〔特別講演〕

〔第7回人工呼吸研究会論文集〕

Curreut Concepts in the Treatment of Acute Lung Injury

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Introduction

For more than four decades, clinicians have recognized with increasing frequency a characteristic form of pulmonary insufficiency in adult patients with no apparent preexisting lung disease. Termed acute lung injury (ALI), this condition affects both medical and surgical patients. Thousands of adults each year suffer from ALI,[1] and current reported survival rates vary between 30 and 80%[2)3)]. Recent attention has been directed to the length of hospitalization and intensive care required to treat these patients since the socio-economic consequences of ALI are impressive, especially when one considers the effects of long-term morbidity. Many authors have assumed that successful treatment of ALI occurs only in a minority of patients.[4] Similarly, many believe that currently available treatment modalities are ineffective for the vast majority of patients. For example, in 1973, we reported that 75% of our patients with severe ALI died.[5] Similar survival rates currently are reported by clinicians using standard ventilatory techniques. However, we have signigicantly altered our treatment regimen during the last fifteen years and believe that we can markedly decrease the mortality and morbidity rate[3].

Although researchers have isolated many possible etiologic factors associated with ALI, the pathophysiologic responses of the lung to acute injury are similar. Clinically, patients are tachypneic and dyspneic, often in spite of normal alveolar ventilation and carbon dioxide excretion. Frequently, chest wall retraction is present, in spite of shallow tidal breathing. Decreased tidal volume is responsible for an increase in the physiologic dead space-to-tidal volume ratio, rather than an actual increase in physiologic dead space. Functional residual capacity (FRC) is reduced, as is vital capacity, indicating significant reduction in total lung capacity. Frequently, early manifestations of ALI are not evident with chest roentgenograms but may become progressively evident during later stages as interstitial edema and alveolar flooding occurs. Laboratory analysis reveals few abnormalities, with the exception of a marked decrease in arterial blood oxygenation. Frequently, hyperventilation is associated with hypocarbic alkalosis. Early in the process, hyperventilation may maintain arterial oxygen tension in a near normal range, but the alveolar-to-arterial oxygen tension difference is always abnormal when low inspired oxygen concentrations are applied. Usually, a protein-rich fluid fills the lung interstitium and alveolar spaces. Eventually, the protein-filled alveolar spaces organize with

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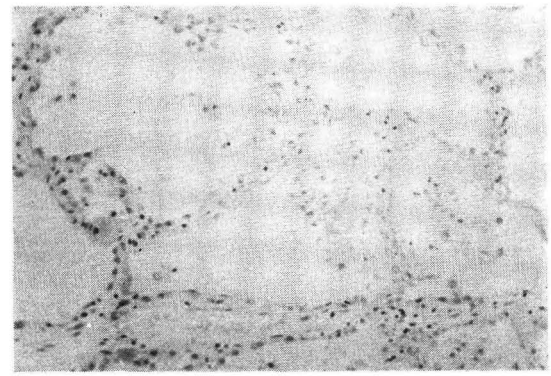
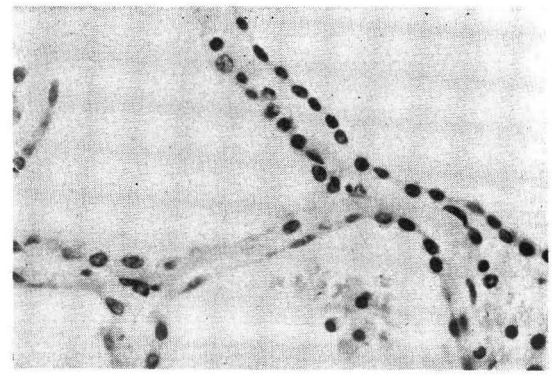
hyaline membrane formation and fibrosis. Unless death occurs, alveolar epithelum eventually becomes a continuous cuboidal epithelial lining with a marked proliferation of fibroblasts.

