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# Adult respiratory distress syndrome (ARDS): current management, future directions

## ■ KEY POINTS:

The mortality rate in ARDS ranges from 40% to 60%. Sepsis accounts for at least half of all cases of ARDS, and carries the worst prognosis.

Survivors generally recover a good functional status, with approximately 75% of survivors enjoying normal or nearly normal lung function.

Conventional management is with flow-controlled, volume-cycled ventilation with positive end-expiratory pressure, although critics believe this approach can further damage the lungs through excessive pressure and volume.

Although corticosteroids do not prevent or cure acute ARDS, there is increasing anecdotal evidence that they may be effective in the late (fibroproliferative) phase.

■ **ABSTRACT:** The adult respiratory distress syndrome, marked by severe, refractory hypoxemia, noncardiogenic pulmonary edema, and stiff, noncompliant lungs, demands quick recognition and intensive care. This article reviews the disease process and current and experimental treatments for it.

Almost half of all patients who develop the adult respiratory distress syndrome (ARDS) still die of it, in spite of advances in understanding its cell biology, physiology, and pathology.<sup>1</sup> However, a number of new ideas about supportive management and specific therapies offer hope of reducing the mortality rate in ARDS, long an elusive goal.

## ■ WHAT IS ARDS?

Ashbaugh and coworkers<sup>2</sup> coined the term “adult respiratory distress syndrome” in 1967. Since then, ARDS has become widely recognized as a cause of respiratory failure in medical, surgical, and trauma patients.

However, ARDS is not a new disease or syndrome. For example, Osler,<sup>3</sup> in his 10th edition of *The Principles and Practice of Medicine* (1925), recognized that “uncontrolled septicemia leads to frothy pulmonary edema that resembles serum, not the sanguinous transudative edema fluid seen in dropsy or congestive heart failure.” Without mechanical ventilation or other forms of supportive therapy found in the modern intensive care unit, nearly all of such patients in Osler’s time had a rapidly fatal outcome.



TABLE 1

### COMMON CAUSES OF THE ADULT RESPIRATORY DISTRESS SYNDROME

#### Direct lung injury

Aspiration of gastric contents  
Inhalation of a toxic gas  
Pneumonia  
Near-drowning  
Lung contusions (thoracic trauma)

#### Systemic processes

Sepsis (50% of all cases)  
Nonthoracic trauma  
Acute pancreatitis  
Multiple blood transfusions  
Fat embolism  
Heroin abuse  
Shock

### Pathophysiology

ARDS usually appears within 12 to 72 hours of an identifiable clinical event such as a direct lung injury or a systemic process (TABLE 1), and progresses through three phases.

**Exudative phase.** In the first few days, damage to the alveolocapillary membranes allows fluid and proteins to leak into the alveolus, resulting in pulmonary edema, atelectasis, and influx of acute inflammatory cells (including polymorphonuclear neutrophils).

**Proliferative phase.** Next, in the proliferative (or organizing or reparative) phase, myofibroblasts proliferate and collagen begins to be deposited in the pulmonary interstitium.

**Fibrotic phase.** In this last phase, more collagen is deposited and fibrosis occurs. Inflammatory cells are often absent, and pulmonary edema may be minimal.

### Clinical findings

Roentgenograms of the chest reveal diffuse and bilateral lung infiltrates (due to noncardiogenic or “capillary leak” pulmonary edema). The lungs are stiff and poorly compliant. Severe hypoxemia occurs, due to shunting, in which blood passes the damaged alveoli without being oxygenated (FIGURE).

The Joint European-American Consensus Conference on ARDS<sup>4</sup> proposed defining ARDS as:

- Oxygenation impairment ( $\text{PaO}_2 \leq 200$ ), regardless of positive end-expiratory pressure (PEEP) level, or a  $\text{PaO}_2/\text{FIO}_2 \leq 200$ .
- Bilateral infiltrates compatible with pulmonary edema seen on the frontal chest radiograph.
- A pulmonary artery occlusion pressure of 18 mm Hg or less (or no clinical or radiographic evidence of left atrial hypertension, if the pulmonary artery occlusion pressure is not measured).

