Respiratory Intensive Care

Henning Pontoppidan, M.D.,* Roger S. Wilson, M.D.,† Michael A. Rie, M.D.,‡ Robert C. Schneider, M.D.‡

I. Evolution of Respiratory Care

A. Development of Early Respiratory Units

The history and development of intensive care units were recently reviewed by Hilberman. This year marks the twenty-fifth anniversary of the application of anesthesiologic principles to large-scale respiratory care. In 1952, Scandinavia, especially Denmark, was struck by a poliomyelitis epidemic of unprecedented severity, and thousands of patients were hospitalized. From July 24 to December 3, the Hospital for Communicable Diseases in Copenhagen admitted 2,722 patients, of whom 315 had respiratory muscle paralysis requiring respiratory support. Early in the epidemic all patients were treated in the one tank and six cuirass respirators available. Uncuffed tracheostomy tubes were used to secure an open airway; adequate humidification of inspired gas was not available, and effective chest physical therapy was hampered by body-enclosing respirators. Of the first 31 patients with respiratory paralysis admitted in 1952, 27 died, most within three days. When the thirty-second patient, a 12-year-old girl, was nearing a terminal state of respiratory failure, an anesthetist, Dr. Bjørn Ibsen, was consulted. A tracheostomy was promptly performed, followed by insertion of a cuffed endotracheal tube and initiation of manual artificial ventilation with a conventional to-and-fro system. Improved oxygenation and correction of respiratory acidosis were followed by shock, but blood was transfused and adequate circulation re-established. Thus, "the patient had been improved by the measures usually carried out by the anaesthetist in the operating theatre." The therapeutic principles demonstrated by Ibsen now became the accepted methods for management of respiratory paralysis throughout the region. Teams of "ventilators" consisting of nurse anesthetists, interns and medical students provided manual artificial ventilation and respiratory care in shifts. At the peak of the epidemic such teams ventilated 70 patients simultaneously at the Communicable Disease Hospital in Copenhagen. Similar regional centers were soon established throughout the country. The overall mortality rate of patients with respiratory paralysis was reduced to less than 30 per cent.

Most of the essential principles of positive-pressure mechanical ventilation and airway care were implemented during the 1952 epidemic. Chest physical therapy with meticulous attention to postural drainage, manual assistance to coughing, and tracheobronchial aspiration of secretions were universally applied. Inspired gas was partially, albeit incompletely, humid-
ified in the to-and-fro system with partial rebreathing, and more effective bypass humidifiers soon became available. Pulmonary oxygen toxicity was avoided by the use of a mixture of equal parts of nitrogen and oxygen. Orotracheal intubation preceded tracheostomy, thus avoiding the hazard of emergency tracheostomy without airway control. Large-bore, cuffed tracheostomy tubes were used to facilitate controlled ventilation and airway protection. pH and blood-gas electrodes were not available, but adequacy of manual ventilation was monitored with acceptable accuracy by measurement of end-tidal carbon dioxide concentration, and occasionally by total bicarbonate content of plasma. Adequacy of oxygenation was judged by clinical observation and by measurement of arterial oxygen saturation or by oximetry. Intermittent pulmonary hyperinflations were empirically applied to overcome the complaint of dyspnea commonly “expressed” by patients with ventilatory failure despite what appeared to be adequate oxygenation and ventilation. Weaning was accomplished by gradual reduction in the number of assisted breaths as the patient's ability to breathe spontaneously improved, a forerunner of present-day intermittent mandatory ventilation (IMV) methods. In many respects, and on an entirely empiric basis, the ventilation pattern provided by “an educated hand” proved to be physiologically superior to that provided by earlier mechanical ventilators. (The essential physiologic role of sighing in preventing progressive atelectasis during shallow breathing was not established until 1959, by Mead and Collier. 6,7) The ventilatory pattern employed emphasized the importance of a brief inspiratory phase with rapid return to zero pressure during expiration in accordance with the studies by Cournand et al. 8 of the circulatory effects of positive-pressure breathing.

In 1955, the New England region was struck by a severe epidemic of paralytic poliomyelitis, and anesthesiologists again assumed an important role in the care of patients with respiratory paralysis. At the Massachusetts General Hospital an entire floor was converted to a poliomyelitis respiratory failure unit. At the height of the epidemic, 49 patients were mechanically ventilated at one time, 46 in tank respirators and three with the Jefferson ventilator, an early version of the volume-preset device capable of providing controlled ventilation. The superiority of intermittent positive-pressure ventilation (IPPV) was once more demonstrated, as it had been in 1948–49 by Bower et al. 3 and in 1952. 2,4 However, complications from inadequate humidification and tracheal trauma from tracheostomy tubes with high-pressure cuffs were evident. Measurement of arterial oxygen saturation was still the only clinically available method for assessing adequacy of oxygenation. Therefore, it was not possible to take advantage of the linear portion of the oxygen-dissociation curve above full saturation for estimation of the alveolar–arterial oxygen tension difference (A–aD0.5) and the right-to-left intrapulmonary shunt. Prediction nomograms, such as that developed by Radford, 9 were used to estimate minute ventilation requirement, and adequacy of carbon dioxide elimination was checked by measurement of bicarbonate content of plasma. Systematic study of the efficiency of gas exchange and the optimal ventilatory pattern was hardly feasible until blood-gas electrodes became available for routine clinical use in the early nineteen-sixties. 5,10

Poliomyelitis became a rare disease with the advent of the Salk vaccine, and during the next several years the use of mechanical ventilation declined sharply. Most patients treated were those in whose cases therapeutic parallels to paralytic poliomyelitis were easily drawn, such as those who had potentially reversible neuromuscular disease, drug-induced coma, and chest trauma with mechanical instability of the chest wall. 11 As poliomyelitis-oriented units were largely abandoned, most patients on ventilators were cared for on hospital wards; their complication and mortality rates were high, in large measure due to mechanical failure of airway equipment and ventilators (H. Pontoppidan, personal observation). This, along with the steady increase in the number of patients requiring mechanical ventilation, ultimately prompted the re-establishment of respiratory units in several centers. 1

The Respiratory Unit at Churchill Hospital, Oxford University, was opened in 1958, primarily as a center for treatment of patients with neuromuscular disease and respiratory failure (A. Crampton-Smith, personal communication). In North America a multi-disciplinary Intensive Care Unit was opened at University Hospital of Baltimore in 1958, 12 and Respiratory Units were started at Toronto General Hospital in 1958, 13 and at the Massachusetts General Hospital in 1961. A full-time staff of nurses, physicians and chest physical therapists set the standards for present-day staffing patterns of multidisciplinary intensive care units. Although these early respiratory units were generally small, with capacities of five or six beds, they served an important role in teaching and clinical research, and in developing quantitative, physiologically sound methodology for prevention and treatment of acute respiratory failure. In table 1 we have identified some of the most notable advances and the approximate times when they were incorporated into the management of...
Table 1. Notable Events in Management of Acute Respiratory Failure