Apparently, alveolar type Ⅱ cells dedifferentiate and assume a reparative function. (**Fig. 1**) We have found that such a reparative process begins within hours to days of the onset of ALI and may continue for weeks or months in surviving patients[3]. Thus, early supportive therapy may allow restoration of normal lung function, as long as the etiologic factors are eliminated and subsequent insults are prevented. We base our current approach to the treatment of patients with ALI upon the philosophy that the condition is often precipitated by a short-lived insult and that early aggressive supportive therapy will allow normal reparative mechanisms to eventually restore normal pulmonary function. However, this simplistic philosophic approach is often difficult to achieve in actual practice.



(a)



(b)

Fig. 1

a. Microscopic view of regenerating lung tissue from a patient with severe ALI who died of severe cardiac failure secondary to septicemia. The patient was spontaneously breathing 30% oxygen with 15 cmH_2O CPAP and had a Pa_{O_2} of 70 mmHg when he died. In spite of continuing pulmonary edema, lung function was excellent and alveolar type Ⅱ cells are seen in markedly increased numbers. In the absence of CPAP, lung collapse and hypoxemia occurred within seconds.

b. Higher power view of the same lung tissue.

Physiologic approach

Ample past and current evidence suggests that patients with appropriate supportive therapy rarely die of arterial hypoxemia secondary to ALI; rather, they succumb to the secondary effects of ALI and the complications of therapy[6]. With this fact in mind, we may logically approach the treatment of patients with ALI with the intent to maintain normal pulmonary physiology and to discontinue therapy as soon as possible. Specifically, we attempt to maintain normal alveolar ventilation ($\dot{V}_A$), adequate cardiac output ($\dot{Q}$), normal matching of $\dot{V}_A$ and $\dot{Q}$ within the lung, and adequate lung compliance to minimize spontaneous work of breathing. In addition, the approach places equal emphasis on efficient termination of therapeutic interventions.[7] Application of this approach has led to remarkable improvement in morbidity and mortality statistics.

Alveolar ventilation

Tidal breathing is accomplished by increases in transpulmonary (transalveolar) pressure during spontaneous or mechanical ventilation. Patients with ALI have a marked decrease in

lung compliance; therefore, tidal breathing is accomplished at the expense of marked increases in transpulmonary pressure. During spontaneous breathing, the stiff lung mandates a marked decrease in intrapleural pressure and increase in work of breathing.[8] For these reasons, many clinicians have recommended control of ventilation by application of positive airway pressure. Although such an approach almost always produces adequate arterial blood carbon dioxide tension, side effects are significant. Positive pressure ventilation will induce mismatching of the $\dot{V}_A$ and $\dot{Q}$.[9] In addition, positive pressure applied to the airway of patients with ALI will result in significant increase in intrapleural pressure with an undesirable decrease in venous return and $\dot{Q}$.

We have found that most patients with ALI will experience significant improvement in lung compliance when continuous positive airway pressure (CPAP) is applied, and such patients will tolerate a significant amount of spontaneous breathing.[8] If mechanical ventilatory support is required, low mechanical ventilator rates may be employed with intermittent mandatory ventilation (IMV), and normal alveolar ventilation may be maintained without marked increases in mean intrapleural pressure. In addition, physiologic dead space and right-to-left intrapulmonary shunting of blood may be minimized. Although claims to the contrary have been made, we have found that assisted ventilation cannot maintain normal alveolar ventilation and optimal matching of $\dot{V}_A$ and $\dot{Q}$. Rather, hyperventilation, alkalosis and decreased cardiac output are common.[10]

Pulmonary blood flow and cardiac output

Venous return and cardiac output may be markedly deranged in patients with ALI during both spontaneous and mechanical breathing. Venous return is directly related to mean intrapleural pressure and right atrial pressure. Application of positive pressure to the airway will increase intrapleural pressure and central venous pressure. Therefore, positive airway pressure will routinely decrease venous return. During assisted or controlled mechanical ventilation, increases in mean intrapleural pressure are significant compared to spontaneous breathing, even when CPAP is applied.[9] Therefore, it is not surprising that most investigators and clinicians believe that mechanical ventilation with an elevated expiratory pressure (EPAP) will decrease cardiac output. However, when CPAP is applied to spontaneously breathing patients, even during IMV, the spontaneous ventilatory effort reduces intrapleural pressure. Thus, spontaneous breathing, with or without IMV, may maintain increased venous return and cardiac output in most patients.[9] The degree of increase in intrapleural pressure depends upon several physiologic variables.[11] The non-compliant lung, frequently observed in patients with ALI, will transmit less pressure. However, a non-compliant thoracic cage, or increased abdominal pressure, increases the transmission of pressure from the airway to the intrapleural space. The fractional transmission of pressure from the airway to the intrapleural space is defined by the following equation:

$$\frac{\Delta P_{pl}}{\Delta P_{aw}} = \frac{C_L}{C_L + C_T}$$

where P_{pl} is intrapleural pressure, P_{aw} is airway pressure, C_L is lung compliance, and C_T is thoracic compliance. Thus, under normal circumstances, 50% of the applied airway pressure will be transmitted to the intrapleural space. It has been our experience that patients with ALI may transmit from 30 to 70% of the pressure applied to the airway to the intrapleural space. Thus, one should attempt to maintain increased transpulmonary pressure,

while working to minimize the increase in intrapleural pressure. Clearly, these two goals best may be achieved with spontaneous breathing.

Numerous reports have indicated that the application of positive pressure to the lung will produce increased pulmonary vascular resist ance (PVR). However, experimental confirmation of this hypothesis was based upon experiments of either anesthetized animals with normal lung volume or patients in whom application of positive airway pressure resulted in abnormally increased lung volumes. Our clinical experience suggests that application of positive pressure to the airway, sufficient to normalize lung volume, results in decreased PVR as would be expected.[12] Thus, the application of CPAP at appropriate levels will probably not increase PVR and right ventricular afterload. Although right heart failure has occurred in patients with ALI, inappropriate and inadequate therapy is a more likely cause than is the application of higher levels of CPAP.

Similarly, numerous reports have suggested that application of positive airway pressure may cause left ventricular dysfunction. Evidence, however, suggests that an opposite effect may occur.[13][14] Positive pressure from the airway may be transmitted to the left ventricle. Such pressure transmission may serve to "unload" the left ventricle. In patients with left ventricular dysfunction, such an "unloading" may improve left ventricular function.[13] Thus, as long as adequate left ventricular preload is maintained, appropriate application of positive pressure to the airway may benefit cardiovascular function. Clearly, positive airway pressure may have detrimental cardiopulmonary effects. However, appropriate application with accurate monitoring will optimize cardiopulmonary physiology.

Matching of ventilation and perfusion

Gravitational effects are significant in the distribution of pulmonary blood flow. However, the distribution of ventilation depends upon transpulmonary pressure and regional lung compliance. Research has determined that the combination of these effects results in marked maldistribution of ventilation and perfusion during mechanical ventilation, often doubling physiologic dead space during controlled mechanical ventilation.[9] In contrast, spontaneous breathing allows a better matching of ventilation and perfusion, minimizing areas of lung with decreased $\dot{V}_A/\dot{Q}$ as well as poorly perfused lung regions which would be converted to dead space-units during controlled mechanical ventilation. Thus, a rationale exists for us to allow patients with ALI to maintain spontaneous respiration during therapy. Many clinicians believe that patients with ALI have significant arterial hypoxemia secondary to areas of lung with decreased $\dot{V}_A$. Ample evidence indicates that application of CPAP will improve ventilation to such lung regions, markedly increasing arterial oxygenation. In addition, application of CPAP during spontaneous breathing will cause far fewer detrimental cardiovascular effects than during controlled ventilation or assisted ventilation. Therefore, we may safely achieve higher levels of CPAP during IMV. We have also found that many patients who could not be adequately oxygenated with lower levels of CPAP could maintain optimal arterial oxygen tension with low inspired oxygen concentrations when we allowed spontaneous breathing to persist.[3]

Current practice dictates that the fractional concentration of inspired oxygen ($F_{I_{O_2}}$) should be maintained less than 0.6 to avoid oxygen toxicity. Evidence suggests that an $F_{I_{O_2}}$ greater than 0.21 may result in absorption