Because ARDS is the severe manifestation of a spectrum of lung injury that begins with an early and subclinical phase, the term “acute lung injury” has been proposed to describe clinically recognized lung injury that is less severe or earlier than full-blown ARDS. The Consensus Conference definition of acute lung injury includes the same radiographic and pulmonary artery occlusion pressure criteria as for ARDS, but allows for a less severe oxygenation impairment ( $\text{PaO}_2/\text{FIO}_2 \leq 300$  regardless of the amount of PEEP).<sup>4</sup>

### PROGNOSIS

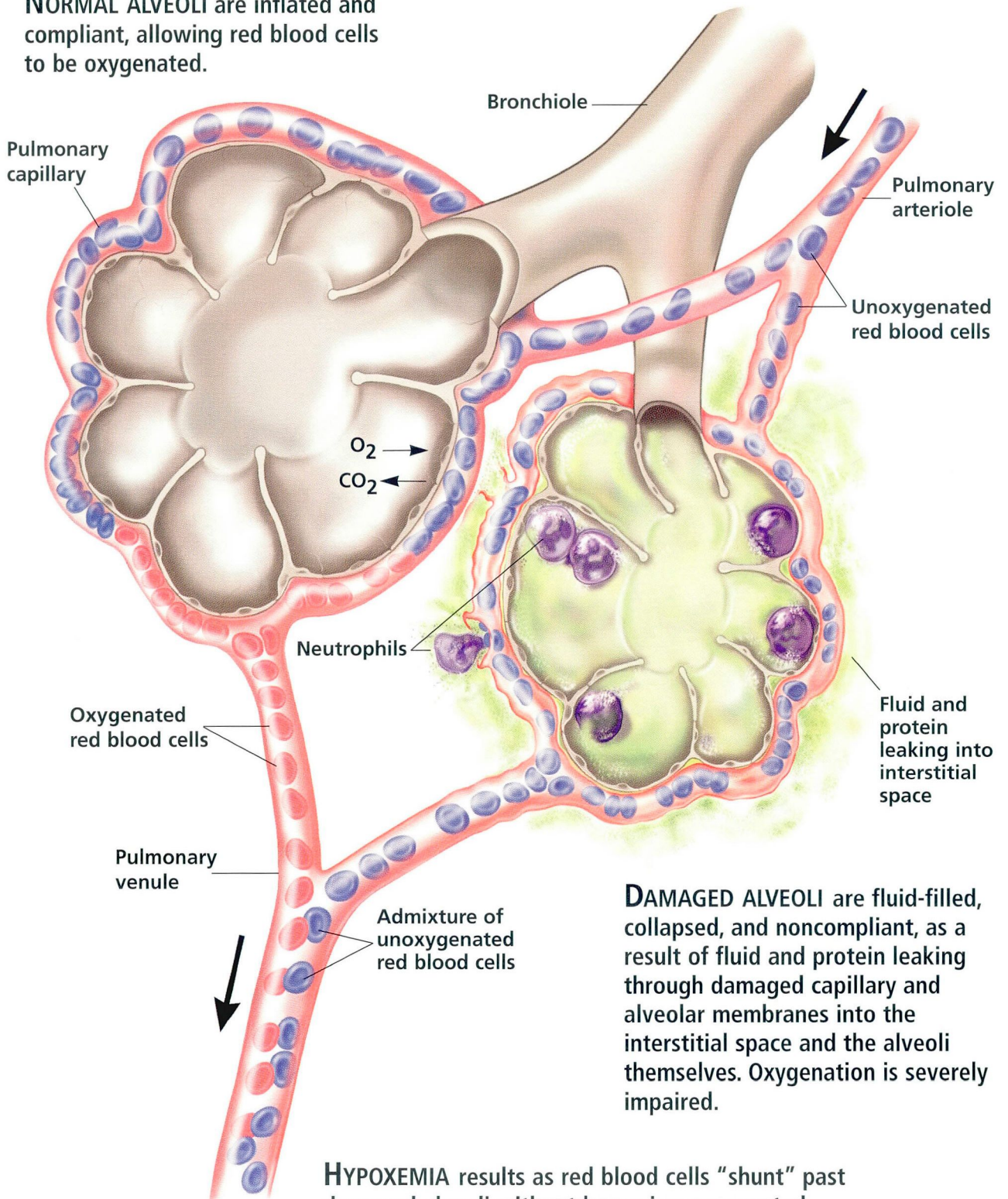
The mortality rate in ARDS has declined to about 40% in recent years, presumably due to improved general supportive care.<sup>5</sup> Most experts feel that this figure is close to the maximum survival that can be achieved without specific new therapies for ARDS. Perhaps 15% to 20% of the deaths result from unmanageable and refractory respiratory failure (severe hypoxemia and/or progressive hypercapnia with respiratory acidosis).<sup>6</sup> Most of the other deaths result from dysfunction of other organs (eg, sepsis syndrome, systemic inflammatory response syndrome, renal failure, hepatic failure, coagulopathy). Nearly all of the deaths occur within 30 days of the onset of the syndrome.

