ARDS. Unfortunately there are no good data that allow identification of those factors which predispose patients with ARDS to airflow limitation or airway reactivity.

LUNG VOLUMES
Lung volumes are reduced in many patients immediately after the episode of ARDS, but tend to improve during the first six months of recovery (Fig 2). Elliott and colleagues found that seven of 16 patients (46%) had a reduced TLC when tested less than two months after the onset of ARDS which returned to normal by three months in all instances. Similar observations were made by Peters et al and by others. An occasional patient may have severely reduced lung volumes which, without apparent explanation, do not improve.

Some patients have residual volumes that remain chronically elevated with TLC being either normal or reduced, and with spirometric testing showing no evidence of airflow limitation. These patients may be manifesting the results of small airway injury during the acute phase of their ARDS. Churg and colleagues recently reported a series of patients who developed progressive radiological signs of air trapping before death. Extensive cyst formation was found at postmortem examination (Fig 3). Histologically these cysts were lined by bronchiolar or metaplastic squamous epithelium. Marked bronchiolectasis has also been described. The airflow obstruction that occurs in some patients might have a similar pathophysiological explanation. These findings are in many ways similar to the severe bronchopulmonary dysplasia that occurs as a consequence of the infant respiratory distress syndrome. Bronchopulmonary dysplasia is usually seen in premature infants who require mechanical ventilation and high concentrations of oxygen for prolonged periods. In its most severe form it results in cyst formation, dilated terminal airways, air trapping, and chronic airflow limitation in those who survive.

Because air trapping may be missed when lung volumes are measured by gas dilution techniques, plethysmographic determination is preferred when evaluating patients complaining of dyspnoea following ARDS.

GAS EXCHANGE
Reduced carbon monoxide transfer factor (TLCO) is the most common pulmonary function abnormality seen in patients recovering from ARDS. Soon after the acute episode 75–100% of patients will have abnormal values. Although some of these patients improve during the first year, 40–80% of those studied had reductions that persisted even after one year. Fortunately, although chronic severe reductions of transfer factor may occur, the degree of abnormality observed is generally mild (Fig 4). Most patients have normal resting arterial blood gas tensions after recovering from ARDS. Exercise, however, may reveal more subtle gas exchange abnormalities. Elliott and colleagues found that 11 of 13 patients (85%) had an alveolar-to-arterial oxygen difference (A–aDO₂) that was normal at rest (measured one month after ARDS) but increased in all seven of those who were exercised. In

**Figure 2** Variation of total lung capacity (TLC) with time in survivors of ARDS. ○ = single values, ● = multiple values.
several studies have found that the proportion of wasted ventilation (Vd/VT) is often increased early in recovery from ARDS. In many patients the Vd/VT improves with time, but a substantial number are left with persistently elevated values. Dead space tends to decrease with exercise, although the degree of decrease is reduced over that generally found in normal subjects. After recovery, shunt fraction may be normal or only mildly elevated, although one patient reported by Buchser et al had a shunt fraction that remained elevated at 15% of the cardiac output more than one year after ARDS.

The failure of TLco to return to normal in most survivors of ARDS contrasts with the improvement in spirometric values and lung volumes in these patients. Low TLco values together with persistent abnormalities in Vd/VT suggest that destruction or obstruction of the pulmonary vasculature may have occurred. There are abundant histological data to indicate that vascular loss does occur in the acute phase of ARDS. Bachofen and Weibel found striking reductions in the numbers of pulmonary capillaries seen in specimens obtained after the first 24 hours of ARDS. Extensive thrombosis of pulmonary arteries has also been shown by both antemortem and postmortem arteriography (fig 5). Snow et al estimated morphometrically that the density of precapillary arterioles was reduced by 50%. Extensive occlusion of the microvasculature by fibrin thrombi and non-thrombotic vascular obstruction caused by intimal proliferation and endothelial cell swelling is also seen in acute ARDS. Early vascular occlusion may correlate with the severity of ARDS and with survival from the acute event. In a study of six patients recovering from ARDS who underwent exercise testing, Buchser calculated a reduced pulmonary capillary blood volume. At this time a complete understanding of the causes of gas exchange abnormalities after ARDS is lacking. There are inadequate data available to conclude that finding these abnormalities in the immediate period after ARDS is predictive of long term pulmonary dysfunction.

