Back To Basics In The Treatment Of Respiratory Failure

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Abstract

HISTORICAL OVERVIEW

The evolution of ventilatory support and the disease processes treated have gone hand in hand. Initially, patients were ventilated for illnesses which resulted in the inability of the patient to perform the necessary work of breathing. In the 1950's, polio epidemics resulted in a large number of patients treated, first with "iron lungs" and then with positive pressure ventilation. Chronic obstructive pulmonary disease with acute exacerbations formed a second large group of patients treated in that era. However in the 1960's, another entity emerged, an acute failure of oxygenation. This was a form of pulmonary edema associated with low pulmonary microvascular pressures, which thus differentiated it from acute heart failure. Other elements of the syndrome included bilateral diffuse infiltrates, a decreased arterial PO2 which was unresponsive to increasing inspired oxygen tension and decreased pulmonary compliance ([1]). Later in the course of the disease, if untreated, PCO2 increased and this constellation of symptoms became known as the adult respiratory distress syndrome (ARDS). It was characterized by abnormalities in matching of ventilation and perfusion (V/Q mismatch). As these patients often had been subjected to trauma or had sepsis, hypovolemia was common. One result of the V/Q mismatch was an increase in dead space ventilation, which was accentuated when positive pressure ventilation was used. At the other extreme, increased intrapulmonary shunting due to alveolar collapse was well recognized as was a "shunt-like effect" due to alveoli with a low V/Q ratio. Initially the same forms of ventilatory support were provided to these patients, i.e., continuous mechanical ventilation (CMV) with increasing FIO2 to try and overcome hypoxemia. However, this was unsuccessful and hypoxic deaths were common in the ICUs in the 1960's. In 1968, Petty and Ashbaugh ([2]) re-introduced positive end expiratory pressure (PEEP), now for the treatment of ARDS rather than high pressure pulmonary edema. In the early 1970's, the availability of invasive cardiovascular monitoring, the then new technique of intermittent mandatory ventilation (IMV) ([3]) and the unique responsiveness of individual patients to varying levels of PEEP ([4]) led some investigators to combine these modalities for the treatment of ARDS. At the time, PEEP was recognized to affect an improvement in oxygenation which was correlated with an increase in functional residual capacity, a decrease in intrapulmonary shunt and an improvement in ventilation to the areas of low V/Q ratios. Secondly, changing from CMV (usually involving muscle paralysis) to techniques that allowed spontaneous breathing, such as IMV, was postulated to have a number of salutary effects. These included minimizing the increase in intrathoracic pressure which could diminish cardiac output as well as decreasing the number of peak inflation pressures occurring. Since the patients' spontaneous activity can contribute significantly to alveolar ventilation, low IMV rates are often compatible with adequate alveolar ventilation with a lesser degree of cardiovascular depression and a smaller risk of barotrauma.. Invasive cardiovascular monitoring allowed identification of abnormalities in preload, afterload and contractility. Sequential measurements could be used to judge the effect of chosen therapeutic interventions. In addition, gas exchange could be quantitated with the calculation of intrapulmonary shunt and oxygen delivery and other variables related to oxygen transport.

Over the next two decades, this combination was generally accepted for the treatment of mild to moderate degrees of respiratory impairment. Although some groups used high levels of positive end expiratory pressure with the resultant high peak inspiratory pressures ([5]), others were fearful of such an approach. Despite this seemingly orderly progression in the understanding of disease pathophysiology and how this affected therapy, perceptions today about

patients with ARDS have wandered from this approach. In my opinion, the misperceptions that accompanied this "Diaspora" have resulted in poor outcomes and excessive costs. The excessive use of sedation and muscle relaxants was responsible for a longer duration of ventilation and considerable iatrogenetic illness, such as critical illness polyneuropathy. Perhaps it would be worthwhile at this point to recreate the recognition of respiratory failure, how it presented clinically , the "best treatment" then available and the unfortunate outcome. Perhaps a case history might illustrate the futility felt by clinicians in the late 1960's.

