Advances in the Management of Acute Respiratory Distress Syndrome

Protective Ventilation

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The approach to mechanical ventilation has been revolutionized by new insights into the pathogenesis of respiratory failure in acute respiratory distress syndrome (ARDS). Concepts such as low-volume ventilation, permissive hypercapnia, inverse ratio ventilation, best and intrinsic positive end-expiratory pressure, airway shear, pressure volume curves, inflection points, and prone positioning have radically transformed thinking about ventilator management. Since 1966, more than 8000 ARDS-related publications have appeared. Studies highlighting the experimental basis for innovations in mechanical ventilation are presented. Selected clinical series that exemplify the use of these new strategies are reviewed, to demonstrate how key experimental and clinical research has altered our understanding about what works, and why. Mismanagement of mechanical ventilation causes lung injury and increases mortality. The strategy of protective ventilation has provided the first substantial reduction of mortality in the history of ARDS.

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The observation that trauma and sepsis might exert a remote effect on pulmonary function was proposed in case reports dating as far back as World War I. However, it was not until the Vietnam era that this association came to be recognized as a discrete clinical entity. In 1967, the term "acute respiratory distress syndrome" (ARDS) was introduced into the medical literature. The initial series remains remarkably representative of this syndrome's signal aspects. The 12 patients were a mixed medical and surgical population. Major trauma was the leading diagnosis in 7 of these patients. The original criteria for the syndrome included the acute onset of severe respiratory distress, cyanosis refractory to oxygen therapy, diffuse infiltrates on chest radiograph, and decreased lung compliance. Numerous causes were postulated, resulting in an equally diverse spectrum of interventions that included antibiotics, steroids, diuretics, digitalis, pressure-cycled ventilation, and positive end-expiratory pressure (PEEP). The mortality rate in this series was 58%.

During the intervening 3 decades, there have been thousands of publications that encompass every aspect of ARDS. Interest remains high because ARDS is a significant source of morbidity, mortality, and expenditure among critically ill patients. It is estimated that there are approximately 150,000 cases of ARDS in the United States annually. Mortality falls between 40% and 50%. There have been isolated reports of improved outcome. However, a recent analysis of 101 clinical series from 1967 to 1994 was unable to demonstrate a significant trend toward overall reduction in mortality when comparing those before 1990 (53%) with those after 1990 (52%).

Among survivors, hospitalization is prolonged, morbidity is high, and the cost of care prohibitive. As a consequence, extensive efforts have been directed at improving outcome. Recent insights into the pathogenesis of ARDS have given rise to refinements in traditional therapy and innovative new strategies. However, the myriad definitions and etiologies for ARDS have precluded an accurate determination of incidence or mortality. With these issues in mind, the American-European...
Consensus Conference on ARDS was convened in 1994. A simplified definition for ARDS was formulated as follows:

- Acute onset of symptoms
- Ratio of PaO₂ to fraction of inspired oxygen (PaO₂/FIO₂) ≤ 200 mm Hg
- Bilateral infiltrates on chest x-ray film
- Pulmonary artery wedge pressure ≤ 18 mm Hg

or

No clinical signs of left atrial hypertension

The Consensus Conference also addressed mechanisms, risk factors, prevalence, outcomes, and ways to promote coordination of clinical studies. The guidelines will facilitate assessment of new treatment modalities and outcomes. The second part of the Consensus Conference report, focusing primarily on therapy, was recently published. Part 2 also addressed the resolution of acute lung injury and returned to the important issue of coordinated clinical studies.

Currently, areas of intensive research include new ventilator strategies, intracorporeal and extracorporeal oxygenation techniques, and new pharmacologic approaches, such as inhaled agents and antimediator therapy. Some interventions are directed at improving supportive care, while others are designed to target the cellular events that give rise to ARDS. From the clinician’s perspective, these recent advances in the treatment of ARDS fall into 2 categories: (1) those that can be put into practice immediately using currently available ventilators, monitoring devices, and pharmacologic agents; and (2) those that use devices or agents not widely available, or that are experimental in nature. The most important contributions of immediate utility to the clinician are in the realm of mechanical ventilation.

NEW VENTILATOR STRATEGIES

By definition, patients with ARDS are profoundly hypoxic and require mechanical assistance for gas exchange. The thinking about how to ventilate patients with ARDS has evolved as we have come to better understand the disease process. A major conceptual leap has been the recognition that total lung volume is reduced in patients with ARDS. The reduction may be profound—in some cases greater than 50%. Ventilation with a “normal” tidal volume may approach total lung capacity and lead to excessively high airway pressures. Barotrauma is a misnomer, since it is now known that the resulting lung injury is actually due to hyperinflation, or volutrauma. In an experimental model that studied the effects of pressure and volume on lung injury in a paired fashion, animals subjected to high airway pressures but normal tidal volumes were similar to control animals. Those exposed to high tidal volumes and high airway pressures showed gross edema and increased lung weight with associated cellular damage. Overdistention has been shown to be additive or even synergistic with a toxin-induced pulmonary endothelial injury at high tidal volumes.