The mortality rate varies according to the cause. For example, patients with sepsis-induced ARDS generally have the worst prognosis, whereas patients with pancreatitis or fat embolism as the predisposing factor generally have the best. ARDS due to gastric aspiration has an intermediate mortality rate.

The mortality rate has decreased to 40%, possibly the limit without specific new therapies

# How shunting causes hypoxemia in ARDS

**NORMAL ALVEOLI** are inflated and compliant, allowing red blood cells to be oxygenated.



**DAMAGED ALVEOLI** are fluid-filled, collapsed, and noncompliant, as a result of fluid and protein leaking through damaged capillary and alveolar membranes into the interstitial space and the alveoli themselves. Oxygenation is severely impaired.

**HYPOXEMIA** results as red blood cells "shunt" past damaged alveoli without becoming oxygenated.



TABLE 2

### COMPONENTS OF THE LUNG INJURY SCORE\*

Finding	Value
<b>Chest roentgenogram score</b>	
No alveolar consolidation	0
Alveolar consolidation in 1 quadrant	1
Alveolar consolidation in 2 quadrants	2
Alveolar consolidation in 3 quadrants	3
Alveolar consolidation in 4 quadrants	4
<b>Hypoxemia score (PaO<sub>2</sub>/FIO<sub>2</sub>)</b>	
≥ 300	0
225–299	1
175–224	2
100–174	3
≤ 100	4
<b>Respiratory system compliance score (when ventilated) (mL/cm H<sub>2</sub>O)</b>	
≥ 80	0
60–79	1
40–59	2
20–39	3
≤ 19	4
<b>Positive end-expiratory pressure (PEEP) score (when ventilated) (cm H<sub>2</sub>O)</b>	
≤ 5	0
6–8	1
9–11	2
12–14	3
≥ 15	4
(The final value is obtained by dividing the aggregate sum by the number of components that were used)	
<b>Severity</b>	<b>Score</b>
No injury	0
Mild to moderate injury	0.1–2.5
Severe injury (ARDS)	> 2.5

\*From Murray et al, reference 7

The NIH is setting up an ARDS network to study new therapies

Age is also an important predictor of outcome; patients older than 60 years have the highest mortality rate.

Survivors generally recover a good functional status. In fact, approximately 50% of survivors enjoy essentially normal lung function, 25% have mild impairment, 20% have moderate impairment, and only 5% have severe impairment. Most of the recovery from

ARDS occurs within the first 6 to 12 months; pulmonary function tests obtained 12 months after recovery generally indicate the patient's new baseline.

Murray and colleagues<sup>7</sup> have proposed a scoring system for acute lung injury and ARDS (TABLE 2). Although it has not been validated as a predictor of outcome, this system provides a quantitative method for grading and following serial pathophysiologic changes in patients with ARDS.

### CONVENTIONAL TREATMENT FOR ARDS

No specific therapy for ARDS currently exists. The principles of supportive management are to:

- Identify and treat the underlying cause.
- Give mechanical ventilation with PEEP.
- Maintain adequate cardiac output and oxygen delivery.
- Give general supportive care (nutrition, avoidance of nosocomial infections).

**Ventilator therapy** traditionally aims to maintain normal arterial blood-gas values by using flow-controlled, volume-cycled ventilation, tidal volumes of 10 to 15 mL/kg, and the minimal PEEP level (usually about 8 to 15 cm H<sub>2</sub>O) that provides an adequate PaO<sub>2</sub> (≥ 55 to 60 mm Hg) at a “nontoxic” FIO<sub>2</sub> (≤ 0.6).

Using PEEP has apparently reduced the number of ARDS deaths caused by refractory respiratory failure (severe hypoxemia or severe hypercapnia and respiratory acidosis). Now, refractory respiratory failure causes only about 16% of ARDS deaths; the underlying condition accounts for most deaths occurring within the first 3 days of the syndrome, and sepsis or multiple organ dysfunction syndrome or both account for most deaths thereafter.<sup>6</sup> Thus, PEEP appears to have primarily affected the cause and time of deaths (preventing early deaths due to respiratory failure), but has not reduced overall mortality. Further, PEEP does not prevent or cure ARDS.