CASE HISTORY

In May 1967, a 67 year old male presented to the Emergency Room with hypotension, back pain and a pulsatile abdominal mass. He was transported to the operating room and had a resection of a ruptured but contained abdominal aortic aneurysm. The operation lasted 2 1/2 hours, estimated blood loss was 1.5 liters and the patient was transported to the recovery room with a normal blood pressure and a high urine output. CMV using paralytic agents was accepted as the ventilatory support for all ruptured aneurysms in that hospital in that era. Over the next 24 hours, the patient became cyanotic despite the administration of 100% oxygen. Tidal volumes of 15-20 milliliters per kilogram did not improve oxygenation. Arterial blood gas samples were sent to the anesthesia research laboratory for analysis. When the arterial PO2 had fallen to 40 mm Hg, hypothermia was induced to decrease oxygen consumption. However, the arterial PO2 continued to fall. At the last recorded PO2 value of 20 mm Hg, the patient developed a ventricular arrhythmia and died 36 hours after operation.

PEEP

PEEP had been introduced in the treatment of ARDS at about this time. Over the next 3 or 4 years, what I term "desperation PEEP" was the way it was used. Clinicians used CMV with paralysis first. When the arterial PO2 fell to 50 mm Hg or below on 100% oxygen, 5, 10, or occasionally 15 centimeters of PEEP were added. At the time, (prior to the introduction of the Swan-Ganz catheter) the diffuse infiltrates were often interpreted as pulmonary edema and diuresis instituted. The combination of mechanical ventilation, PEEP and diuresis resulted in hypotension, oliguria and acidosis. Mortality results from this plan of treatment was approximately 90% ([6]). In this study (patients were accumulated in the early 1970's) extra-corporeal membrane oxygenation (ECMO) was considered an alternative to "rest" the lungs. However, mortality in the treatment arm was also 90%. It was this background that led to the events previously described. The introduction of the pulmonary artery catheter revealed that many patients with respiratory failure who had high CVPs had low wedge pressures and needed not diuresis but fluid administration. Further, as the entity of hypoxemia was recognized earlier in the patient's course, hypocarbia was a common accompaniment. CMV was not only unnecessary but harmful because of its pressure related phenomena and its tendency to induce respiratory alkalosis. The utilization of high levels of PEEP (> 15cm) was an alternative to standing by the bedside and watching the patient die of fatal ventricular arrhythmias due to progressive hypoxia. In fact, the 59% survival seen in initial paper (6) should be contrasted with the 90% mortality that was the result of conventional mechanical ventilation with paralysis, but without high PEEP. Given the alternative, the prior limit of 15 centimeters of PEEP was discarded, resulting in striking improvements in oxygenation. However, despite the improvement in outcome, this technique always evoked skepticism. Twenty years later the results were repeated at another institution ([7]). In this institution, patients treated with conventional ventilation who were in a steady downhill course of progressive hypoxemia despite 100% oxygen, were treated with high levels of PEEP. Hypoxemia was reversed and survival achieved at approximately the same rate as the study published 20 years earlier. Yet this simple technique remains underutilized, even today. There remains a prevailing fear of barotrauma and lung damage induced by high volumes and high pressures. This fear of those "high" numbers have been translated into elaborate (yet costly, unproved, less effective, but widely utilized) forms of ventilatory support.

MECHANICAL VENTILATION

The advent of microprocessor ventilators ([8]) and the introduction of pressure support and pressure controlled ventilation led to other therapeutic innovations ([9,10]). A problem hampering correctly tailoring ventilatory support to patient effort was the inability to monitor patient work of breathing. It had long been recognized that neither cardiac nor pulmonary performance could tolerate high pressure loads. When the afterload increases, cardiac output often falls due to a decrease in stroke volume. Compensatory tachycardia is an inefficient compensatory mechanism in terms of myocardial oxygen consumption. Vasodilators work by "unloading" the left ventricle. Recognition of the problem and therapy awaited the introduction of the flow directed pulmonary artery catheter, the thermodilution