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive-pressure attachment first used with tank respirator; ventilation monitored with anemometer; oxygenation and acid-base status measured; mortality from poliomyelitis with respiratory failure reduced to 17 per cent. (1949)</td>
<td>Pulmonary oxygen toxicity “rediscovered” and its therapeutic implications recognized.</td>
</tr>
<tr>
<td>Severe poliomyelitis epidemic in Scandinavia. (1952)</td>
<td>Water retention in ventilatory failure and its effects on pulmonary mechanics and gas exchange described.</td>
</tr>
<tr>
<td>Adoption of anesthesiologic principles (cuffed endotracheal tubes, positive-pressure breathing, shock therapy) in management of ventilatory failure.</td>
<td>Sepsis emerges as leading cause of death in ARF.</td>
</tr>
<tr>
<td>Principles of chest physical therapy and airway care established.</td>
<td>Controlled oxygen therapy in acute–chronic respiratory failure described.</td>
</tr>
<tr>
<td>1955–1959</td>
<td>Cardiovascular response to IPPV quantified.</td>
</tr>
<tr>
<td>Respiratory care transiently centralized in “poliounts.”</td>
<td>Preventive role of mechanical ventilation accepted.</td>
</tr>
<tr>
<td>Multidisciplinary respiratory care units established. (Oxford University, University of Toronto, 1958)</td>
<td>1970–1976</td>
</tr>
<tr>
<td>Ventilation nomograms widely adopted.</td>
<td>Positive end-expiratory pressure, continuous positive airway pressure and closing volume era.</td>
</tr>
<tr>
<td>pH electrodes in clinical use.</td>
<td>Tracheal stenosis, its causes, prevention and therapy described.</td>
</tr>
<tr>
<td>Military atelectasis and role of sigh defined.</td>
<td>Technology no longer limiting factor in survival from acute ventilatory failure.</td>
</tr>
<tr>
<td>Continuous mechanical hyperventilation introduced in management of critically crushed chest.</td>
<td>Pulmonary circulation and fluid dynamics elucidated.</td>
</tr>
<tr>
<td>Respiratory ICU’s proliferating.</td>
<td>Extracorporeal membrane oxygenation evaluated.</td>
</tr>
<tr>
<td>Polymorphic oxygen electrodes in clinical use.</td>
<td>Open-lung biopsy developed as diagnostic procedure in severe acute respiratory failure.</td>
</tr>
<tr>
<td>Indications for mechanical ventilation broaden to include medical and surgical acute respiratory failure.</td>
<td>Ethics, cost and role of intensive care debated.</td>
</tr>
<tr>
<td>Gas exchange in acute respiratory failure quantified.</td>
<td>1967, described pulmonary morphologic changes consistent with oxygen toxicity and mechanical ventilation at F1O2 exceeding 0.85–0.9. Several factors may account for this delay: The morphologic manifestations of oxygen toxicity are nonspecific and virtually undistinguishable from other causes of injury to pulmonary microcirculation, alveoli and airways; it was not known whether arterial hypoxemia or normoxemia would prevent or delay the onset of pulmonary oxygen toxicity; the iatrogenic role of mechanical ventilation per se had not been thoroughly investigated; finally the functional characteristics of the oxygen-powered, pressure-limited ventilator were not understood. After 1955, pressure-limited ventilators had become the most common type of mechanical ventilator in North America. Powered by compressed oxygen, with an air-entraining ventiluri device in operation, they were erroneously assumed to deliver an inspired oxygen concentration of less than 50 per cent. Therefore, physicians did not suspect that oxygen toxicity might have a role in progressive pulmonary dysfunction that developed</td>
</tr>
</tbody>
</table>
RESPIRATORY INTENSIVE CARE

during mechanical ventilation. That the actual inspired oxygen concentration was more likely to approach 100 per cent during actual clinical use, especially in conjunction with an in-line humidifier, was demonstrated by Fairley and Britt\textsuperscript{24} in 1964 and again in our laboratory in 1967.\textsuperscript{25} Thus, with pressure-limited, oxygen-powered ventilators, there was a need for deliberate reduction of the inspired oxygen concentration to below a toxic range by adding compressed air. For several years the terms "oxygen-toxicity lung" and "respirator lung" were indiscriminately used to describe the nonspecific radiographic, physiologic and pathologic manifestations of acute respiratory failure and its complications. The latter term was abandoned when Kaplan\textsuperscript{26} and Kapanec\textsuperscript{27} produced the characteristic manifestations of oxygen toxicity in spontaneously breathing primates without the "benefit" of mechanical ventilation. Prolonged mechanical ventilation with air in goats\textsuperscript{28} exonerated the ventilator, as did the realization that patients with ventilatory failure could be successfully ventilated at low F$_{10}$ for months or years without apparent harmful effects on pulmonary function.\textsuperscript{7,23} Prolonged spontaneous ventilation with continuous positive airway pressure (CPAP) does not appear to harm the lung. Tracheotomized lambs were allowed to breathe ambient, humidified air with 10 cm H$_2$O CPAP for one week without any physiologic or morphologic pulmonary change other than an increase in lung volume.\textsuperscript{20} In this study CPAP did not modify or delay the onset of pulmonary oxygen toxicity resulting from breathing of oxygen at ambient pressure.

Respiratory function-related morbidity and mortality rates are now very low in patients with ventilatory failure and minimal or no underlying pulmonary disease.\textsuperscript{17,19,20} In contrast, despite major advances in knowledge of pathophysiology and management of respiratory failure, the mortality rate has remained discouragingly high when respiratory failure develops secondary to direct pulmonary injury or disease or in association with severe multisystem illnesses.\textsuperscript{7,17,19,20,21,23}

Interpretation of morbidity statistics and comparison of survival rates are difficult, since criteria for use of mechanical ventilation have changed over the past two or three decades. Mechanical ventilation is now only one of many factors influencing survival from multisystem failure. Furthermore, early detection and effective prevention of respiratory complications of major surgery and trauma are now widespread.\textsuperscript{17} However, failure to respond to adequate preventive measures can be expected to identify patients who have more severe and poorly reversible illness. As discussed below, in these cases it is necessary to use life-sustaining techniques of known potential for further injury to the lung.

C. Extracorporeal Membrane Oxygenation in Acute Respiratory Failure

Pulmonary function in patients who have severe acute respiratory failure (ARF) is characterized by extremely low compliance and functional residual capacity (FRC) (25 per cent of normal or less) and high Q\textsubscript{V}/Q\textsubscript{a}. To provide effective mechanical ventilation and gas exchange, high inspiratory and expiratory airway pressures and F$_{10}$, approaching 1.0 are often necessary for prolonged periods. The potential for serious additional injury to the already damaged lung is obvious. An alternative approach to support of such patients became feasible with the development of efficient membrane lung devices.\textsuperscript{26,31} The initial hope was that extracorporeal membrane oxygenation (ECMO) might promote healing of the lungs in selected patients by ameliorating the iatrogenic pulmonary injury of such "maximal conventional" respiratory therapy. To investigate the therapeutic role of ECMO, the National Heart, Lung and Blood Institute (NHLBI) has sponsored a three-year, multicenter randomized study. Although ventilatory management during ECMO was not uniform among the nine centers, an effort was made to reduce inspired oxygen concentration and to lower peak inspiratory and end-expiratory pressures and tidal volume. Whether such maneuvers are conducive to repair of the damaged lung is uncertain. It is now obvious that ECMO works well as a support device. Efficiency of gas transport has improved and the complication rate due to technical failures has decreased with added experience in several centers around the world. However, in most patients ECMO has failed to alter the course of acute respiratory failure and to provide a substantial increase in survival.\textsuperscript{20,34,35} Furthermore, morphologic studies of biopsy and autopsy material from the study group support the view that despite modern, sophisticated technology, we lack the ability to arrest the progression of pulmonary disease in most patients who have severe, advanced acute respiratory failure. An improved survival rate for these patients will depend on a better understanding of the etiology and mech-

\*The criteria for entry into the NHLBI-supported study of ECMO are severe.\textsuperscript{34} The initial hope was to identify a patient population with an expected mortality rate from ARF of approximately 70 per cent. In retrospect, the criteria may have been too rigid, since they have identified a patient population with only an 8-10 per cent chance of survival whether or not bypass is used.\textsuperscript{25}
anisms of pulmonary injury and destruction. In the following paragraphs some of the recent data on physiologic and morphologic changes in ARF and on the effects of mechanical-ventilation patterns on circulation, lung volume, right-to-left shunt, and mechanics are reviewed.