Predictors of pulmonary dysfunction

It is difficult to attach prognostic importance to demographic or other patient characteristics that are unrelated to the episode of ARDS. In most studies patient numbers are too small to draw conclusions regarding whether the event associated with ARDS is correlated with outcome. Ghio and colleagues found no relationship between the precipitating cause and long term abnormalities of pulmonary function. Case reports have suggested that patients with ARDS caused by viral pneumonia may be predisposed to developing fibrosis and suffering long term functional abnormalities.

Although several studies have suggested that older age predisposes to persistent abnormality of pulmonary function, Ghio and associates also recently noted that patients younger than 20 had an increased risk of residual dysfunction.

The acute cellular response in ARDS is a neutrophilic alveolitis. Because cigarette smoking also increases the bronchoalveolar lavage neutrophil content, particularly in the setting of chronic bronchitis, smoking might be expected both to contribute to more severe acute disease and to worsen pulmonary function in survivors. Unfortunately this supposition is not supported by the available data. Elliott et al and Peters et al found no significant differences in follow up measurements of TLC, FVC, FEV1, or TLco between smokers and non-smokers, although the maximum improvement in pulmonary function did seem to take longer in smokers.

Nosocomial bacterial pneumonia is common in ARDS and is associated with worse acute pulmonary function and...
with increased mortality. In survivors of ARDS there
is significant differences in local alveolar compliance such
that areas of normal lung (that have normal compliance)
will expand to a greater extent than areas that are injured
(with lower compliances). Although no well designed
trials have investigated whether ventilating with low tidal
volumes can reduce mortality or acute or long term
morbidity in humans, a recent retrospective uncontrolled
study suggests that this may be the case. Hickling and
colleagues reported the results of 50 patients with severe
ARDS who were ventilated with low tidal volumes. The
partial pressure of arterial CO₂ was allowed to rise to a
mean of 60 mm Hg. The mortality in these patients was
only 16%, considerably better than other published re-
sults. Decreased mortality has also been reported using
"permissive hypercapnia" in ventilated patients with
status asthmaticus.

If tidal volume is kept constant, PEEP will increase peak
and mean airway pressure as well as end inspiratory and
end expiratory lung volumes. Accordingly, the level of
PEEP can also cause or contribute to lung injury. Because
the most severe cases of ARDS generally are treated with
higher levels of PEEP to prevent hypoxaemia, it is difficult
to distinguish between the deleterious effect of PEEP and
the effects of ARDS itself.

Most experimental evidence argues that low levels of
PEEP protect the lung from ventilator associated injury.
Webb and Tierney first noted in animals that 5 cm H₂O of
PEEP reduced the amount of oedema caused by ventila-
tion at high inflation pressures (and volumes). This
protective effect has been supported by other investigators
using models of both hydrostatic oedema and increased
permeability oedema. Although PEEP does not reduce lung
water and may actually increase it, it redistributes the
oedema away from alveoli into the interstitium, and
also prevents depletion of surfactant that results from
lung being ventilated at low end expiratory volume.

The level of PEEP has been shown by some to correlate
inversely with long term pulmonary function. Elliott
and coworkers reported that survivors of ARDS with
abnormalities of lung function were more likely to have
received higher levels of PEEP than those with normal
function. In contrast, Peters et al reported that higher
levels of PEEP during the first week of ventilator support
were associated with more normal values of TLC and
FVC measured more than six months after the acute
episode. Patient characteristics, predisposing conditions,
and severity of disease do not seem to explain these
differences.

FiO₂. The level to which FiO₂ must be raised to correct hypoxae-
mia is another marker for the severity of the acute episode.
The effect of oxygen on the course of patients with ARDS
is difficult to ascertain because those with the worst disease
require the most intensive support. In addition, there is no
histological difference between ARDS and oxygen tox-
icity. Amply animal data suggest that hyperoxia can create
or worsen pulmonary injury. In animal models of oleic
acid-induced acute lung injury, breathing 40% or 50% oxygen
causes no additional lung injury while 100% oxygen results in
progressive oedema and dysfunction.