A second conceptual leap has been the understanding that although ARDS is a diffuse process, it is heterogeneous, ie, not all lung parenchyma is uniformly affected. Areas of relatively normal lung and diseased lung are interspersed, and there are regional differences in ventilation. It has long been known that higher peak inspiratory pressures (PIPs), positive end-expiratory pressures (PEEPs), and tidal volumes lead to a higher incidence of clinical barotrauma, such as pneumothorax and pneumomediastinum. However, damage from overdistention may be far more insidious, and ultimately more lethal. This is particularly true since the more normal alveoli are less stiff and more easily stretched, making them preferentially more susceptible to injury by overinflation. It follows that strategies to limit tidal volume and airway pressure should be advantageous. These include the routine use of smaller tidal volumes, permissive hypercapnia, pressure-limited ventilation, and inverse ratio ventilation. New insights into regional underventilation have also led to a reevaluation of the concept of “best PEEP” and the introduction of prone ventilation.

SMALLER TIDAL VOLUMES AND PERMISSIVE HYPERCAPNIA

One of the simplest ways to reduce alveolar overdistention is to reduce the tidal volume. The effect on airway pressure is immediate. Conventional teaching would then dictate an increase in the respiratory rate to maintain a normal carbon dioxide (CO₂) level. Up to a point, such compensation is possible. However, as the rate of mechanical ventilation rises (>25-30 breaths per minute), there may be insufficient time for the previous breath to be fully expired before the next is delivered. This results in breath stacking. The physiologic effect is the buildup of intrinsic PEEP (also called auto-PEEP or inadvertent PEEP). Like deliberately applied PEEP, inadvertent PEEP can have adverse hemodynamic and respiratory side effects. Unlike therapeutic PEEP, the dose of inadvertent PEEP cannot be controlled. Higher ventilator rates, even in the absence of intrinsic PEEP, may impair cardiac function. As rate increases, more of each breath cycle is spent in inspiration, at intrathoracic pressures unfavorable to venous return, ultimately affecting cardiac output. An approach that helps to avoid such pitfalls is to simply let the CO₂ rise: permissive hypercapnia.

The technique of permissive hypercapnia is now an accepted practice. Reduction of tidal volume and minute ventilation, with subsequent rise in CO₂, can be implemented with any volume-cycled ventilator. Numerous clinical series have shown that high levels of PCO₂ can be tolerated and that this technique may improve survival. Clearly, some patients are not candidates for permissive hypercapnia. In patients with severe closed head injury, CO₂ should be maintained at mildly reduced or normal levels. For patients with a rapidly progressing metabolic acidosis, the deliberate addition of a respiratory component may result in a pH that becomes unacceptable low.

How high can the CO₂ be allowed to rise, and how fast? There
are a number of reports of CO₂ levels in excess of 100 mm Hg, while averages run in the 50- to 77-mm Hg range. Associated pH values have generally been in the range of 7.2 to 7.3, although levels below 7.0 are recorded. Some series report the use of sodium bicarbonate to keep pH above 7.2, and extracorporeal CO₂ removal has also been used, but there is no evidence that these interventions offer a survival advantage. A gradual increase of CO₂ over a period of 10 to 12 hours has been advocated to permit intracellular adjustment to alterations in pH. To determine whether a more rapid rise in CO₂ was detrimental, Thorens and colleagues induced hypercapnia in 11 mechanically ventilated patients over a 30- to 60-minute period and maintained this state for 2 hours. Average Pco₂ rose from 40 to 59 mm Hg and average pH fell from 7.4 to 7.26. Mean arterial pressure, pulmonary vascular resistance, and oxygen consumption did not change. Changes were noted in systemic vascular resistance (decrease from 865 to 648 dyne · s · cm⁻²), cardiac index (increase from 4.0 to 4.7 L/(min · m²), and oxygen saturation (SaO₂) from 93% to 90%.