## ■ EXPERIMENTAL TREATMENT OF ARDS

To investigate the potential role of new specific therapies in the management of ARDS (TABLE 3), the National Institutes of Health (NIH) recently selected 10 centers (including the Cleveland Clinic) to constitute a treatment evaluation network (TABLE 4). Enrollment of patients in the initial trials began in 1996, and trials are planned to extend through 2000.

### Corticosteroids

Large, multicenter, randomized controlled trials in the late 1980s demonstrated that corticosteroids do not improve the outcome in sepsis or acute ARDS.<sup>8,9</sup> For example, Bernard and colleagues<sup>8</sup> found that, in patients with acute ARDS of less than 24 hours' duration, methylprednisolone (30 mg/kg every 6 hours for 24 hours) had no measurable effect on gas exchange, total thoracic compliance, pulmonary artery pressure, radiographic appearance, reversal of ARDS, or the mortality rate (approximately 60% in both the treatment and placebo groups).

Although corticosteroids do not prevent or cure acute ARDS, there is increasing anecdotal evidence that they may be effective in the late (fibroproliferative) phase.<sup>10</sup> This putative benefit requires confirmation in randomized controlled trials. One such trial is now underway under the auspices of the NIH ARDS network.

### Inhaled nitric oxide

Nitric oxide was identified in 1987 as an endothelium-dependent relaxing factor. Preliminary uncontrolled reports in severe ARDS suggested that inhalation of low concentrations of nitric oxide reduces intrapulmonary shunting and pulmonary hypertension.<sup>11,12</sup>

The pulmonary vasodilatation produced by nitric oxide inhalation tends to be most pronounced in well-ventilated regions of the lung, thereby "stealing" perfusion from relatively unventilated regions. This reduces intrapulmonary shunting and improves systemic arterial oxygenation. Further, the vasodilator effect remains local, because nitric oxide is rapidly inactivated by binding to hemoglobin. Therefore, the pulmonary circulation is selectively vasodilated, and the systemic circulation remains relatively unaffected.

Thus, inhaled nitric oxide has theoretical

TABLE 3

### EXPERIMENTAL TREATMENTS FOR THE ADULT RESPIRATORY DISTRESS SYNDROME

Corticosteroids (for late or fibroproliferative ARDS)

Inhaled nitric oxide

Surfactant replacement therapy

"Lung-protective" ventilator strategies

(not all mutually exclusive)

Low tidal volume

Pressure-controlled inverse ratio ventilation

Permissive hypercapnia

Extracorporeal gas exchange

Liquid ventilation (with perflubron)

Fluid restriction, diuresis

Anti-inflammatory agents

Ketoconazole

Prostaglandin E<sub>1</sub>

Anti-cytokine therapies (eg, anti-tumor necrosis factor)

Antioxidant therapies (eg, *N*-acetylcysteine)

Nonsteroidal anti-inflammatory agents

Antiproteases

Lysophylline

TABLE 4

### MEDICAL CENTERS PARTICIPATING IN THE NATIONAL INSTITUTES OF HEALTH ADULT RESPIRATORY DISTRESS SYNDROME NETWORK

Duke University, Durham, NC

Johns Hopkins University, Baltimore, Md

The Cleveland Clinic Foundation

University of California at San Francisco

University of Colorado, Denver

University of Michigan, Ann Arbor

University of Pennsylvania, Philadelphia

University of Utah, Salt Lake City

University of Washington, Seattle

Vanderbilt University, Nashville, Tenn

Corticosteroids may be effective in late ARDS

advantages over other currently available vasodilators such as calcium channel blockers, which tend to worsen shunting by overriding hypoxic pulmonary vasoconstriction and cause systemic hypotension because of their nonselective effect on the systemic circulation. Tachyphylaxis to nitric oxide inhalation has not been observed in short-term studies.



Controlled clinical trials are now in progress to test the efficacy and safety of inhaled nitric oxide therapy.