II. Hemodynamic Performance during Acute Respiratory Failure

Understanding cardiovascular function during acute respiratory failure demands knowledge of hemodynamic changes during spontaneous (negative-pressure) breathing. These effects are reviewed as a basis for understanding biventricular hemodynamic effects of positive-pressure breathing and PEEP. In section IIIB we attempt to integrate the pathophysiological effects of acute pulmonary injury and positive-pressure breathing on circulatory function. Our aim is to define factors that affect cardiovascular function and the modalities used in its assessment.

A. Circulatory Dynamics in Spontaneously-Breathing Man

Lauson et al.37 were the first to report that the stroke volumes of the two cardiac ventricles are unequal in man during deep breathing. The increasingly negative intrapleural pressure during inspiration results in increased effective (transmural) right ventricular filling pressure, and stroke volume increases. On the other hand, left ventricular stroke volume decreases. The conventional explanation for the latter was that negative intrapleural pressure resulted in decreased left ventricular filling due to a transient increase in pulmonary blood volume. If this postulate were to be correct, it would then be necessary to demonstrate a simultaneous decrease in left ventricular transmural filling pressure and a decreased left ventricular end-diastolic volume. Lichtenstein et al.38 presented evidence in normal volunteers that during inspiration and the Mueller maneuver (forced inspiration against a closed glottis) transmural left atrial filling pressure increased. They showed further that left atrial and left ventricular volumes determined by echocardiography either increased or remained unchanged. Summer et al.39 found similar results with the Mueller maneuver in dogs with chronically implanted endocardial ultrasound probes. These investigations demonstrated that a decrease in left ventricular preload is not the explanation for a decreased left ventricular stroke volume during inspiration, and suggest that an increased left ventricular systolic afterload ($P_{aortic} - P_{pleural}$) is a primary determinant of this event. A more detailed explanation of the effects of right ventricular pressures and volumes upon diastolic pressure-volume relationships in the left heart40-44 and the effects exerted upon left ventricular diastolic pressure-volume relationships by the intact pericardium45,46 during acute respiratory failure follows.

B. Circulatory Dynamics during Positive-pressure Breathing in the Normal Cardiopulmonary Setting

Ventricular Preload Effects

Courmand and co-workers4 were first to report that intermittent positive-pressure breathing in normal unanesthetized subjects with therapeutic pneumothorax decreases cardiac output in direct relation to mean airway pressure elevation. Different mean airway pressures were provided by varying the configuration of the generated airway pressure. Courmand's Type III curve (I:E ratio < 1:1, mean airway pressure 5.7 mm Hg, with rapid passive return to ambient pressure on expiration) was found not to depress cardiac output, and served as the basis for the design of mechanical ventilators for the next quarter of a century. Other pressure curves with mean generated airway pressures of 8–12 mm Hg were associated with 15–25 per cent decreases in cardiac output from baseline. Peak depression of cardiac output (25 per cent below baseline) occurred 10 minutes after the onset of positive airway pressure, with return toward baseline at 40 and at 70 minutes. Qvist and co-workers,47 in studying halothane-anesthetized, paralyzed beagles, found that addition of 12 cm H$_2$O PEEP to intermittent positive-pressure breathing resulted in a 45–50 per cent decline in cardiac output, which showed no significant return toward baseline over the next eight hours. This has been confirmed by several other investigators.48-51 Some unknown variables in this situation are: 1) Does cardiovascular adaptation to increased mean airway pressure occur in normovolemic man? 2) How do sedation, neuromuscular-paralyzing drugs, and other abnormalities of autonomic nervous function alter such adaptation if indeed it exists?

The decline in cardiac output found by Courmand correlated directly with the decrease in transmural right ventricular filling pressure, while measured right ventricular end-diastolic pressure rose. Qvist et al.47 confirmed these findings in normovolemic dogs and demonstrated that intravascular volume expansion resulting in return of transmural right ventricular filling pressure to control values was associated with return of cardiac output to baseline. In
short, absolute hypervolemia resulted in functional normovolemia. In different experimental preparations, Morgan and Sykes showed that hypervolemic animals were protected from the decrease in cardiac output generated by elevations of mean airway pressure, while hypovolemic animals demonstrated a greater decrease. When positive end-expiratory pressure was removed in the hypervolemic dogs of Qvist et al., cardiac output rose above baseline while right ventricular transmural filling pressure was only slightly greater than baseline levels. In contrast to right-sided pressures, the left-sided transmural filling pressures doubled, for unknown reasons.

Ventricular Afterload Effects

Elevation of mean airway pressure with PEEP has been shown to elevate pulmonary vascular resistance (PVR) in the normal pulmonary vasculature. Presumably, the increase in FRC due to PEEP results in compression of pulmonary vessels. This rise in PVR is not decreased by volume expansion and restoration of cardiac output to baseline. Acute elevation of right ventricular afterload as expressed by PVR or pulmonary arterial diastolic pressure requires increased right ventricular stroke work to overcome the imposed pressure load. Such acute afterloading of the right ventricle presumably leads to right ventricular dilatation, increased right ventricular myocardial wall tension, increased right ventricular myocardial oxygen consumption, and displacement of the interventricular septum toward the left ventricular free wall with alteration of diastolic pressure-volume relationships in the left ventricle. Menkes et al. demonstrated with the Starling heart-lung preparation subjected to PEEP at constant cardiac output and left ventricular afterload that right atrial pressure rose from 4.1 to 7.0 mm Hg while left atrial pressure increased from 6.9 to 10.1 mm Hg, which they attributed to interdependence of biventricular hemodynamics shown to occur even in the absence of an intact pericardium. How this right ventricular afterload affects biventricular function in man in the presence of a rigid pericardium, autonomic reflexes, etc., is unknown. Pressure and blood-flow measurements are insufficient to detect acute volume and geometric changes during dynamic circulatory events. New clinically feasible methods for measuring biventricular volumes during systole and diastole and ejection fractions are needed to deal with these questions.

The effect of PEEP on left ventricular afterload must also be considered. If increasing degrees of negative intrathoracic pressure increase left ventricular systolic afterload, can it be that increases in positive intrathoracic pressure result in decreased left ventricular afterload (P_{aortic} - P_{pleural})? Data to answer this question are not available. If true, this may explain why some patients with cardiopulmonary disease respond to PEEP with increases in cardiac output.

C. Interpretation of Cardiovascular and Flow Measurements in the Clinical Situation

We may summarize the foregoing discussion as follows: 1) Increased airway pressure alters circulatory function in proportion to the rise in pleural pressure. This in turn is determined by the compliance of the lung and chest wall. 2) The greater the increase in FRC with increments of airway pressure (PEEP), the greater the depression of cardiac output and increase in pulmonary vascular resistance. 3) Prior intravascular volume state will determine the circulatory response to increases in FRC and pleural pressure. 4) It is impossible to predict the accompanying hemodynamic changes and their magnitude in an individual patient.