Carvalho and coinvestigators also studied the hemodynamic effects of rapidly induced hypercapnia in 25 patients receiving relatively high doses of PEEP (average, 16 cm H₂O). The initial precipitous rise in Pco₂ (35 mm Hg to 58 mm Hg) was accompanied by several hemodynamic changes. Heart rate, cardiac index, wedge pressure, and mean pulmonary artery pressure all rose rapidly, and systemic vascular resistance fell. The change in the latter 2 parameters was most marked, approaching 25% of baseline. (Because PEEP was increased simultaneously to 6 to 16 cm H₂O, part of the increase in central pressures might be due to higher PEEP.) By 36 to 48 hours, the acute hemodynamic changes had resolved. With intact renal function, pH also corrected to baseline within the same time frame. The authors did not note any adverse side effects. These results demonstrate that an almost instantaneous rise in CO₂ is well tolerated in patients with normal cardiac reserve and an appropriate volume status.

Since smaller tidal volumes represent the foundation of permissive hypercapnia, is there a size where they are harmfully small? The answer appears to be yes. If tidal volume is so reduced that small airways close and open with every breath (“tidal recruitment,” “airway winking”), shear injury can result. Experimentally, this phenomenon has been reported at tidal volumes of less than 4 to 5 mL/kg. In the clinical setting, the minimum volume at which airway shear occurs is variable. The level of PEEP applied and the phase (early vs late) of ARDS have a bearing on the potential for shear injury. Although it is difficult to set an absolute lower limit for tidal volume, 4 mL/kg has been commonly suggested. A pressure-volume curve can be used to more accurately detect the presence of airway shear. PEEP can be adjusted to attenuate or eliminate airway injury (see the “Best PEEP and Inflection Points” section).

**PRESSURE-LIMITED VENTILATION**

Eleven of the 12 patients in the original series of Ashbaugh et al were initially managed with pressure-cycled ventilators, which proved unsatisfactory because adequate tidal volumes could not be provided. This experience underlines the limitation of pressure-cycled ventilators in the treatment of ARDS. Due to the stiffness of the lungs and fluctuations in airway pressure, minute ventilation is not predictable. Using the current volume-cycled ventilator, the clinician can provide “volume-assured” pressure-limited ventilation by limiting tidal volume and adjusting PEEP appropriately. In this situation, the bedside personnel become part of the feedback loop by adjusting the ventilator and monitoring minute ventilation. Although effective, the process is very labor intensive. A better solution is offered by contemporary ventilators that have the ability to simultaneously control airway pressures and adjust delivery to ensure a set minute ventilation. Thus they incorporate the most desirable features of both volume and pressure-control ventilation.

In one prospective randomized trial comparing pressure-limited and volume-controlled ventilator modes in 27 patients with acute hypoxemia, the pressure-limited group exhibited a significant improvement in static lung compliance over the 72-hour monitoring period, while compliance in the volume-controlled group fell. Survivors in the pressure-limited group were also extubated more rapidly. Mortality was decreased in the pressure-limited group (56% vs 64% in the volume-controlled group), but this did not attain statistical significance. While the numbers are small, these results support limiting airway pressure, regardless of whether it is the ventilator or the bedside provider who provides the feedback control.

**INVERSE RATIO VENTILATION**

Another technique that has been proposed to reduce airway pressure is inverse ratio ventilation. In the spontaneously breathing patient with normal airways, the ratio of time spent in inspiration to that in expiration (I/E ratio) is 1:2. During mechanical ventilation, I/E times are controlled by the flow velocity with which the tidal volume is given (determining I time) and the rate. By slowing the flow velocity, the time taken to deliver the tidal volume is lengthened. As inspiratory time lengthens, the time remaining for expiration shortens. The ratio of I/E times within any one respiratory cycle changes so that inspiratory and expiratory time are equal, or even reversed: inverse ratio.

There are 2 potentially beneficial effects. First, because the tidal volume is delivered more slowly, the driving pressure does not need to be so high and PIP is reduced. Second, the prolonged inspiratory time may improve oxygenation in some patients. The initial rush of enthusiasm for inverse ratio ventilation has been tempered by the realization that mean rather than peak airway pressure is the more critical parameter in barotrauma. Inverse ratio ventilation typically causes a decrease in the mean pressure. Lessard and colleagues compared pressure-controlled inverse ratio ventilation...
at 2:1 and 3:1 to pressure-controlled and volume-controlled ventilation at 1:2 in 9 patients with severe ARDS. There was no advantage in respiratory mechanics or gas exchange. Mean airway pressures were higher at inverse ratio of 2:1 (27 cm H2O) and 3:1 (31 cm H2O) compared with a 1:2 ratio (22 cm H2O). In this small group, oxygenation did not improve with inverse ratio ventilation.

