Alveolar Recruitment during Lung Protective Ventilation in Acute Respiratory Distress Syndrome

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Abstract

This study analyzes the ARDSNet Protocol, Alveolar Recruitment for ARDS Trial (ART), and other smaller studies for the most appropriate method(s) for recruiting collapsed alveoli (atelectrauma) without causing ventilator induced lung injury (VLI).

The ART trials compared a strategy of alveolar recruitment maneuvers (RM) utilizing optimum PEEP and prone positioning (PP) against the survival rates of the ARDSNet Protocol patients.

A study by De Matos et al. (2012) demonstrated through the use of CT imaging that RM’s such as step-wise PEEP increases increased P_{a}O_{2}/F_{I}O_{2} ratios from 125 to 300 and non-aerated alveoli reduced from 53% non-recruited to 8%.

Airway pressure release ventilation (APRV) or Bi-Level has been shown to be very beneficial for lung recruitment and can have a positive effect on oxygenation, cardiac performance, pulmonary vasculature, and end-organ blood flow (Maung & Kaplan, 2011). High PEEP is maintained for most of the respiratory cycle thereby maintaining recruited alveoli.

More studies are needed to fully conclude if P/F ratios are increased after RM’s followed by adequate PEEP to maintain lung recruitment. Does that translate into reduced mortality from ARDS?

Key Words: Acute respiratory distress syndrome (ARDS), lung protective ventilation, recruitment maneuvers (RM), prone positioning (PP) high frequency ventilation (HFOV), Bi-level/airway pressure release ventilation (APRV), atelectrauma, and ventilator induced lung injury (VLI).
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Introduction

Acute Respiratory Distress Syndrome (ARDS) is when illness or injury create inflammation in the alveolar capillary membrane causing the small vessels to leak fluid into the alveoli. The fluid filled alveoli lose surfactant and begin to collapse in mass causing widespread atelectasis and refractory hypoxemia.

There is no direct cure for ARDS and management of hypoxemia plus the underlying causes usually necessitates the use of artificial ventilation via mechanical ventilator. The underlying causes of ARDS are wide ranging. Sepsis, pneumonia, severe physical injury from accidents or trauma, and inhalation injuries can manifest into ARDS.

ARDS is an often fatal disease process. To wit, according to Brodie and Bacchetti (2011), mortality rates range from 22-41%, whereby 20% die of refractory hypoxemia. It can be defined by the presence of bi-lateral pulmonary infiltrates, pulmonary artery wedge pressure (PCWP) ≤ 18 mmHg, and the ratio of arterial oxygen tension (PaO2) and fraction of inspired oxygen (FiO2) PaO2/FiO2 < 200 (Pomprapa et al., 2014). A patient suffering from ARDS suffers increased shortness of breath and work of breathing due to pulmonary edema, and loss of surfactant which leads to alveolar collapse and atelectasis in the dependent regions of the lungs. Opening collapsed alveoli and preventing further collapse by using alveolar recruitment maneuvers (RM) and positive end expiratory pressure (PEEP) titration may be the best prevention for atelectrauma (The ART Investigators Trials [ART], 2012).

Very few treatments have lessened the mortality of ARDS but newer lung protective ventilation strategies along with alveolar recruitment maneuvers have shown positive results.
Modern ventilator modes and volumes that protect the lungs from further injury has been key to increasing the survival rates of ARDS patients.

One primary accepted strategy of managing an ARDS patient is to utilize much lower tidal volumes by predicted weight ($V_{TPW}$) $\leq 6$ ml/Kg while on mechanical ventilation. Maintaining a plateau pressure ($P_{PLAT}$) of $\leq 30$ cmH2O is a primary objective. There is an established survival benefit to maintaining $P_{PLAT}$ of $\leq 30$ cmH2O (Neto et al., 2012). The theory behind these reductions in $V_T$ and $P_{PLAT}$ revolve around the discovery of ventilator induced lung injury (VLI). VLI is caused by the constant over distention (barotrauma) and repetitive alveolar collapse with shearing (atelectrauma) that occurs when mechanical ventilation is utilized at previously acceptable $V_T$ of 8-12 ml/Kg (The ART Investigators Trials [ART], 2012).

Decreases in $V_T$ during mechanical ventilation have helped deal with barotrauma. Modest levels of PEEP have failed to adequately resolve the massive amounts of atelectasis and atelectrauma taking place during the typical ARDS episode. Recognizing early on when dorsal dependent regions of lung tissue are collapsed due to atelectasis should remain a goal for which corrective action should be taken.

Bi-Level or airway pressure release ventilation (APRV) have proven useful in managing ARDS and atelectasis. The higher levels of PEEP utilized with spontaneous breathing at both PEEP levels with a shorter release phase from PEEP (HIGH) to PEEP (LOW) maintain more of an open lung than conventional ventilator settings.

Other strategies for ARDS management include the use of alveolar RM’s and higher PEEP. A RM can consist of any combination of prone positioning (PP), a single maneuver of PEEP increases until PEEP is at 40 cmH2O then decreasing, and/or combining any or all with higher PEEP utilizing mode changes such as Bi-Level. Prone positioning may help to recruit the
dependent regions of the lung. High frequency oscillating ventilation (HFOV) has also been studied as a viable method to keep $V_T$’s low and still effectively treat hypoxemia although the jury is still out on whether this mode is superior to volume ventilation utilizing high PEEP, low $V_T$ strategy.

Inhaled nitric oxide (INO) has been studied as well as extracorporeal membrane oxygenation (ECMO) as a salvage therapy.

ECMO provides an opportunity to rest the lungs and deal with barotrauma during an ARDS episode. ECMO does not, in it of itself, maintain an open lung as desired for the management of a typical ARDS patient but allows for decreases in $FIO_2$ to take place.