technique for monitoring cardiac output and the advent of computers to perform repetitive mathematical calculations. In the pulmonary system, a decrease in compliance as is associated with ARDS increases the pressure component of the work of breathing. According to the "minimal work concept", this pressure work is decreased by targeting a smaller tidal volume. Again an increase in respiratory rate to maintain alveolar ventilation is inefficient and results in respiratory muscle fatigue and then failure. Mechanical ventilation alone does not correct the problem as it completely unloads the respiratory musculature and does not affect oxygenation much. The effects of CMV have often been postulated to create respiratory muscle atrophy just as casting a broken bone results in skeletal muscle atrophy. Animal experimentation by Anzueto ($_{11}$) showed there is an approximately 50% decrease in strength of diaphragmatic contraction after seven days of CMV. With the advent of pressure support ventilation, there was a theoretic improvement over the integration of spontaneous efforts and programmed mechanical breaths termed IMV. These spontaneous breaths in a patient with poor compliance during IMV were inefficient and still a fatiguing work load.. The programmed mechanical breaths increased dead space ventilation and, if the rate was high enough, would result in over ventilation and muscle atrophy. The IMV or SIMV rate commonly written as ventilatory orders in the range of 16 to 22 totally misuses the advantages possible when this technique is used correctly. Thus underventilation with IMV could cause fatigue and over ventilation could cause atrophy.

There is an even more important effect of augmenting spontaneous breaths with pressure support. Spontaneous efforts direct ventilation to areas of low ventilation perfusion ratios. Mechanical ventilation on the other hand directs ventilation to areas of high V/Q ratio, i.e., increased dead space ventilation. Thus maintaining the normal work of breathing encourages ventilation perfusion matching and increases the efficiency of mechanical ventilation. Although IMV has certain advantages over CMV, titrated tidal volume using pressure support can prevent muscle injury due to fatigue and muscle atrophy due to over ventilation. When the patient makes a normal contribution to the work of breathing, the resulting tidal volume is usually 7-8 ml/kg. This is much less than the 12-15 ml/kg used to prevent micro-atelectasis when either IMV or CMV are employed. This low tidal volume however is more effectively distributed due to the patient's spontaneous inspiratory effort. This results in a decrease in dead space ventilation and an increase in ventilation perfusion matching in the dependent portions of the lung where low V/Q ratios predominate.

Pressure support represents a vertical integration of the patient and ventilator effects in creating the tidal volume. If titrated properly, the patient can be limited to a normal intrathoracic pressure change - this would obviously not create an adequate tidal volume if compliance was decreased. However pressure support ventilation would then add sufficient gas to augment the tidal volume by the added positive pressure to provide adequate alveolar ventilation. When this concept was introduced and ventilators manufactured with this capability, the adequacy of titration and pressure support was usually judged by spontaneous respiratory rate. Tachypnea was taken to mean that insufficient ventilation was being provided and thus pressure support would be increased. During the weaning process, recurrence of tachypnea would call a halt to weaning efforts and ventilatory support would be increased.

In fact, ventilatory support can be divided into initiation, augmentation, diminution and extubation. Diminution and extubation are commonly called weaning. While there has been a great deal of clinical interest concerning indications for initiating ventilatory support and a great deal of controversy concerning the proper end points and methodology of augmenting ventilatory support, the phase of diminishing ventilatory support and selecting the moment for pre-extubation trial is rarely discussed. There are many criteria for the pre-extubation trial, again a source of controversy, but most do use tachypnea as an indication that the patient is not yet ready for extubation.