Inverse ratio ventilation has several known adverse effects. Patients do not tolerate reversals of the I/E ratio well. Ratios of greater than 1.5:1 must usually be accompanied by neuromuscular blockade. Additionally, as the time spent for inspiration increases, expiratory time is shortened, creating the potential for intrinsic PEEP. At inversions greater than 2:1, some amount of auto-PEEP is liberated, which has less effect on mean airway pressure. At best, it would seem that there is not great benefit in the use of inverse ratios up to 1.5:1 and several good reasons not to deliberately invert the I/E ratio beyond this. It should be appreciated that inverse ratio ventilation can inadvertently occur with mechanical ventilation at rates in excess of 25 to 30 ventilator breaths per minute, as in the tachypneic patient on assist-control ventilation.

BEST PEEP AND INFLECTION POINTS

In the original series,1 PEEP was the only therapeutic intervention that seemed to hold promise for the broad spectrum of patients with ARDS. Over the last 3 decades, PEEP has been a fundamental adjunct in ARDS. It is known that PEEP improves oxygenation by decreasing pulmonary shunt and dead space ventilation, often permitting a decrease in the FiO2. Recent refinements in our understanding of how PEEP works have resulted in the use of PEEP to prevent airway shear injury, particularly in the setting of small volume ventilation. Thus, the choice of a “best PEEP” should be based on consideration of both oxygenation and lung mechanics.

Despite the current emphasis on ventilator-related lung trauma, it is important not to lose sight of the fact that oxygen can be toxic to the lungs. Reports of oxygen-mediated lung damage appear as far back as the 1920s.37 In 1967, Nash and colleagues38 reported the pathologic changes found post mortem in 70 patients ventilated on an FiO2 of 90% to 100%. The incidence of fibrin membranes was double that of a control group (approximately 30% vs approximately 15%). Interstitial edema and fibrosis was present in 78% in the subgroup with prolonged exposure (>10 days). There was also a marked increase in alveolar cell hyperplasia in the long-term, high FiO2 group. All these changes were similar to those found in animals that died from acute oxygen toxicity.

Three years later, Barber et al39 studied the short-term effects of 100% oxygen in 10 patients with isolated fatal closed head injury. Five patients were ventilated on room air, and 5 on 100% oxygen, for a period of 72 hours. By 41 hours, the 100% oxygen group was significantly more hypoxic than the room air group. Chest radiographs of every patient receiving 100% oxygen showed evidence of diffuse infiltrates and volume loss, beginning as early as 20 hours after institution of therapy. This is the only comparative human study in the literature, but it clearly documents the profound effects of 100% oxygen after a relatively short exposure. These results, as well as other experimental and epidemiological data, lead to the recommendation that an FiO2 of greater than 60% for longer than 3 days be avoided whenever possible. Oxygen saturations in the low 90s to high 80s are acceptable in most patients. PEEP helps to minimize oxygen-mediated lung damage by enabling the use of lower FiO2 levels. In many incidences, it is possible to bring the FiO2 down to 60% or less by adding PEEP.

Positive end-expiratory pressure also provides protection against ventilator-related lung trauma. The selection of a PEEP level for optimal protection is best understood in the context of static lung compliance, static pressure-volume curves, and inflection points (Pflex). Static compliance is a measure of lung and chest wall stretch for a given tidal volume. The tidal volume is delivered and paused at end inspiration to measure pressure in the airway: plateau pressure. If a series of static compliance values are calculated for progressively increasing volumes, a static pressure-volume curve is generated (Figure 1). Most of the curve is linear, but there may be flattening at both the top and bottom, where small changes in volume are associated with large changes in pressure. Sites of transition to the linear part of the curve are called the lower and upper inflection points.

The presence of a lower inflection point indicates that small airways are opening and closing with every breath. This causes shear injury. To prevent cyclical closure, PEEP can be added in an amount slightly greater than the lower transition point. The addition of PEEP should attenuate or eliminate the lower inflection point. The best effect may not be evident for 20 to 30 minutes or longer because full airway recruitment may take a number of respiratory cycles. Above the upper inflection point, there is very little stretch left in the system and high pressures are needed to load even small amounts of additional tidal volume. This is a zone in which most barotrauma is likely to occur. A simple reduction in tidal volume will bring ventilation back down onto the more compliant part of the curve. Inflection points are not always present, but when they are, ventilating “between the inflection points” is believed to offer the best means of minimizing both shear injury and barotrauma.

The landmark work ofGattinoni and colleagues40,41 using computed tomographic (CT) scans has done much to further our understanding of how PEEP might both help and harm the lung in ARDS. Following administration of different amounts of PEEP, alveolar recruitment was demonstrated by assessing lung density radiographically.