We must understand the limitations imposed by mechanical ventilation and acute respiratory failure on the measurements of pulmonary artery (PAP) and pulmonary capillary wedge pressure (PCWP) obtained from balloon-tipped flow-directed pulmonary-artery catheters. Lozman et al. studied patients who were receiving mechanical ventilation with PEEP after coronary revascularization. The patients had pulmonary-artery and left atrial catheters in place. These investigators demonstrated significant correlation of pulmonary capillary wedge pressures and left atrial pressures at low PEEP (5 cm H_{2}O or less). However, at high PEEP (10 cm H_{2}O or more), pulmonary capillary wedge pressures failed to predict directly measured left atrial pressures. An example of this phenomenon can be seen in figure 1. This case demonstrates that a Swan-Ganz catheter positioned in an area of lung where alveolar pressure exceeds left atrial and pulmonary arterial pressures (Zone I) will tend to reflect alveolar pressure and not downstream vascular pressure. As pulmonary arterial pressure rises above alveolar pressure, perfusion is re-established (Zone II), and the catheter reflects downstream vascular pressure. From this example, it is apparent that measurements of PCWP must be correlated with cardiac output, PEEP, and Q_{s}/Q_{t} in order to arrive at rational therapeutic decisions. This does not imply that acute disconnection of the ventilator is the appropriate method for measuring vascular pressure, as this is the unstable transient situation.
FIG. 1. Differential effects of PEEP on left atrial and PCWP pressures in nonperfused and perfused lung zones. A 61-year-old man underwent coronary revascularization that necessitated four hours of cardiopulmonary bypass. Postoperative ventilation with a tidal volume of 13 ml/kg resulted in hypoxemia, necessitating 80 per cent oxygen to maintain PaO₂ above 80 mm Hg. The lungs and chest were relatively compliant, with a plateau inspiratory pressure of 25 cm H₂O. At 5 cm H₂O PEEP, left atrial and wedge pressures differed by 2.5 mm Hg. As PEEP was increased in 5 cm H₂O increments over a one-hour period to 15 cm H₂O, cardiac index and left atrial pressure remained unchanged, while wedge pressure doubled (9–18 mm Hg). Over the next 12 hours, chest pain and acute mitral regurgitation developed despite intra-aortic balloon diastolic-pressure augmentation. Throughout this period the Swan-Ganz catheter remained in the same location on chest x-ray (upper lung field, extreme anterior position) and the ventilatory pattern with 15 cm H₂O PEEP was unchanged. The left atrial pressure and wedge pressures were now identical at 18 mm Hg, while cardiac index was slightly reduced from the previous day.

III. Etiology and Pathophysiology of Acute Respiratory Failure

A. ETIOLOGIC FACTORS

Table 2 lists factors considered important in the etiology of acute respiratory failure (ARF). This area has recently been reviewed, and only selected aspects are treated here. Numerous animal experiments seeking to define etiologic factors in ARF have been performed, but the relevance of these studies to the patient remains to be established. However, they are included because understanding mechanisms of injury is essential to improved patient therapy. Also, no one factor has been proven primary in initiating the events leading to the pathologic and physiologic changes seen in clinical ARF, possibly because the histologic response of the lung to acute injury is nonspecific, making difficult the determination of a specific etiologic mechanism.

Alveolar surfactant production, necessary for alveolar stability at low lung volumes, decreases as a result of injury to type II alveolar cells from hypoperfusion or through interaction with plasma proteins during pulmonary edema. Oxygen administered therapeutically in high concentrations for long periods also inhibits production of surfactant, contributing to atelectasis, pulmonary edema, and decreased compliance.

Acute respiratory failure frequently develops in patients with hypovolemic or septic shock. Although short periods of ischemia per se have not been shown to cause significant pulmonary damage, prolonged ischemia may do so. Ischemia also results in the release of histamine and serotonin from pulmonary perivascular mast cells, prostaglandin endoperoxides from pulmonary endothelium, and increases in circulating ADP levels. Histamine increases pulmonary capillary permeability, lymph flow, and pulmonary extravascular water. Histamine, serotonin and prostaglandin endoperoxides cause intense pulmonary vasoconstriction and may injure pulmonary capillary endothelium, increasing permeability.

The fluid administered to resuscitate patients from shock or sepsis, or to maintain adequate blood flow during major surgical procedures, has frequently been implicated in the etiology of ARF. Recently, the plasma colloid osmotic pressure (COP)-to-left atrial pressure (LAP) gradient has been used to evaluate the magnitude of fluid losses across the pulmonary capillary. Although a low gradient with elevated LAP following myocardial infarction is associated with pulmonary edema, this is not true when COP is reduced in animals with normal LAP or patients undergoing abdominal surgery. There is no convincing evidence that moderate volumes of crystalloid solution result in ARF in the absence of pulmonary capillary injury despite significant reductions in serum albumin concentrations and plasma oncotic pressure. Patients who have ARF usually manifest low pulmonary capillary wedge pressures and pulmonary edema. Thus, pulmonary capillary injury, rather than the amount or type of fluid administered, appears to be primary in ARF. It is also evident that following capillary injury, albumin rapidly appears in pulmonary lymph and alveolar secretions and that the administration of colloid to dogs with pulmonary injury slows the resolution of ultramicroscopic changes in the pulmonary interstitium. There is no evidence that treatment with protein-containing solution results in more rapid recovery from ARF. Crystalloid solutions may be preferable.
during the capillary leak phase, and protein-containing solutions once capillary integrity is re-established. The role of pulmonary vascular occlusion in the pathogenesis of ARF is receiving increasing attention. A marked distortion of pulmonary vascular architecture in autopsy specimens from patients dying with ARF has been well documented. Clinically, it is impossible to determine whether elevation of pulmonary vascular resistance (PVR) is secondary to vascular obstruction (microembolism) or vasoconstriction. As reported above, several vasoactive mediators occur in lung cells and are released during injury. Platelet aggregation causes increases in pulmonary arterial and venous pressures unrelated to microembolization. However, diffuse pulmonary microemboli have been found at autopsy in patients dying in ARF by several investigators, and were associated with inhibition of fibrinolysis and fibrin accumulation.

To investigate the role of platelets in ARF we have studied the kinetics and sequestration pattern of chromium-labelled autologous platelets in 13 patients. Lifespan was shortened in patients to one-quarter that of control subjects. Platelet lifespan correlated significantly with the initial platelet count, but not with levels of fibrinogen degradation products, indicating a mechanism other than disseminated intravascular coagulation. Bone marrow was not depressed as platelet turnover rates were elevated to three times normal. ARF patients showed a rapid and progressive increase in radiochromium over the liver and spleen, but not over the lungs. Figures 2 and 3 illustrate the platelet lifespan and sequestration pattern in a typical patient. Thus, our studies do not demonstrate the presence of significant pulmonary platelet accumulation. The finding by others of radio-labelled fibrinogen accumulation in the lungs of patients with posttraumatic ARF, however, indicates the need for further research in this area.