The salutary effect of PEEP on arterial oxygenation led clinicians to decrease inspired oxygen tension. Because there was controversy about high PEEP, many clinicians have accepted perhaps deleterious inspired oxygen tensions. All agree that 100% oxygen is harmful and that there are no detrimental effects below 30-40%. Most agree that true oxygen toxicity does not occur below 60% oxygen. There are two additional effects that may be important to consider. The pathogenesis of ARDS seems to be related to free radical injury to capillary endothelium and the production of cytokines from WBCs marginating along the endothelium as well as those produced in the interstitium. Experimentally, these affects are enhanced by hyperoxia. As a treatment principle, lung damage may be minimized by utilizing the lowest FIO2 possible. Secondly, absorption atelectasis is well recognized at 100% oxygen. However, it has been demonstrated that absorption atelectasis at inspired oxygen

tensions that range from 40-50% occurs not in 15 minutes but over many hours. Thus refocusing the argument about what levels of PEEP are "safe" and "effective" may be appropriate. If oxygenation can be improved to the point that inspired oxygen tension can be decreased to < 40%, pulmonary injury may be minimized and ventilation perfusion abnormalities may not progress to absorption atelectasis and increased intrapulmonary shunting.

Thus the combination of PEEP, combined patient and ventilator efforts in producing a single tidal volume and hemodynamic monitoring can be updated individually. The titration of PEEP is important not because it improves arterial oxygenation and minimizes intrapulmonary shunt but because FIO2 can be reduced to 0.4 or less.

One final piece of the puzzle was contributed by Dreyfus in an animal study titled "High Inflation Pressure Pulmonary Edema" ([12]). Animals were studied with low pressures and normal tidal volumes, high pressures and high tidal volumes (40 ml/kg) high pressure and high tidal volume plus PEEP, high pressure and low tidal volume and finally low pressure and high tidal volume (accomplished by using negative inspiratory pressure). Lung damage was evaluated by extravascular lung water, albumin space and ultrastructure. High tidal volumes with both high and low pressures were associated with interstitial edema, type 1 cellular damage and endothelial cell destruction. High pressure, high volume plus PEEP showed a marked decrease in damage whereas the high pressure with low tidal volume had no ultra structural damage and minimal extravascular lung water accumulation. Thus it is high tidal volumes not high pressures that cause damage and even in these situations, PEEP ameliorates the edema and cellular damage. Yet current concepts of mechanical ventilation have focused on pressure despite recognizing that volume is responsible for the damage. As stated by Tobin,([13]) "To minimize this risk, one would ideally like to monitor alveolar volume, but this is not feasible. A reasonable substitute is to monitor the peak alveolar pressure as estimated from the plateau pressure." In my opinion this appears to be an unwarranted inference since the high pressure, low volume experiments did not produce damage. Pressure controlled ventilation often necessitates either heavy sedation or paralysis. It might lead to deconditioning and prolongation of the entire extubation process. ([14])

Low FIO2 permitted by higher levels of PEEP and pressure support ventilation, monitored by patient work of breathing combine to create less injury. The patient continues normal work of breathing, which will diminish both atrophy of the muscles. It may therefore decrease the number of pre-extubation trial failures ([15]) ([16]). The decrease in total ventilation time will decrease the likelihood of nosocomial infections. Ultimately this avoids the "heavy hand" approach of over ventilation,([17]) prevents iatrogenic complications and ventilator dependency. It is simpler, cheaper, more effective and should result in more survivors who have less residual pulmonary damage.

In the February 5, 1998 issue of the New England Journal of Medicine, 3 articles were published with an accompanying editorial that should have put the fear of high PEEP and high peak inspiratory pressures to rest. It should have curtailed the fascination with "protective ventilation strategies" and should have prompted clinicians to go back to the utilization of "high PEEP", now 25 years old. The first paper by Weg ([18]) evaluated the incidence of pneumothorax and other air leaks in a population of 725 patients with ARDS secondary to sepsis. The data was drawn from a database of a prospective study of aerosolized synthetic surfactant. In a subsequent letter to the editor, they broke down the patient groupings according to peak inspiratory pressure: If the PIP was < 30 cm, there was a 7.9% incidence of pneumothorax. If the PIP was between 50 and 110 cm, the incidence was 7.8%. When patients were divided into no air leaks, pneumothorax or any other type of air leak, there were no differences in the level of PEEP used, the peak inspiratory pressures, the mean airway pressure, the tidal volume or minute ventilation. When patients were examined by the level of PEEP employed, there was a 5.9% incidence of air leak if 0-4 cm were used, 6.6% if 10-14 cm were employed and 7.5% in the range from 20-50 cm. These differences were not statistically significant. There was no difference in 30 day mortality rates. They concluded "our findings do not provide support for the idea that ventilatory pressure should be limited to predefined values such as the static pressure of 35-40 cm water since conventional ventilatory pressures do not appear to effect the lungs adversely". Stewart ([19]) evaluated a ventilation strategy to prevent barotrauma. It has been alleged that pressure or volume limited means of ventilation would decrease the risk of barotrauma and improve the mortality rate. Their study design included limiting tidal volume (7.2 ml/kg in the treatment group vs. 10.8 mL/kg in the control group). Peak inspiratory pressures were 24 cm in the limited ventilation group and 34 in the control group. In the limited ventilation group, 10% developed barotrauma, 38% were treated with