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with CT scanning. Results of CT were then compared with traditional parameters of lung mechanics. The amount of lung available for recruitment could be estimated by a ratio of the slopes of the curves below and above the lower inflection point. According to CT scan results, “best PEEP” was identified as the pressure at which the curve became linear, just above the lower inflection point.

Using the same technique, Gattinoni’s group also demonstrated that the consolidation and volume loss in ARDS was due to the hydrostatic pressure of superimposed lung. There was a reproducible anterior-posterior gradient with more unventilated tissue density in the dependent parts of the lung posteriorly. This milestone study also convincingly proved that, for purposes of alveolar recruitment, the maximum PEEP dose in a supine patient should not exceed the ventrodorsal height of the patient in centimeters. Although higher doses of PEEP might improve oxygenation, the effect could not be explained on the basis of reversing compression atelectasis.

In another group of patients with severe ARDS, Ranieri et al demonstrated that PEEP improved oxygenation in all 8 patients. In some this was through alveolar recruitment; in others it was not. The latter subset had a smaller improvement in oxygenation, accompanied by changes on the pressure-volume curve, suggesting that the PEEP was causing overdistention. Since the study was short term, the risk-benefit ratio of using PEEP to improve oxygenation in the absence of recruitment could not be assessed. These results must be balanced against an important experimental study by Muscedere and co-workers. In an isolated rat lung model, it was demonstrated that ventilating lungs below the lower inflection point caused a significant decrease in lung compliance and injury in a pattern involving membranous bronchioles and alveolar ducts, consistent with airway shear. This effect was dose dependent, with an increasing degree of injury the lower the PEEP.

Thus we are left with the possibility that too little PEEP can be as harmful as too much. Since PEEP can be protective, the working question becomes, just how much PEEP is enough? The accurate determination of “least PEEP” requires a pressure-volume curve. This is because inflection points are variable (and sometimes absent). Generation of a static pressure-volume curve can be cumbersome and potentially dangerous. Interrupting mechanical ventilation for the required series of plateau pressure measurements may cause decompensation in marginally stable patients. An alternative that can provide similar information is the dynamic pressure-volume curve. Such a loop represents a series of dynamic compliance measurements calculated as the tidal volume is moving, without interrupting ventilation. Beaking at the top end of the loop corresponds to overdistention just as with the static curve. At the bottom, beaking may be the result of unopened airways, or it may be caused by increased resistance to flow within open airways from a variety of causes.

The lower beak and inflection point of a pressure-volume loop are not as specific for shear injury as in the static pressure-volume curve. It has been suggested that by temporarily slowing peak flow to very low rates, the contribution of the flow component can be minimized. This maneuver results in inverse ratio ventilation that may not be well tolerated by the spontaneously breathing patient. An alternative is to add PEEP and determine whether the lower inflection point is attenuated or eliminated. As with the static pressure-volume curve, the beneficial effect of PEEP may take some time to fully manifest. The use of dynamic pressure-volume curves is only possible in ventilators with a liquid crystal display (LCD) screen and the appropriate graphics software. If the addition of PEEP has the desired effect on the lower inflection point but results in the appearance of an upper inflection point, the response should be to decrease tidal volume, keeping ventilation between the inflection points. In the absence of information about pressure-volume relationships, one can only estimate the highest PEEP that could be expected to recruit lung units. Follow-
ing the work of Gattinoni and colleagues, this is equivalent to the patient’s thoracic anterior-posterior diameter. PEEP would generally not exceed 25 cm H₂O. Empiric application PEEP based on improvement of PaO₂ only offers no guarantee of avoiding either shear injury or barotrauma.

A final consideration in determining “best PEEP” is cardiac performance. PEEP affects almost every phase of cardiac output. It can compromise the preload, afterload, and inotropic state of the right ventricle. Since right ventricular output represents the preload for the left ventricle, left ventricular stroke volume can be profoundly depressed by PEEP, especially if the patient is hypovolemic. In the previously cited series of Ranieri et al., the average cardiac index decreased linearly from 4.99 to 4.14 L/(min · m²) (17% reduction) as PEEP was increased from 0 to 15 cm H₂O. In patients with limited cardiac reserve or increased oxygen demands, the addition of PEEP may adversely affect tissue perfusion even as it improves PaO₂. Continuous cardiac monitoring is advisable in such patients. A cardiac index of 3.0 L/(min · m²) represents an acceptable lower limit, if global oxygen delivery and consumption are within normal range.