Sepsis is of extreme importance as an etiologic factor in ARF, and its first manifestation may be hypoxemia. In other instances, sepsis will exaggerate existing pulmonary damage, prolonging recovery and

| Table 2. Mechanisms of Injury Producing Acute Increases in Pulmonary Dysfunction |
|---------------------------------|---------------------------------|
| **Mechanism**                   | **Comments**                    |
| Infection                       |                                 |
| Bacterial/viral pneumonia       | Inflammatory edema secondary to direct alveolar and/or pulmonary capillary injury. |
| Endotoxin                       | Animal models and clinical reports of increased capillary permeability and pulmonary edema: may be mediated via other mechanisms listed below. |
| Toxins                          |                                 |
| Inhaled                         | Altered permeability with inhaled toxin; phosgene, ozone, oxides of nitrogen, etc. |
| Circulating                     | Picture of diffuse vasculitis and endothelial injury; alloxan and oleic acid animals models. Similar to endotoxin in man. |
| Vasoactive substances           | Injury produced secondary to liberation of histamine, serotonin, and prostaglandins. Vasoactive substances may play major role in inflammatory, immunologic, endotoxin and hemorrhagic shock injury. |
| Microembolization               | Diffuse endothelial damage of pulmonary capillaries—many etiologies are possible, including embolization, endotoxemia, tissue trauma. Major role in "adult RDS." |
| Fat embolism                    | Most often associated with trauma (skeletal and/or tissue) burns, shock. Pathophysiology is uncertain; mechanisms include alveolo-capillary damage from free fatty acids. Vasoactive substances and intra-vascular coagulation. |
| Oxygen                          | Animal models show early damage to capillary endothelium and other ultrastructures within several days of 100 per cent O₂ administration. |
| Massive transfusions            | Pulmonary vascular obstruction by platelet–leukocyte aggregates with marked degenerative cellular changes in interalveolar septum. Cardiopulmonary bypass in man shows similar pathology: preventable with fine-pore filters. |
| Immunologic reactions           | Etiologies include: drug hypersensitivity; idiosyncratic reactions; anaphylaxis (e.g., heroin, antibiotics); allergic alveolitis. Injury appears to result from release of chemical mediators. |
| “Shock”                         | Pulmonary insufficiency associated with trauma and hemorrhage: additional factors, e.g., myocardial failure, overhydration and mechanisms listed above, may play essential roles. |
| Loss of surfactant              | Decreased surfactant from O₂, toxins, dilution with plasma cause atelectasis and increased shunt. |
increasing mortality. Proper antibiotic therapy is essential, but loss of vascular integrity may prevent distribution of inhibitory concentrations to the most diseased areas of the lung. Recent clinical investigations have also shown decreased immunologic competence of phagocytes following trauma, surgery and sepsis, increasing susceptibility to infection. 

Also, there is evidence for a circulating polypeptide toxin, in association with increased pulmonary capillary permeability. These findings are consistent with the high incidence of infection and altered pulmonary hemodynamics in patients requiring intensive care.

The importance of proper mechanical ventilation in preventing iatrogenic pulmonary damage and the effects of ARF on the heart are discussed elsewhere in this article. The roles of oxygen toxicity and fat embolism have been the subject of other reviews.

Continued investigation of etiologic factors is necessary to permit a direct attack on the mechanism of pulmonary injury. For the present, improvement in survival rate depends largely on meticulous supportive management and prevention of sepsis.

**B. Pulmonary Circulatory Pathophysiology**

As reviewed above, numerous etiologic factors have been implicated in the pathogenesis of the adult respiratory distress syndrome. To the clinician, diffuse opacification of the chest X-ray, hypoxemia secondary to increased pulmonary venous admixture, decreased pulmonary compliance, and increased physiologic deadspace typify the findings in these patients, and the inexperienced physician may lump all cases into one syndrome. Recent studies suggest that hemodynamic criteria in conjunction with other physiologic and pathologic indices may serve a useful role in defining the severity of disease, clinical course, and prognosis.

Few studies of early pulmonary hemodynamic measurements in ARF have been published. Gopinathan et al. studied eight patients who had heroin-
induced pulmonary edema within 24 hours of hospitalization and found an elevated cardiac index (mean 4.5 l/min^2·min), slight elevation of mean pulmonary arterial pressure (20 mm Hg), normal pulmonary capillary wedge pressure, and a pulmonary arterial diastolic–wedge pressure difference of less than 5 mm Hg. Pulmonary-artery saturation and oxygen tension data were not given. Gelb and coworkers\textsuperscript{100} studied 11 previously healthy patients who had sustained a variety of acute pulmonary insults within 15 hours of admission when \(P_{aO_2}\) was more than 70 mm Hg. Cardiac output values were not reported. These investigators found normal pulmonary capillary wedge pressures in all patients during an expiratory pause while disconnected from the ventilator. Pulmonary compliance data were not reported. Pulmonary arterial pressures were either normal or slightly elevated, and no patient had a mean pulmonary arterial pressure exceeding 25 mm Hg. In no patient in this study did the pulmonary diastolic–wedge pressure difference exceed 5 mm Hg. A-aD\(_{O_2}\)'s during breathing of 100 per cent oxygen in this group ranged from 100 to 481 mm Hg. In all cases diffuse opacification was seen on radiographic examination of the chest. Warshaw \textit{et al.}\textsuperscript{101} studied four patients who had acute pulmonary edema associated with pancreatitis within 24 hours of onset of respiratory symptoms. All these patients manifested normal pulmonary arterial pressures (mean = 20 mm Hg), normal wedge pressures, and elevated cardiac indices (greater than 4.0 l/min^2·min). Pulmonary arterial diastolic–wedge pressure differences were 7 mm Hg or less and pulmonary vascular resistance was normal.

These studies indicate that pulmonary hemodynamics within the early phase of ARF are normal despite serious, and occasionally life-threatening, impairment of pulmonary gas exchange.\textsuperscript{102}

In contrast to the paucity of data relating to the early stage, more detailed studies of pulmonary hemodynamics during the later clinical stages of ARF have been reported. Zapol \textit{et al.}\textsuperscript{102} reported detailed data from 16 previously healthy patients with a wide variety of illnesses. Hemodynamic data were available within one to three days of the onset of respiratory symptoms for eight of these patients and for the duration of ARF in every case. The patients in this selected series had predominantly pulmonary failure and minimal dysfunction of other vital organs at the onset of the study. Ten of these patients entered the NHLBI randomized ECMO study, and one of the ten survived. Six other patients were studied prior to the NHLBI study, and three of these survived. With progression of time and disease, pulmonary hypertension and elevated pulmonary vascular resistance were universally found. Fixed pulmonary hypertension with either increases or decreases in pulmonary blood flow resulted in an inverse (curvilinear) relationship between cardiac output and pulmonary vascular resistance during conditions of arterial normoxemia and \(P_{vO_2} > 28\) mm Hg. An example of this finding is illustrated in figure 4.
Pulmonary vascular resistance was elevated at all levels of pulmonary blood flow, but especially when cardiac indices were below 4 l/m²·min. This series has recently been expanded to include 30 patients.103

Fallat et al.104 and Lamy et al.105 obtained similar data in a study of severe ARF with Q/Qs 31–51 per cent. Again, the patients were similar to those of Zapol, with poor responses to all forms of therapy and an overall in-hospital mortality rate of 67 per cent. Again, severe pulmonary hypertension with an inverse relationship of pulmonary blood flow and pulmonary vascular resistance was evident in the three groups of patients reported by these authors. Clowes et al.106 studied 38 surgical patients who had non-thoracic sepsis and divided them into high-cardiac-output (30 observations) and low-cardiac-output (18 observations) groups. Patients in both groups had Q/Qs 30 per cent or more. Pulmonary hypertension was evident in both groups (mean = 28 and 29 mm Hg), but mean pulmonary vascular resistance was 3.5 mm Hg/l·min in the high-flow group versus 7.7 mm Hg/l·min in the low-flow group.

Powers et al.32 also found an inverse correlation of cardiac output and pulmonary vascular resistance.