neuromuscular blocking agents, the average ventilator duration was 17 days, 22% received dialysis and the ICU stay was 20 days. In the conventionally treated group, barotrauma was 7% (not different), 22% were treated neuromuscular blocking agents (statistically lower) time of ventilation was 10 days and ICU stay was 14 days. 8% received dialysis (significantly lower). The authors concluded that a strategy of mechanical ventilation that limits peak inspiratory pressure and tidal volume does not appear to reduce mortality and may increase morbidity. Amato ($_{20}$) also reported on a protected ventilation strategy. They performed a static pressure volume curve to determine an inflection point. PEEP was then added at 2 cm above the inflection point. The mean level of PEEP was 16 cm after determination by the static pressure volume curve and, if the P-V curve could not be created for an individual patient,16 cm PEEP was arbitrarily utilized. They also used tidal volumes of 6 ml per kg and driving pressures (PIP-PEEP of < 20cm). Although the 28 day mortality rate was statistically lower in the protective ventilation group, survival to hospital discharge was not different (45% in protective ventilation group and 71% in conventional ventilation group). 66% of patients were weaned from mechanical ventilation in the protective ventilation group compared to 29% in conventional ventilation and the rates of clinical barotrauma were 7% and 42% respectively, despite the use of higher PEEP and mean airway pressures in the protective ventilation group. They found that higher PEEP values and lower driving pressures were independently associated with better survival. Hudson ($_{21}$), a practitioner from those early dismal days described earlier, reviewed the information. He drew the following conclusions. The routine use of tidal volumes of < 10 mL/kg is not warranted or necessary in the great majority of patients with acute lung injury. Second, routine application of the "lung protection approach" as described by Amato can not be recommended until the benefits are confirmed in a multicenter trial. Finally the data of Amato raised questions about the trend toward to use of so called minimal PEEP in patients with ARDS (levels of 5-10 cm water in most cases). The data suggests that the use of more liberal PEEP, and the range of 10-20 cm, might be warranted.

An update of the old concept of optimal PEEP is appropriate. IMV is no longer the preferred mode of ventilation; rather pressure support in association with monitoring patient work of breathing allows more accurate titration of needed ventilatory support. By sustaining patients' own muscle activity and diminishing the initial levels of mechanical support, the concept of weaning is eliminated. In fact, augmentation of spontaneous ventilation using pressure support does result in low peak pressures and low tidal volumes but does not employ neuromuscular blocking agents to achieve that end. It has a less deleterious effect on the cardiovascular system than continuous mechanical ventilation or SIMV at rates of 20 (a common pretense). Having avoided the pressure related effects, higher levels of PEEP continue to be safe and effective means of correcting hypoxemia and allowing FiO2 to be lowered.

Today's combination, spontaneous augmented low volume ventilation, is similar to the concept of optimal PEEP introduced in the early 70s. Better application of pulmonary physiologic monitoring more properly focus the clinician's attention on maintaining the patient's contribution to ventilation and truly utilizing ventilatory support in a far safer and more physiologic manner than controlling ventilation.

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