Appropriate volume loading is essential to minimize the hemodynamic side effects of PEEP. But because PEEP can artifically elevate all central pressures, it may be difficult to be sure that the patient is cvo1emic. It has been generally suggested that hemodynamic effects are insignificant at PEEPs below 10 cm H₂O. Factors such as local lung compliance and zone of the lung around the tip of the pulmonary artery catheter, as well as high mean airway pressure and occult (intrinsic) PEEP, may contribute to erroneous pressure measurements. More accurate readings may be obtained if the patient is transiently disconnected from the ventilator (after preoxygenation when possible). This maneuver should be used with caution, and only when absolutely necessary because it can precipitate decompensation in marginally stable patients. If a pulmonary artery catheter is in place, it may be more prudent to give a fluid bolus and determine response by cardiac output. Bedside echocardiography is also a safe and useful way to noninvasively assess volume status, ventricular preload, cardiac performance, and response to volume loading.

Occasionally when the ventilator is disconnected, blood pressure increases. This is a sign that the mechanical ventilation is adversely affecting cardiac output, because of PEEP, auto-PEEP, or continuously high airway pressures. The “deliberate disconnect” can be used diagnostically in the setting of progressive hypotension, when PEEP-like side effects are suspected, but it is not possible to check for auto-PEEP. If the blood pressure rebounds within seconds of the disconnect (much as when a tension pneumothorax is relieved), auto-PEEP or excessive positive airway pressure is usually the cause.

A final clue to the presence of relative hypovolemia is the appearance of cyclical variations in the arterial line tracing. This is the “waving A-line sign” (Figure 3). In the presence of mild to moderate hypovolemia, there are cyclical increases and decreases in the height of the pulse pressure tracing, in synchrony with the ventilator rate (Figure 3, top). More profound hypovolemia results in undulation of the entire tracing, including the baseline (Figure 3, bottom). Hypovolemia may be present in the absence of the wavering A-line sign, especially if pressors are in use, so it cannot be considered a highly sensitive finding. If present, the diagnosis of hypovolemia (relative to the positive pressure ventilation in use) should be entertained. Consideration should be given to volume loading or reducing airway pressures. A simple test is to transiently reduce airway pressures by decreasing the PEEP or tidal volume to determine if the “waver” disappears.

**PRONE VENTILATION**

Although the concept of prone ventilation is not new, the recent CT studies of patients with ARDS have led to renewed enthusiasm for its use in ARDS. These studies have shown...
that there is a gravity-dependent distribution of volume loss in the lungs of supine patients with ARDS. The dependent parts of the lung are better perfused. By turning patients to place the aerated lung dependent, ventilation-perfusion V/Q matching and oxygenation should improve. As predicted, oxygenation does improve, in approximately two thirds of patients who are positioned prone. Langer and coworkers were the first to assess prone ventilation with CT scanning. In their series, 8 (62%) of 13 patients responded to prone positioning. In the 2 patients who underwent CT scanning, lung density shifted with prone positioning so that the dependent lung was always densest. In a larger series of 10 patients with moderate and severe ARDS, Gattinoni et al demonstrated that this redistribution of lung density occurred very rapidly after turning patients prone—within 10 minutes. The same phenomenon was demonstrated to a lesser extent in 7 normal volunteers. Patients were kept prone for only a short time (10-45 minutes). There was an improvement in oxygenation (PaO₂ 67.5 mm Hg vs 78.0 mm Hg; P = not significant).

If dependent lung perfusion was always greatest, the improvement in ventilation-perfusion matching would be short-lived because the nondependent part of the lung rapidly loses aeration when placed prone. As it turns out, more blood continues to perfuse the dorsal parts of the lung, even after turning. Experimental work has demonstrated that there is minimal redirection of pulmonary blood flow when position is altered. As the ventilation gradient redistributes with repositioning, a more homogeneous matching of ventilation and perfusion occurs. Using multiple inert gas technique, Pappert et al confirmed that the improvement in ventilation-perfusion matching seen in prone responders corresponded to a shift in perfusion from unventilated to ventilated lung following alveolar recruitment.

Clinical series have also demonstrated a decreased shunt fraction in patients who respond to prone positioning. Blanch and colleagues found a reduction of intrapulmonary shunt fraction from 44% to 34%, accompanied by a PaO₂/FiO₂ ratio that almost doubled (70 to 121) in 16 of 23 patients treated with prone positioning. The responders also showed a small but statistically significant improvement in static compliance. This relationship between response and improved compliance was also noted by Servillo and colleagues. In a carefully done series of 19 patients, Jolliet et al found that in patients who responded to prone positioning, shunt fraction was reduced from 50% to 36% after 12 hours prone. Concurrent with a rise in PaO₂ (58 mm Hg to 69 mm Hg), it was possible to lower the FiO₂ (.85 to .66), resulting in improvement of the PaO₂/FiO₂ ratio by 53%.