Elevated pulmonary vascular resistance imposes an increased pressure workload on the right ventricle and results in increased right ventricular stroke work index at all levels of cardiac output during ARF.102,103 This will result in the previously detailed sequence of events. Unfortunately, measurement of CVP, PCWP, and cardiac output does not allow for dynamic assessment of biventricular function during this right ventricular afterloading. The physician is therefore left “in the dark” in predicting the effects of further increments in PEEP and deciding when to employ inotropic agents for right ventricular failure. We have recently employed gated cardiac blood pool scanning106 at the bedside of a patient with severe ARF (See fig. 5). With this noninvasive technique it can be shown that a poorly contractile dilated right ventricle (ejection fraction approximately 30 per cent of normal) provides the same stroke volume (91 ml/beat) as the smaller-than-normal hypercontractile left ventricle. Serial PCWP measurements over the course of time may give the misleading impression of true left ventricular failure when in fact the problem may lie primarily with the right heart. Findings in chronic cor pulmonale have been similar to our observation in ARF.107–109 In figure 5 we also indicate the reversible nature of right ventricular failure with clinical convalescence. The patient underwent repeated right heart catheterization and gated cardiac blood pool scan seven weeks after ARF. At this time both ventricles were seen to be of normal size and contractility, while pulmonary arterial pressure and vascular resistance had returned to normal ranges.

What is the etiology of pulmonary hypertension in severe ARF? Zapol et al.101 have recently reported results of pathologic examinations of six postmortem ARF lungs maintained inflated and perfused at 50–100 mm Hg with silicone polymers. They found markedly diminished alveolar capillary network, in comparison with normal lungs. Additional findings included occasional areas of pulmonary infarction.

Regional or generalized vasoconstriction may account for pulmonary hypertension, although supporting data are sparse. As a rule, increasing flow by whatever means reduces pulmonary vascular resistance.102,103 As anatomic destruction occurs, patients become refractory to both inotropic and vasodilator therapy (fig. 6). In pre-terminal stages a low-cardiac-output syndrome and an elevation of CVP refractory to all pharmacologic support may be seen. There would seem to be evidence for both flow-dependent recruitable components and destroyed elements within the pulmonary circulation in severe ARF.
Fig. 6. Absent pulmonary vascular response to vasodilator therapy in severe ARF. The patient had severe ARF secondary to aspiration pneumonitis following drug overdose. This patient initially responded to isoproterenol with a modest increase in cardiac index and decrease in PVR. Note (arrow) the absence of response to increased isoproterenol infusion (8 μg/min) plus addition of two vasodilators with progression of the illness. The patient died with refractory low-cardiac-output state. Reproduced with permission from Zapol WM, Snider MT, Schneider RC, et al: Pulmonary hypertension in severe acute respiratory failure. Artificial Lungs for Acute Respiratory Failure, Edited by Zapol WM, Qvist J. Washington, D. C., Hemisphere Publishing, 1976.

In using the Swan-Ganz catheter for hemodynamic assessment of severe ARF, one must account for the effects of both positive airway pressure and vascular injury on PCWP. Eberhart et al. reported results of simultaneous left ventricular retrograde catheterization and PCWP measurement during ECMO in four patients; without PEEP, PCWP was 4–7 mm Hg higher than left ventricular end-diastolic pressure. Zapol and Snider studied 20 patients who had severe ARF with mean pulmonary arterial pressures of 32.43 mm Hg during 20.5 cm H₂O PEEP. Acute airway disconnection for 5 seconds resulted in a decrease of only 3 mm Hg in mean pulmonary arterial pressure with a similar (2.33 mm Hg) decrease in pulmonary capillary wedge pressure. The same group also studied one patient with simultaneous left ventricular retrograde catheterization (fig. 7) and found close correlation of PCWP with left ventricular end-diastolic pressure in increments of PEEP from 0 to 30 cm H₂O. It would thus seem that with severe hypoxemia and marked reductions in pulmonary compliance there is a relative isolation of the pulmonary vasculature from airway pressure. The discrepancy between PCWP and left atrial pressure will also depend on the presence of anatomically preserved blood vessels in the lung distal to the Swan-Ganz balloon. When infarction and thrombosis are present, recordings will not be those of downstream vascular pressure. Again, the clinician must be aware of the peculiarities and limitations of wedge pressure measurements and correlate pressure with flow measurements and other indicators of physiologic performance in arriving at rational therapeutic decisions.

IV. Mechanical Ventilation and Weaning

A. Objectives of Mechanical Ventilation

Several objectives must be met when using mechanical ventilation. The first is to provide adequate oxygenation and carbon dioxide elimination.

Fig. 7. Isolation of cardiac filling pressures from PEEP in severe ARF. Pulmonary viral pneumonia in a young woman. Static compliance was 13 ml/cm H₂O. The patient underwent venoarterial partial bypass, which permitted wide variations in PEEP. Left-heart retrograde catheterization via ECMO arterial return permitted comparisons of simultaneous PCWP and left ventricular end-diastolic pressure. Reproduced with permission from Zapol WM, Snider MT: Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 296:476–480, 1977.
without short- or long-term harmful consequences, to the respiratory or any other organ system, especially the circulatory and renal systems; second, create optimal conditions for the potential healing of the primary pulmonary injury; third, initiate resumption of spontaneous ventilation as early as possible in the course of recovery. When treating patients who have pure ventilatory failure, these objectives can all be met with meticulous application of available knowledge and techniques.

The optimal approach to management of severe acute pulmonary disease and respiratory failure is still in dispute. We believe that patients differ so much in pathophysiologic and clinical manifestations that individual management, based on careful assessment of responses, is necessary. Some of the pertinent considerations are discussed in the following paragraphs.

B. Effect of Ventilatory Pattern on Gas Exchange

The Inspiratory Phase

Many investigators have explored the influence of the inspiratory pressure waveform on the efficiency of gas exchange. Experimental and clinical investigations and extensive use of mathematical and computer modeling have failed to show convincingly that the configuration of the inspiratory pressure flow pattern is of major clinical importance. Nonhomogeneous properties of diseased lungs with regional variations of resistance to airflow and compliance, in part caused by gravitational effects, induce an uneven distribution of inspired gas. In addition, small-airway and alveolar closure may further contribute to maldistribution of inspired gas, gas trapping, and ventilation–perfusion inequality.

Jansson and Johson, using a two-compartment lung model and computer analysis, showed that when flow resistance of lung compartments differed, a more uniform distribution of ventilation was favored by: 1) a low flow rate with prolonged inspiration, 2) a decelerating inspiratory flow, and 3) use of end-inspiratory pause (no-flow state at end inspiration; lung volume equal to FRC plus tidal volume). In contrast, when compliance differed among compartments, the three maneuvers listed above contributed to a slightly more uneven distribution of ventilation.

Similar findings have been reported by Lyager, who used a lung model, and confirmed the fact that faced with increased airway resistance the overall distribution of inspired gas is improved with low flow rates, without volume acceleration, and use of an end-inspiratory pause. In the presence of a regional increase of elastic resistance (decreased compliance), the distribution of inspired gas is improved with rapid inspiration and high-volume acceleration; an inspiratory pause offers no advantage under such circumstances. Both studies confirm that in the presence of abnormal airway resistance the use of the end-inspiratory pause results in optimal distribution of ventilation regardless of flow rates used.

Studies in healthy dogs under general anesthesia confirmed the results of modeling, namely that an end-inspiratory pause improves the overall ventilation–perfusion ratio, shunt fraction, and Vp/Vt when used with square-wave or accelerating waveforms. When unilateral bronchial occlusion was produced in an animal model, Sabar et al. found that an even inspired gas distribution and CO2 elimination are favored at low-frequency ventilation with use of an end-inspiratory pause, compared with other patterns. Recently, Fuleihan et al. showed that use of the end-inspiratory pause in patients with acute respiratory failure had minimal effects on gas exchange. Arterial oxygen tension remained unchanged when such a pause was added to a large-volume (12 ml/kg) square-wave pattern. Improvement in deadspace ventilation and Paco2 was produced with end-inspiratory pauses 0.6 and 1.2 seconds in duration, compared with the same pattern without the pause.