### Surfactant replacement therapy

Studies have established that surfactant replacement therapy improves pulmonary function and reduces mortality in premature infants with the respiratory distress syndrome.<sup>13</sup> Two surfactant products are approved and marketed for use in infants: Exosurf (a totally synthetic surfactant) and Survanta (a modified natural bovine surfactant). These appear roughly equally effective in treating the infant respiratory distress syndrome.

Unlike the infant respiratory distress syndrome, ARDS does not have surfactant depletion as its underlying pathophysiologic feature. However, patients with ARDS do have quantitative and qualitative abnormalities of surfactant that likely perpetuate the physiologic abnormalities (shunt hypoxemia, reduced lung compliance) seen in ARDS.

Preliminary controlled trials suggested that Exosurf (delivered via a nebulizer) and Survanta (delivered by bolus installation) improve physiologic function and decrease mortality in acute ARDS.<sup>13</sup> However, a recent, large multicenter trial of nebulized Exosurf in acute ARDS was discontinued because of lack of efficacy after approximately 580 patients were enrolled; the mortality rate in both the placebo and the treated groups was 41% at 30 days.<sup>14</sup>

Further studies will be necessary to elucidate what role, if any, surfactant therapy has in the treatment of ARDS. A strong theoretical foundation supports its use. Clinical efficacy may depend on the timing and duration of therapy, the dose and delivery mechanism, and the product formulation (eg, whether it contains surfactant-associated proteins).

In addition to reducing alveolar surface tension (thereby improving lung compliance and reducing intrapulmonary shunting), surfactants may have other, unanticipated properties that may be of substantial therapeutic benefit. For example, pretreatment or concur-

rent treatment with surfactants markedly reduces mortality in a rabbit model of hyperoxic lung injury.<sup>13</sup>

We demonstrated in our laboratory that surfactants decrease the release of inflammatory cytokines (tumor necrosis factor and interleukins 1, 6, and 8) from normal alveolar macrophages activated by endotoxin and other stimuli.<sup>15,16</sup> This finding has potential clinical significance because bronchoalveolar lavage studies reveal high concentrations of inflammatory cytokines in most patients with ARDS, even in the absence of elevated circulating levels, suggesting that local production occurs in the lung, and because these inflammatory cytokines (especially tumor necrosis factor and interleukin-1) are strongly implicated in the organ dysfunction and tissue injury of sepsis and ARDS.

### Unconventional ventilator management

Several lines of evidence suggest that the conventional ventilator management of ARDS patients may, under certain circumstances, superimpose an iatrogenic lung injury.<sup>17</sup> This may occur in part because lung injury in ARDS is relatively nonuniform, despite the diffuse bilateral infiltrates typically seen on the chest roentgenogram. Large tidal volumes (10 to 15 mL/kg) may overdilate the small fraction of relatively normally compliant lung that is still capable of gas exchange, thereby inflicting "volutrauma."

Alveolar volume cannot be measured directly, but can be indirectly assessed by estimating transalveolar pressure at end-inspiration. The safe upper limit of end-inspiratory transalveolar pressure (the difference between end-inspiratory alveolar and pleural pressures) probably does not exceed 30 to 35 cm H<sub>2</sub>O, as determined in experiments in animals.<sup>17</sup> This is of interest, since this is the same range of transalveolar pressure that is associated with total lung capacity in humans with normal lungs. Thus, maintaining a transalveolar pressure less than 30 cm H<sub>2</sub>O is probably safe. In practice, pleural pressure is rarely measured, and therefore transalveolar pressure is not directly calculated. End-inspiratory alveolar

A lung-protective strategy is being tested

pressure is approximated by the inspiratory plateau pressure, which can be measured. This provides only an indirect assessment of transalveolar pressure, since a poorly compliant chest wall (eg, after burns, extensive surgery, or trauma) may cause inspiratory plateau pressure to significantly overestimate true transalveolar pressure.

Several strategies have been proposed to reduce mechanical ventilation-induced lung injury in ARDS.