The use of prone ventilation has been associated with improved outcome in several small series. Nine of 13 profoundly hypoxic patients treated with prone ventilation by Mure and colleagues survived. These patients began with an average SaO₂ of 84% on an average FiO₂ of .80. Among responders (12/13), SaO₂ rose to an average of 94% while the FiO₂ was decreased to .72. Also of interest is that a number of patients were kept prone for periods in excess of 40 hours at a time. Patients initially not responding were left prone for as long as 24 hours to allow for a response. Stocker and
colleagues report a series of 25 patients with a predicted mortality of 35% by Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring in which there was an actual mortality rate of 12%. The authors used a combination of prone positioning (in 17 of 25 patients) and low-volume, pressure-limited ventilation with permissive hypercapnia. All 17 patients responded to prone positioning with significant improvements in oxygenation. Eight patients were excluded from being placed prone because of spine fractures or severely elevated intracranial pressure.

Reported complications of prone ventilation are remarkably few. The data of Jolliet et al revealed no change in mean arterial pressure, systemic vascular resistance, cardiac index, or pulmonary artery wedge pressure. Central venous pressure was also not statistically altered by the prone position. In the series by Stocker and coworkers, there was one case of corneal ulceration requiring a corneal transplant, which emphasizes how essential it is to avoid pressure on the eyes. Inadvertent extubation has been reported, drawing attention to the importance of securing the airway prior to repositioning. In patients with intracranial hypertension, positioning of the head may impede venous return and increase intracranial pressure. In this subset of patients, prone positioning should be used with caution and under strict intracranial pressure monitoring. Prone positioning is probably not advisable in the setting of a temporary abdominal closure for abdominal compartment syndrome in the absence of a secure closure and accurate pressure monitoring. Facial edema is an expected side effect of prone positioning. In general, awake patients must be treated with sedation and neuromuscular blockade. It is far easier for the determined patient to crawl out of bed from the prone position.

The safe duration of prone positioning is unknown. If the patient is a responder, improved oxygenation will usually be seen within the first 30 minutes to 2 hours. Occasionally, patients who do not respond on the first trial show a response when turned at a later time.

Some series have reported turning patients as frequently as every 2 hours. In other studies, patients have been left prone longer than 40 hours without adverse effects. One of the few with a schedule was that by Jolliet et al: 12 hours prone alternating with 30 minutes supine. The protocol was continued until it was no longer effective or no longer needed, as assessed by maintenance of acceptable parameters with supine ventilation. Because of the labor entailed and the absence of data to suggest that more frequent turning is beneficial, a schedule of prone 12 to 24 hours followed by supine for 30 to 60 minutes appears to be practical.

PROTECTIVE VENTILATION: DOES IT WORK?

As one begins to examine the complex interplay of variables when considering just the single issue of mechanical ventilation, it is easy to see why results of therapy in ARDS have been diverse, and sometimes even contradictory. In many of the early studies important parameters were unknown, thus not monitored or controlled. The majority of recent series have been too small to provide meaningful statistical power. What is evident is a trend toward improved survival when the treatment regimen includes maneuvers to avoid overdistention of the lung. Support comes from a subset analysis of the 101 clinical series reviewed by Kraft et al. Taken as a group, mortality was 53% and there was no trend toward improved survival over time. However, in the 21 studies where use of pressure-limited ventilation was documented, the mean mortality rate was 35%.

In early 1998, the New England Journal of Medicine published back-to-back studies that addressed the issue of protective ventilation. One said it worked. The other said it did not, and suggested that morbidity might actually be increased by strategies limiting PIP and tidal volume. Amato and colleagues hypothesized that a protocol limiting both airway shear and overdistention would improve outcome. In the study group of 29 patients, small tidal volumes (PIP<40 cm H2O), permissive hypercapnia, and PEEP slightly in excess of the lower inflection point were used to protect the lungs. If a lower inflection point was not present on the static pressure-volume curve, a PEEP of 16 cm H2O was selected. The control group of 24 patients was ventilated with 12 mL/kg tidal volume at rates to keep patients eucapnic, without limiting airway pressure. PEEP was adjusted to keep FIO2 at 60% or less when possible. Significant differences among the ventilation parameters for the study and control groups included tidal volume (350-90 mL vs 740-70 mL), PIP, plateau pressure, and PEEP (approximately 14.5 cm H2O vs 8 cm H2O) (Figure 4). The incidence of clinical barotrauma (7% vs 42%),
weaning rates (66% vs 29%), and 28-day mortality (38% vs 71%) were all significantly better in the protective ventilation group. However, there was no survival advantage to hospital discharge.