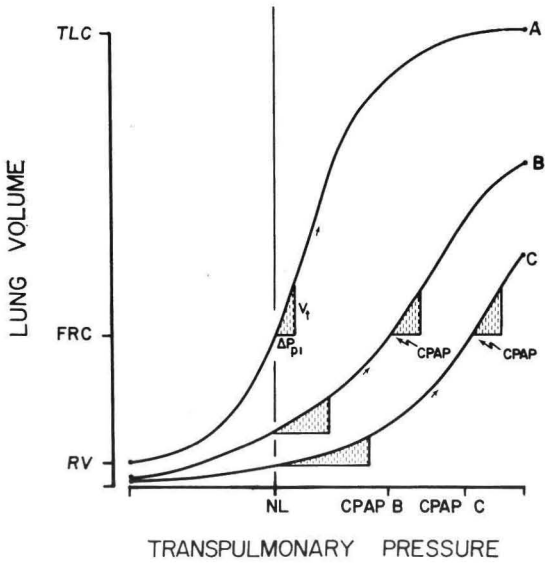


Fig. 2

Curve A represents the pressure volume curve of a normal individual who requires only a small decrease in intrapleural pressure (ΔP_{pl}) to accomplish normal tidal volume (V_t). The elastic work (W_{el}) required for each breath is represented by the shaded area ($1/2 \cdot V_t \cdot \Delta P_{pl}$). A decrease in lung compliance (C_L), represented by a decrease in slope of the pressure-volume curve (curve B), will require a greater change in P_{pl}, in spite of decreased V_t. In addition, W_{el} is increased. In order to maintain alveolar ventilation, respiratory rate must increase. Addition of continuous positive airway pressure (CPAP) will increase functional residual capacity (FRC), C_L, and V_t, and decrease ΔP_{pl}, respiratoay rate and W_{el}. When C_L is severely decreased maximal ΔP_{pl} is insufficient to maintain V_t, even with marked increase in respiratory rate (curve C). Usually, mechanical ventilation is initiated, but CPAP may cause FRC, C_L and V_t to increase sufficiently to allow unassisted spontaneous respiration. Occasionally, this may require high levels of CPAP.

atelectasis and increased right-to-left intrapulmonary shunting of blood in some patients.[15)16)] Therefore, we have made vigorous attempts to maintain the lowest F_{IO_2} possible when treating patients with ALI. The aggressive application of CPAP will allow adequate arterial oxygenation with lower F_{IO_2} than will lower levels of CPAP. Research has yet to determine whether a lower F_{IO_2} promotes more rapid return to normal pulmonary function than will higher inspired oxygen levels. However, substantial evidence suggests that such may be the case. Should absorption atelectasis be a significant problem in patients with ALI, the use of a lower F_{IO_2} and higher levels of CPAP should minimize this abnormality. In addition, application of lesser F_{IO_2} may permit the clinician to decrease CPAP levels with greater success, since alveolar collapse will be less likely to occur with a higher inspired nitrogen level. Clearly, clinicians who have reported higher survival rates and the most rapid rates of discontinuation of mechanical ventilatory support also utilized lower inspired oxygen concentrations than did those clinicians who have reported higher mortality rates and prolonged periods of mechanical ventilatory support.

Work-of-breathing

We may minimize or avoid many problems inherent in controlled ventilation if we allow spontaneous breathing to persist. To this end, the work of spontaneous breathing should be maximally efficient. ALI results in marked decrease in lung compliance and increased work-of-breathing. Application of CPAP will increase lung volume and, will often increase lung compliance, so that work-of-breathing is lessened (**Fig. 2**). To accurately assess change in lung compliance, we must evaluate respiratory mechanics. If the lung pressure-volume curve, shifts to the right and downward, both FRC and lung compliance may decrease, causing a greater intrapleural pressure change for tidal breathing and increased work-of-breathing. The greater negativity of intrapleural pressure may cause subcostal, suprasternal, or intercostal retractions that can be observed clinically. To minimize the work-of-breathing, patients will inhale with decreased