The Expiratory Phase

Regional reduction in lung volume with secondary small-airway closure, atelectasis, ventilation–perfusion inequality, and increased shunting are the most common pulmonary complications in hospitalized patients. Restoration of functional residual capacity (FRC) towards normal values using positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) is among the greatest therapeutic advances of the past decade. Therapy is usually guided by the effect on arterial oxygenation, since measurement of thoracic gas volume and demonstration of airway closure do not lend themselves to routine clinical use.

The greater the pulmonary compliance, the greater the improvement in FRC and thus oxygenation per cm H2O end-expiratory pressure applied. PEEP influences the distribution of both ventilation and blood flow, and probably has many additional effects, e.g., on the quantity and distribution of extravascular lung water, on pulmonary and systemic lymphatic drainage, and on the right ventricular afterload. The effect of PEEP on altered distribution of ventilation and perfusion was recently demonstrated by
Hammon et al.\textsuperscript{120} in primates. In mechanically ventilated, normal primate lungs addition of 5 cm H\textsubscript{2}O PEEP produced an increase in ventilation and improvement in $V_A/Q$ distribution in dependent regions (Zone III). Levels of PEEP exceeding 5 cm H\textsubscript{2}O, however, produced hyperventilation of all lung zones, more prominent in Zone I, and increased $V_d/V_T$. Acute pulmonary injury (oleic acid infusion) created marked regional changes in ventilation-perfusion ratios with dependent-lung hypoperfusion and apical hyperperfusion. This resulted in reduction of perfusion in relation to ventilation in Zone III and the opposite effect in Zone I. Such maldistribution was associated with arterial hypoxemia and decreased $V_d/V_T$. Step-by-step increases in PEEP from 5 to 15 cm H\textsubscript{2}O led to progressive improvement in the distribution of ventilation and blood flow in Zones I and III.

Most patients who have ARF and increases in $Q_s/Q_t$ respond to incremental levels of PEEP with almost linear increases in FRC and $P_{aO_2}$. Unfortunately, as mean intrathoracic pressure rises, so does pulmonary vascular resistance; right ventricular function may be impaired; and the risk of pulmonary barotrauma with mediastinal and subcutaneous emphysema and tension pneumothorax probably also mounts in proportion to airway pressure.\textsuperscript{121,122} Thus, a balance between benefits and complications of therapy must be attempted.

At present there is no agreement on what level of PEEP should be considered optimal and which criteria should be used to define such a level. An early, conservative approach was to limit PEEP to values sufficient to allow reduction in inspired oxygen concentration to below 50–60 per cent. Suter and co-workers\textsuperscript{124} have recently proposed that the optimal or "best" PEEP is the level associated with the maximal oxygen transport (cardiac output \times arterial oxygen content). In a study of 15 patients with acute respiratory failure, "best" PEEP (maximal oxygen transport) coincided with the maximal total respiratory system compliance as measured by the ratio of delivered tidal volume to plateau inspiratory minus end-expiratory pressure (fig. 8). The "best" PEEP levels varied widely among patients, ranging from 0 to 15 cm H\textsubscript{2}O. Patients who had abnormally low FRC's at zero PEEP required higher levels of PEEP to reach this point, compared with patients with initial normal or high FRC's. Improvement in arterial oxygen tension was linearly related to increases in PEEP, confirming previous observations.

The effect of increasing PEEP on pulmonary elastic recoil is determined in part by the balance between initial recruitment of previously unventilated alveoli and the progressive distention of open alveoli that occurs as airway and alveolar pressures continue to rise. As mean intra-alveolar pressure in communicating air spaces rises, blood flow is impeded and, as a result, the $V_A/Q$ inequality and $V_d/V_T$ become greater. Suter et al.\textsuperscript{124} found that at their definition of "best" PEEP, $V_d/V_T$ was minimal and coincided with the highest total respiratory system compliance.

One difficulty in applying the "best" PEEP concept clinically is the variable blood volume status of many patients who have ARF. The reduction in cardiac output that may follow PEEP, as previously discussed, is largely secondary to a reduction in transmural filling pressures. This is easily corrected by volume expansion, which establishes a higher level of oxygen transport. Another consideration is that peak and plateau pressures, and hence calculated compliance, are a function not merely of end-expiratory
C. Effect of PEEP on Pulmonary Blood Flow in Severe ARF

Measurement of local alveolar distending forces is not possible at present in the clinical setting of ARF. Inferences as to the response of the circulation to airway pressure must be based on global measurements within the limits of physical forces applied to the airway. In the normal lung, pulmonary vascular resistance (PVR) is volume-dependent, being lowest at FRC, and increasing as much as 100 per cent with application of 12 cm H2O PEEP. This presumably is primarily due to transmission of intra-alveolar pressure to perialveolar vessels. In ARF, an increase in the non-gas volume within the thoracic cavity (e.g., blood edema fluid, tissue) displaces gas and in part explains the low FRC characterizing this state. It is not known to what extent this encroachment upon the FRC modifies the normal relationship between PEEP, lung volume, and PVR. In severe ARF, PVR appears relatively independent of PEEP-induced changes in FRC (fig. 7) and more dependent on total pulmonary blood flow, as has been demonstrated by Zapol and Snider. This reduced response of the pulmonary circulation to changes in airway pressure presumably is based on morphologic changes associated with ARF. The mean alveolar pressure during mechanical ventilation must exceed end-expiratory pressure even in terminal air units with very low V̇A/Q̇. With high levels of PEEP, intra-alveolar pressures may exceed mean pulmonary arterial pressure. Despite severe intrapulmonary shunting, most of the cardiac output in patients who have ARF behaves "as if" fully oxygenated (Q̇/Q̇ 25–30 per cent is common in severe ARF). Most blood traversing the lung must, therefore, flow past open, gas-exchanging alveoli, which are likely to have a pressure exceeding that in perialveolar vessels. Incomplete transmission of high alveolar pressures to perialveolar vessels must be assumed and implies major changes in the morphologic and physical characteristics of blood-gas-exchanging structures of the lung. This in turn raises questions concerning the
validity of models proposed for \( V_A/Q \) distribution in ARF.\textsuperscript{128–130}

It is difficult to draw firm conclusions of therapeutic value from the experimental and clinical studies of the effects of PEEP on gas exchange, pulmonary mechanics and circulation. A rational approach would be to employ PEEP of sufficient magnitude to reduce \( Q_s/Q_t \) to levels consistent with use of safe levels of inspired oxygen, a maximum of 60 per cent but preferably below 35–40 per cent. If major circulatory depression and reduction in urinary flow follow, they can usually be corrected by blood-volume expansion. Tidal volume and inspiratory pressure may be reduced if necessary to maintain the lung on the steepest portion of its pressure–volume curve (fig. 9). The time frame of reference must also be considered. The most appropriate level of PEEP as determined by acute studies need not coincide with the most appropriate level needed for chronic administration. Other factors, including pulmonary barotrauma\textsuperscript{231} and effects on circulation, interstitial fluid dynamics, and lymph flow, must also be taken into account.

D. PHYSIOLOGIC CORRELATES OF ABILITY TO SUSTAIN UNASSISTED VENTILATION

There have been many attempts to develop reliable objective criteria predicting a patient’s ability to tolerate weaning from the ventilator, and to sustain spontaneous, unassisted ventilation. Yet the timings of tracheal intubation and extubation, or institution and cessation of mechanical ventilation, remain largely arbitrary clinical decisions.