There are obvious methods of examining the effects of
chronic hyperoxia on normal subjects. Because there are
certain species variabilities with regard to susceptibil-
ty to oxygen toxicity, the relevance of animal studies
to patients with ARDS is uncertain. In humans, Van de
Water et al found no significant physiological differences
between healthy individuals breathing 100% oxygen for
6–12 hours and those breathing air. Singer et al reported

EFFECT OF MANAGEMENT OF ARDS ON SUBSEQUENT PULMONARY FUNCTION

Care of patients with ARDS is often described as being
"supportive" in that no specific treatment for the patho-
physiological abnormalities that is, acute lung inflamma-
tion has been described. It is important to consider the
possibility that some aspects of this support, in particular
mechanical ventilation and hyperoxia, may actually con-
tribute to the severity of the acute episode and therefore
potentially affect the degree of pulmonary dysfunction in
the survivors.

LUNG VOLUME AND POSITIVE END EXPIRATORY PRESSURE

Numerous studies in animals have shown that positive
pressure ventilation at high inspiratory pressures causes
cache lung injury. Two important studies showed that
it is the large tidal volumes generated by the increased
inspiratory pressure, rather than the high pressure itself,
that is responsible for the injury. Hernandez et al compared
the effects of ventilating two groups of rabbits with high
peak inspiratory pressures. One group was placed in
full body plaster casts and the second group was not. The
injury produced by high peak inspiratory pressure in the
control group (manifested as increased microvascular perme-
ability) was completely prevented by the plaster cast which
limited the end inspiratory volume. Dreyfuss and coworkers
made similar findings using chest strapping to control inspiratory volume.

The tidal volume required to cause lung injury in
animals with otherwise normal lungs is generally higher
than that used in clinical practice. Smaller tidal volumes
can cause this type of damage in patients with ARDS
because the lung inflammation, oedema and atelectasis are
not homogeneously distributed. Accordingly, there are

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no physiological or clinical difference between patients breathing 100% oxygen for 24 to 48 hours after cardiac surgery and those breathing 40% oxygen. Bronchoalveolar lavage specimens from normal volunteers obtained after breathing 95% oxygen for 17 hours show evidence of capillary leak and effector cell activation, but these changes resolve completely within two weeks of ceasing exposure. In contrast, in patients with irreversible brain damage, breathing 100% oxygen caused a time-dependent deterioration of pulmonary function and progressive hypoxaemia was first noted at 40 hours.

There is no agreement as to whether breathing high inspired oxygen concentrations affects long term pulmonary function in survivors of ARDS. Elliott et al found that the only variable correlating with a reduced TLco was the duration of exposure to an \( F_{\text{IO2}} > 0.6 \). In contrast, Peters et al and Yahav et al found no correlation between the \( F_{\text{IO2}} \) or the duration of oxygen exposure and impairment of pulmonary function.

PEEP is used to try to reduce \( F_{\text{IO2}} \) to a "safe" level, generally \(< 0.7 \) or \( 0.6 \). This approach seems reasonable, although it should be recognised that the effect of chronic hypoxia on acute lung injury has not been defined, the \( F_{\text{IO2}} \) that can be considered "safe" is not known, and PEEP itself may be detrimental. In an attempt to provide adequate oxygenation without using high \( F_{\text{IO2}} \) values or PEEP, investigators have studied extracorporeal membrane oxygenation and haemofiltration. Unfortunately, these modes of support have not been found to alter morbidity or mortality. The prone position may significantly decrease shunt and increase the \( P_{\text{AO2}} \), allowing a reduction in PEEP, or the level of \( F_{\text{IO2}} \), or both in at least 50% of the patients in whom it is used.

Summary and conclusions

Most survivors of ARDS have persistent mild reductions of TLco even as long as a year after their episode. The lung volumes and flows return to normal in most instances, although a subset of patients will have persistent impairment. Both obstructive and restrictive deficits may be seen. This group may be predicted by the degree of acute lung injury assessed by the level of \( F_{\text{IO2}} \), PEEP, and gas exchange abnormality that exists in the first few days.

In the first year after ARDS most physiological abnormalities will improve, but if deficits persist at one year further improvement is unlikely. Although many patients report dyspnoea following ARDS, the symptom does not correlate with abnormalities of pulmonary function.

The possibility that conventional management may augment the degree of acute injury and worsen outcome must be considered. The effects of chronic hypoxia in humans with acute lung injury or those of high levels of PEEP compared with low levels are not known. Exploring new ventilator management strategies while we await more specific treatment directed at the primary problem of acute lung inflammation will hopefully reduce acute mortality as well as acute and chronic morbidity.

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