Stewart and coworkers also using a prospective randomized format, conducted a trial of pressure and volume limitation in a high-risk group of 120 patients. Although a larger study, the results bear careful interpretation. Despite randomization, the protective ventilation group was significantly more hypoxic compared with the control group (Pao2/Fio2 ratio of 123 vs 145). The actual differences in total volume were smaller (approximately 7 mL/kg vs 10 mL/kg) as were the differences in plateau pressure and PIP. The amount of PEEP was low in both groups (approximately 9 cm H2O vs 7.8 cm H2O) and statistically different only at day 1. Pressure-volume curves and inflation points were not used. In this study, the authors found no reduction in hospital mortality and a possible increase in morbidity, with a greater requirement for paralytic agents and dialysis secondary to acute renal failure in the study group. These 2 well-conducted studies emphasize the clinician’s dilemma. One study, using a more aggressive protocol, seems to show some benefit. Yet, there is no impact on the indisputable end point of in-hospital mortality. The other, with a larger sample size and lower overall mortality, demonstrates no advantage from protective ventilation. Which strategy should be put into effect—more protective ventilation, or less? It was precisely this sort of dilemma that prompted the National Institutes of Health (NIH) ARDS Network to initiate a multicenter trial comparing 12 mL/kg vs 6 mL/kg tidal volume ventilation for the treatment of ARDS. Planned enrollment was 1000 patients with ARDS or acute lung injury (200 < Pao2/Fio2 < 300). Patients were randomly assigned to receive either 6 mL/kg (low) or 12 mL/kg (high) tidal volume. The goal for plateau pressures in the low-volume group was 30 cm H2O or less and in the high-volume group 50 cm H2O or less. There were target values for pH (7.3 ≤ pH ≤ 7.45), Pao2 (55 mm Hg ≤ Pao2 ≤ 80 mm Hg), Sao2 (88% ≤ Sao2 ≤ 95%), and rate (≤35/min). The 2 main outcome measures were percentage of patients alive with unassisted breathing at 180 days and number of days of unassisted breathing at day 28 of the study. Prone ventilation and construction of pressure-volume curves were not part of the established protocol. The sample size and unambiguous end points were chosen to avoid the fatal flaws of virtually every study previously undertaken. The question was simple: Would ventilation with smaller volumes improve outcome in ARDS?

On March 15, 1999, the NIH issued a news release announcing that the study had been terminated after the enrollment of 800 patients because interim analysis had shown 25% fewer deaths among patients receiving smaller tidal volumes. This represents the first large, prospectively randomized study to demonstrate a statistically and clinically significant improvement in survival using smaller tidal volumes and permissive hypercapnia to limit airway pressure. We must await publication of the full analysis to answer questions about higher Fio2 values, hemodynamic parameters, fluid and electrolyte issues, and sedation requirements. However, death and ventilator-days are end points that the clinician can take to the bank. The techniques used in this study, and others, can be incorporated into clinical practice immediately (Table) with the expectation that mortality will be significantly reduced.

### SUMMARY

As one reads the original monograph describing ARDS, scientific writing does not completely obscure the humanity of the physicians or the patients. The authors’ objective analysis defined a new disease process. However, their extensive list of clinical interventions leaves no doubt about the desperate nature of the struggle that was waged at the bedside. To have saved a patient from a lethal injury or infection, only to watch death come through slow asphyxiation, is as heartbreaking now as it was 3 decades ago.

Thanks to the efforts of many, the first great piece of effective therapy for ARDS can finally be put in place. In a discipline where improvements in treatment are often measured in decimal increments and disease-free days, we now have a way to reduce mortality from a highly lethal disease by 25%. It has been more than 3 decades coming, against a backdrop of scientific progress and clinical stalemate. Recognition that our supportive efforts could also be harmful has provided major impetus for the development of protective ventilation. Protective ventilation is not the magic bullet. It is a set of techniques accessible to virtually every clinician treating patients with ARDS. Although predominantly a
form of supportive therapy, it also allows us to minimize the contribution of mechanical ventilation to ongoing lung injury. The results of the NIH ARDS Network trial leave little doubt that mechanical ventilation has been part of the disease process as well as part of the cure.

As our understanding of the pathophysiology of ARDS continues to evolve, we can look toward the development of innovative therapies that will enable us to modulate the effector events leading to irreversible cell damage and death. At the same time, additional refinements in supportive therapy will provide us with further reductions in mortality. We owe a great debt not only to individual clinician-scientists, but also to the contributions of the American-European Consensus Conference on ARDS, the NIH ARDS Network, and other collaborative efforts throughout the world.

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