tidal volume and will increase the respiratory rate in an effort to maintain alveolar ventilation. Upon application of CPAP with an appropriate low-resistance circuit, lung volume and lung compliance will likely increase. This change will decrease retractions and respiratory rate, as well as increase tidal volume. Thus, CPAP may improve both arterial oxygenation and lung mechanics. The clinician should evaluate these beneficial effects independently, and select the appropriate level of CPAP to maximize both beneficial effects. In order to accomplish this goal, circuit resistance must be minimized which at this time requires a continuous flow of gas, since demand-valve function cannot adequately minimize the patient's work-of-breathing[17)18)]. In an effort to minimize work-of-breathing, several manufacturers have introduced a pressure-support mode of ventilation. Prakash and Meij suggest that such pressure-support may decrease work-of-breathing[19)]. However, this effect is accomplished by applying positive pressure ventilation to the patient's airway. Thus, many of the benefits of spontaneous respiration are likely to be alleviated by such pressure-support methodology.

From the above discussion, it is clear that patients with ALI have marked arrangement in lung function which may be altered by application of positive airway pressure. Appropriate application of CPAP to spontaneously breathing patients will likely result in decreased work-of-breathing, improved arterial oxygenation, and more efficient alveolar ventilation. Although we can support alveolar ventilation with controlled mechanical ventilation, the detrimental effects on cardiac output and $\dot{V}_A/\dot{Q}$ render controlled ventilation a less than desirable therapeutic technique.

Weaning

Traditionally, patients with ALI have been given high inspired oxygen concentrations and have received mechanical ventilation when necessary. Positive end-expiratory pressure has been applied to the mechanical ventilatory pattern of such patients when adequate arterial oxygenation cannot be obtained with a non-toxic F_{IO_2}. Often, such patients require relative hyperventilation and/or sedation and/or muscle paralysis if the clinician is to achieve proper ventilatory conditions. However, the weaning of such patients from ventilatory support has not been clearly outlined. The usual practice has been to remove PEEP in 3～5 cmH_2O decrements, as long as arterial oxygenation does not deteriorate. Trials of spontaneous breathing with elevated F_{IO_2} are then attempted until patients can tolerate total spontaneous respiration. Often, this weaning process requires weeks to be accomplished. In contrast, our approach to the treatment of patients with ALI greatly simplifies the weaning process. Because early attempts are made to decrease F_{IO_2}, weaning from oxygen therapy is rarely a problem. In fact, this goal is usually accomplished within the first few hours of therapy. Since application of CPAP often improves lung compliance and the patient's ability to tolerate spontaneous respiration, we may accomplish weaning from mechanical ventilatory support within hours or days after initiation of the therapy. Although the initial therapy may require high levels of CPAP, the lung can often rapidly repair itself ; Thus, CPAP may be weaned without deteriora tion in lung mechanics and arterial oxygenation within 3～5 days of the initiation of the therapy. Once CPAP has been decreased to 5 cmH_2O, the clinician may consider extuba tion. Thus, weaning may occur in a controlled

fashion with a minimal degree of stress to both patient and clinician.

Results of therapy

Treatment of ALI is varied, and, in general, clinicians have been unable to agree as to the most appropriate form of therapy. Some authors have suggested that application of PEEP may not influence the morbidity and mortality of ALI[20]. Conservative therapy consisting of tracheobronchial toilet, tracheal suction, oxygen therapy, intermittent positive pressure breathing treatments, and other forms of general respiratory care may, or may not, influence the ultimate outcome of ALI. Clearly, mechanical ventilation with ambient expiratory airway pressure is associated with the highest morbidity and mortality. When positive end-expiratory pressure is added to the ventilatory pattern, mortality is lessened, but morbidity may actually increase. For example, barotrauma is likely to occur when mechanical ventilation with or without PEEP is applied with equipment commonly available in the early 1970's. Improved equipment, however, has allowed us to apply higher levels of airway pressure to spontaneously breathing patients, resulting in reports of marked reduction in morbidity and mortality[3]. Extracorporeal membrane oxygenation was once felt to be a potential therapy for selected patients with ALI. However, a multi-center study which compared the technique to conventional therapy failed to indicate any significant advantage in using it to treat patients with severe ALI,[21] and currently, extracorporeal membrane oxygenation is not considered a valid form of therapy for most cases of ALI.