**Pressure-controlled inverse-ratio ventilation (PC-IRV)** may protect the lungs by avoiding high peak and static (plateau) inspiratory airway pressures: the ventilator slowly delivers inspiratory volume until a preset maximum pressure is reached. This technique has disadvantages however. Many patients must be deeply sedated or paralyzed. Further, hypercapnia often results, because of the low tidal volume. Since modest levels of respiratory acidosis may be well tolerated without apparent adverse physiologic consequences, clinicians may elect to allow this acidosis to persist (“permissive hypercapnia”), rather than increasing the minute ventilation (the respiratory rate times the tidal volume), which may damage the lungs. If the degree of acidosis is worrisome, bicarbonate can be given. Most authorities recommend bicarbonate therapy if the pH is less than 7.15, and some would also advocate its use for a pH of 7.15 to 7.25. Another consequence of decreased minute ventilation with PC-IRV may be a reduction in PaO<sub>2</sub>, requiring an increase in inspired oxygen and/or PEEP. Thus, the strategies of PC-IRV and permissive hypercapnia have many trade-offs, and the overall clinical benefit needs to be evaluated in careful trials.

In this regard, a recent study by Amato and coworkers<sup>18</sup> is noteworthy. These investigators tested a ventilatory strategy to minimize “cyclic parenchymal stretch,” which involved two facets. First, cyclic reopening of collapsed alveoli was (hypothetically) prevented by setting the PEEP level above the lower inflection point of the pressure-volume curve. This requires sedation and sometimes paralysis, along with a somewhat time-consuming protocol, and is not routinely performed in most clinical settings. Second, alveolar overdistention at end-inspiration was avoided through a low tidal volume, PC-IRV protocol. Compared with conventional ventilation, this combined lung-protective method led to more rapid weaning from mechanical

ventilation and fewer deaths from progressive respiratory failure, but no change in all-cause mortality. However, this study involved a relatively small number of patients (28), and the results require confirmation in larger trials. The NIH ARDS network is currently conducting a randomized trial of a “low stretch” ventilatory protocol that will enroll several hundred patients.

**Extracorporeal gas exchange.** The lung-protective strategy can be taken even further through techniques that combine “lung rest” with intracorporeal or extracorporeal gas exchange. For example, Morris and colleagues<sup>19</sup> have evaluated the concept of low-frequency positive-pressure ventilation with extracorporeal CO<sub>2</sub> removal in a study in 40 patients with severe ARDS. Unfortunately, at 30 days, the survival rate was no better in the 21 patients who received the experimental therapy (33%) than in the 19 patients who received conventional therapy (42%). Also, the intensity of care required to maintain arterial oxygenation was similar in both groups (2.6 and 2.6 PEEP changes per day; 4.3 and 5.0 FIO<sub>2</sub> changes per day).

Full extracorporeal membrane oxygenation (ECMO, or extracorporeal life support—ECLS) failed to show a survival benefit when tested in a randomized trial in the late 1970s. However, with more modern technology, the risks of ECMO appear to be decreasing. A few centers, including the Cleveland Clinic, currently use ECMO as a salvage therapy in carefully selected patients with life-threatening respiratory failure without multiple organ dysfunction; anecdotal evidence suggests that this approach may save some lives.<sup>20</sup>

**Liquid ventilation** with perflubron is an exciting new development.<sup>21,22</sup> This approach may be advantageous because of a number of mechanisms, including recruitment of severely damaged and debris-filled dependent lung units (“liquid PEEP” effect) and reduction in lung inflammation. Follow-up trials are now being designed to more fully evaluate the potential role of this method.

### Other therapies and concepts

**Fluid restriction, diuresis.** Data from Humphrey and colleagues<sup>23</sup> and Mitchell and colleagues<sup>24</sup> suggest that fluid restriction and diuresis should be pursued during the first few days of ARDS, even in patients who are initially euvolemic. This strategy requires careful attention to cardiac function (including oxygen delivery) and renal function.

A few centers use extracorporeal life support as salvage therapy



**Supranormal oxygen delivery.** In contrast, Shoemaker and colleagues<sup>25,26</sup> argue that "supranormal" oxygen delivery (eg, > 600 mL/min/m<sup>2</sup>) is a critical and primary goal in patients with ARDS or at risk for developing it. However, recent randomized trials indicate that hemodynamic therapy aimed at achieving supranormal values for cardiac index and oxygen delivery (by utilizing dobutamine, for example) does not reduce morbidity or mortality in critically ill patients.<sup>27-29</sup>

Additional investigational therapies include antioxidants (eg, *N*-acetylcysteine)<sup>30</sup> and antagonists of membrane phospholipid metabolites such as thromboxane, leukotrienes, and platelet activating factor. Preliminary data from large multicenter trials also indicate that antagonists of tumor necrosis factor or interleukin-1 may help prevent ARDS in patients with sepsis, or help improve the resolution of established ARDS. ■

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