To predict a patient’s ability to sustain unassisted breathing, one must consider not only the work of breathing required but also the ability to perform the necessary work and the extent of reserve power available for coughing and sighing, important elements in pulmonary defense mechanisms. The work of breathing is largely determined by the minute ventilation and the mechanical characteristics of the lung and chest wall, that is, airway resistance and the elastic recoil of lung and chest wall. Minute ventilation requirement is dictated by the magnitude of CO\(_2\) production and efficiency of CO\(_2\) elimination (\( V_p/V_T \)), and is easily measured. However, translation of mechanical characteristics into work per unit volume of ventilation is difficult without access to sophisticated technology.\textsuperscript{131} Respiratory work capacity is even more difficult to assess and can be estimated only by clinical observations of strength, endurance, mental status, motivation, reaction to stress, and respiratory muscle coordination. The ability of the circulation to compensate for abrupt changes in distribution of blood volume and increases in cardiac filling pressures is also of critical importance.\textsuperscript{132,133} It is not surprising that the “trial-and-failure” approach to weaning is common practice.

The physiologic correlates indicative of ability to sustain unassisted breathing have been explored in two recent studies. In a prospective study of 100 patients who had respiratory failure, Sahn and Lakshminarayan\textsuperscript{134} found excellent correlations of ability to tolerate cessation of mechanical ventilation and the following four criteria: 1) adequate oxygenation with 40 per cent inspired oxygen and stable clinical condition; 2) resting minute ventilation less than 10 l/min; 3) ability to double minute ventilation during maximal minute ventilation maneuver; 4) peak negative airway pressure on maximum inspiratory effort (inspiratory force) more than 30 cm H\(_2\)O.

Browne \textit{et al.}\textsuperscript{2**} measured several indices of gas exchange, pulmonary mechanics and circulation in 25 patients during three stages of weaning, each defined by ability to tolerate (as determined by medical and nursing staff providing respiratory care) 10 minutes, 1 hour, and 24 hours of unassisted breathing. Values for ventilatory reserve (vital capacity and inspiratory force), oxygenation (A-aD\(_{O_2}\)), and P\(_{aCO_2}\) change are illustrated in figures 10 and 11. Only vital capacity and inspiratory force correlated with progressive ability to sustain unassisted breathing. A-aD\(_{O_2}\), V\(_p/V_T\) and static total respiratory system compliance (measured during controlled mechanical ventilation) did not change significantly as weaning ability progressed. The mean ± SD for V\(_p/V_T\) associated with successful weaning was 0.50 ± 0.13, and confirmed previous observations that a V\(_p/V_T\) above 0.60 is rarely consistent with an ability to sustain unassisted breathing.\textsuperscript{135} The 25 patients studied by Browne were divided into three groups according to the underlying causes of respiratory failure leading to initiation of mechanical ventilation: 1) ventilatory failure secondary to neuromuscular disease; 2) acute pulmonary failure without chronic obstructive disease (COPD); 3) acute exacerbation of COPD. The only significant difference among the three groups was an elevated P\(_{aCO_2}\) observed throughout the weaning period in patients who had COPD.

The importance of establishing correlates of ability to sustain unassisted breathing is not confined to the management of weaning from mechanical ventilation and positive airway pressure. Definition of reliable, simple criteria for tracheal intubation and mechanical ventilation has potential clinical value in proper

management of the early, evolutionary stages of respiratory failure. There is remarkable agreement among empirically established guidelines for initiation of mechanical ventilation\(^7\) and those compiled from clinical studies of weaning ability summarized above. Although controlled studies are lacking, this agreement enhances confidence in applying objective criteria as guidelines in respiratory care.

A reduction in FRC with atelectasis and small-airway closure is common in mechanically ventilated patients, and a further reduction may follow disconnection from the ventilator. Continuous positive airway pressure (CPAP) of 5–10 cm H\(_2\)O is now widely employed to increase FRC towards normal and prevent progressive atelectasis and small-airway closure attendant upon transition from mechanical to spontaneous ventilation.\(^{136}\) CPAP may also ameliorate the circulatory response to change in cardiac filling pressures attendant upon abrupt reductions in mean airway pressure, as discussed elsewhere in this review.

### E. Intermittent Mandatory Ventilation (IMV)

Intermittent mandatory ventilation has recently been introduced as an attractive alternative to conventional mechanical ventilation and weaning.\(^{137}\) This technique allows a patient to continue spontaneous breathing efforts via the ventilatory circuit with or without addition of positive end-expiratory pressure. The ventilator augments the patient’s minute ventilation by delivering a preset tidal volume at intervals varying from 5 seconds to several minutes. The frequencies of ventilator breaths are progressively
reduced to a minimal rate compatible with an arterial blood pH of 7.35 or more.

Intermittent mandatory ventilation has several potential advantages over other techniques of mechanical ventilation (e.g., patient triggered or controlled) and as a method for weaning during IMV. Spontaneous respiratory muscle activity is maintained throughout the acute course of respiratory failure, in contrast to controlled ventilation, with which such activity is largely abolished. With the latter, disuse of respiratory muscles may contribute to discoordination between chest wall and diaphragmatic function, commonly observed in patients with ARF and with acute exacerbation of COPD. The presence of spontaneous respiratory activity may also be beneficial when considering both cardiovascular function and distribution of inspired gas in the presence of acute pulmonary injury. These potential advantages are, by and large, theoretical, since controlled studies in the laboratory and in clinical settings are not currently available. The intricate relationship between cardiovascular and respiratory functions during mechanical ventilation, including the important roles of mean airway and intrathoracic pressures, has been considered in detail, (Sections II and IV; figure 9). The ability to maintain adequate circulatory function with IMV and high PEEP, as reported by Kirby et al., is probably due to lower mean airway and pleural pressures during IMV, compared with controlled mechanical ventilation at similar PEEP. Thus, higher levels of PEEP, with reductions in \( Q_{\text{oxygen}} / Q_{\text{vent}} \), are possible with this method.

A second theoretical advantage of continued diaphragmatic activity is the theoretical effect on distribution of inspired gas. During spontaneous breathing, inspired gas is preferentially distributed to dependent lung regions, in contrast to positive-pressure ventilation, where distribution favors non-dependent regions. Thus, the presence of both spontaneous and passive ventilation during IMV may provide more uniform gas distribution to all regions of the lung and hence improve \( V_{\text{A}}/Q \) distribution. Finally, use of IMV reduces the need for excessive therapy with adjunctive drugs, including sedatives, narcotics, and muscle relaxants, which are often necessary during controlled ventilation.

Weaning with IMV will generally be initiated at an earlier stage in the course of disease, compared with use of the conventional (e.g., T-piece) techniques. In our experience, weaning from IMV lessens the demand on ICU nursing and technician personnel for concentrated bedside observation, in comparison with conventional methods, where close and continual observation during each weaning episode is mandatory. Thus, in face of limited staffing, IMV may provide a more efficient, safer method.

The gradual transition from mechanical to spontaneous respiration, inherent in the IMV technique, may be advantageous for selected patients in whose cases limited cardiac function and sudden changes in intra-vascular volume status might limit weaning from conventional methods. Although several advantages of IMV have been cited, additional clinical experience and an improved understanding of the physiologic implications of this method are necessary before its ultimate value and true application in ventilatory therapy can be precisely assessed.
58. Menkes HA, Tratman RJ, Bromberger-Barnea B: Interdependence of the chambers of the heart during ventilation with positive end-expiratory pressures (abstr). Circulation 50 (suppl II):22, 1974
RESPIRATORY INTENSIVE CARE