Between 1973 and 1977, some reports of therapy for patients with severe ALI indicated optimistic morbidity and mortality rates.[3,22] Several authors suggested that apparently excessively high survival rates reported in these series might be secondary to a lesser severity of illness. But other considerations may explain the marked difference in the survival, morbidity, and return to normal pulmonary function registered by these reports. In 1977, we reported the results of our methodology for treating patients with ALI, the findings concerned a series of 561 patients[3]. Ten percent of these patients had sufficiently severe ALI to require CPAP in excess of 28 cmH_2O. Forty-three of fifty-four of these patients were alive and asymptomatic three months following discharge from the hospital. Pulmonary function tests conducted one year after discharge from hospital revealed pulmonary abnormalities to be reversible and pulmonary function to be near normal. Subsequently, other investigators have reported similar results using similar methodology[23]. Granted, these optimistic survival morbidity reports may be spurious. However, it is more likely that significant differences in therapy may lead to significant differences in survival. Clearly, patients who have adequate therapy may rapidly experience positive results, and termination of therapy may be possible at an early stage in the clinical course. Meticulous attention to detail in the philosophy of therapy, the equipment utilized to provide therapy, staffing patterns in the intensive care unit and in minimizing complications of therapy may all contribute significantly to the decreasing morbidity and mortality rate of patients with ALI.[24]

A negative correlation exists between the duration of mechanical ventilatory support and overall survival from ALI[24]. One might contend that individuals with less severe ALI may require a shorter duration of treatment than do patients with more severe ALI and, thus, the likelihood of their survival will

increase. However, the comparison of descriptive data among series does not support the contention that patients who require a shorter duration of therapy are less ill. In our series, mean arterial oxygen tension of patients breathing 100% oxygen averaged 80 torr, and no patient had an arterial oxygen tension exceeding 100 torr prior to application of CPAP.[3] All of our patients evinced increased pulmonary vascular resistance and interstitial pulmonary edema of non-cardiac origin. As in most recently reported series, no patient died from ALI alone. Rather, patients who died appeared to have significant disease, or therapy, related complications such as severe septicemia or refractory cardiogenic failure secondary to septicemia. It is possible that if we use early aggressive therapy, we may significantly shorten the duration of treatment and reduce the complications of therapy as well as the disease process. Such therapy may ultimately increase survival. Few reports have stressed the early aggressive and efficient application of therapy in an attempt to reduce morbidity and mortality. In fact, individuals who have stressed such early aggressive treatment have been criticized for attempting to discontinue therapy too soon[25].

Respiratory care should be directed at pathology, not symptomatology. Mechanical ventilation, oxygen, and CPAP should be administered to patients in independently prescribed amounts. Removal of these therapeutic modalities should follow suit. The method of determining optimal mechanical ventilatory support, F_{IO_2}, and CPAP is not unlike that recommended for any other therapeutic modality. Each method should be applied to achieve a pre-determined goal, each should be continually re-evaluated, and each should be withdrawn when no longer required. Optimal CPAP should be applied to improve the matching of $\dot{V}_A$ and $\dot{Q}$ and to assist lung mechanics to reduce the requirement for oxygen and mechanical ventilation. Reduced F_{IO_2} may promote resistance to atelectasis and may allow more rapid discontinuation of mechanical ventilation and CPAP. Minimal mechanical ventilatory support will eliminate iatrogenic respiratory alkalosis and improve distribution of ventilation. Our approach minimizes the detrimental effects of mechanical ventilation and decreases the possibility of barotrauma. Fourteen years of prospective evaluation have demonstrated the numerous clinical advantages of IMV and CPAP.[26] Overall, this approach has simplified the clinical management of patients with compromised respiratory function and has decreased morbidity and mortality.

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