Statement of the problem

In the United States an estimated 75,000 ARDS deaths occur with mortality ranging from 27-45% and include 3.6 million hospital days each year (Beitler et al., 2014). Understanding which method or methods to utilize on a given patient remains highly variable at this time.

ARDS patients receiving mechanical ventilation need to avoid having alveoli over-distended, sheared, and collapsed causing atelectrauma or VLI. This needs to be accomplished while maximizing alveolar recruitment in the process. Managing hypoxemia while allowing for some permissive hypercapnia and avoidance of VLI remain the goal.

Purpose of the study

The purpose of this study is to analyze the ARDSNet protocol and the ART trial as well as various other modalities and studies to describe the best practice guidelines for the treatment of ARDS in the mechanically ventilated patient. Preventative methods for avoiding ALI while recruiting alveoli through prone positioning plus optimum PEEP as well as Bi-level and APRV will be addressed in this study. Alternative forms of managing ARDS instead of or in addition to
include alternative HFOV, INO, and ECMO. Identification of the best single practice guideline as well as combination approaches to best treat the patient while causing no additional harm is the focus of this study.

Research questions

The questions posed in this research paper are as follows:

1. Do RM’s offer lung protection versus over-distention of alveoli already inflated?
2. Is a combination of RM’s and PP a better than each strategy by itself?
3. Are stepwise PEEP increases a better strategy than sustained inflation (SI) (PEEP 40 cmH2O x 40 seconds) for recruiting alveoli?
4. Does HFOV offer any additional benefit over volume ventilation utilizing high PEEP, low VT strategy?

Methodology

This review process encompassed numerous studies from 1995-present with most occurring from 2010-present. A literature search was conducted on Google Scholar, OVID, Sage Pub, PubMed, Biomed Central, ProQuest, and Springer Link to discover the most current treatment modalities for the ARDS patient.

Search terms used were: Acute respiratory distress syndrome, lung protective ventilation, positive end expiratory pressure recruitment maneuvers (RM), prone positioning (PP) high frequency ventilation (HFOV), Bi-level ventilation, airway pressure release ventilation (APRV), inhaled nitrogen oxide (INO), acute lung injury (ALI), extracorporeal membrane oxygenation (ECMO), and ventilator induced lung injury (VLI).

Literature review
The problem with instituting mechanical ventilation in the treatment of ARDS has been the use of traditional parameters such as \( V_T \) in the 8-12 ml/Kg range which has been identified as harmful in this patient group. Even though mechanical ventilation is a life-saving therapy, improper usage through the usage of high \( V_T \)’s can worsen VLI (O Meade et al., 2008). There has also been no standardization of treatments that have been identified as best practice guidelines across the nation and around the world. Recruiting alveoli without causing VLI is a primary concern for the treatment of refractory hypoxemia which is the leading cause of death by ARDS.

There have been two different studies performed which have developed specific protocols for ARDS ventilator management and the avoidance of VLI. The ARDSNet protocol was shown to reduce mortality to 31% vs 39.8% in comparison to traditional \( V_T \) settings (Pomprapa et al., 2014). A major study named the Alveolar Recruitment for ARDS Trial (ART) emphasized alveolar recruitment and PEEP titrations to improve upon the 28 day survival rates (The ART Investigators Trials [ART], 2012).

Atelectrauma is thought to be a major contributor in ARDS thus leading to the high mortality rates seen in the disease (O Meade et al., 2008). Atelectrauma is defined as alveolar collapse and barotrauma or volutrauma is defined as a stretch injury (Daoud, Farag, & Chatburn, 2012). Both of which are forms of VLI. Treating the lungs of an ARDS patient on mechanical ventilation without causing further VLI, in addition to the pulmonary edema, alveolar collapse, alveolar de-recruitment, and atelectrauma already taking place is difficult to say the least. Using higher \( V_T >8 \) ml/Kg causes repetitive over-stretching of alveoli which is termed as volutrauma. This volutrauma has led to the “biotrauma hypothesis” which states the higher volume and
higher peak pressures produce and release inflammatory mediators thru the recruitment of neutrophils (Neto et al., 2012).

Several study methods and various ventilator modes as well as PP and ECMO were analyzed to attempt to determine if a combination exists which can greatly increase ARDS survival rates. Also of interest is if any method of treatment created any harm in the form of VLI or in the form of increased mortality whether short term or long term.

ARDSNet Protocol

The ARDSNet Protocol was able to demonstrate positive outcomes for seven pigs using goal oriented protocols during lavage induced ARDS. They utilized the Servo 300 ventilator to implement mechanical ventilation. Predicted body weight (PBW) formulas for male and female were calculated using the following formulas: PBW (male) = 50 + 2.3(height [inches]-60) or PBW (female) = 45.5 + 2.3(height [inches]-60). The goal was to induce ARDS through pulmonary lavage so the pig’s lungs went into pulmonary edema thereby deactivating surfactant which leads to atelectasis and alveolar collapse (Pomprapa et al., 2014). It was determined the pig was in ARDS when their average P$a$O$_2$/F$i$O$_2$ dropped to 70 mmHg indicating severe ARDS. Using a strategy of $V_T \leq 6 \text{ ml/Kg}$ while maintaining a $P_{PLAT} \leq 30 \text{ cm/H2O}$ and an inspiratory/expiratory (IE) ratio of 1:2 via the ARDSNet Protocol as a primary method in the treatment of ARDS in the intensive care unit has a proven clear benefit to patients. One of the interesting facts of the study were that the pigs were disconnected from the ventilator for a period of 10 seconds after being stabilized on the ventilator for two hours. Each pig had marked increase in carbon dioxide (P$c$O$_2$) and decrease in P$_O2$ for up to 30 minutes after just a 10 second disconnect. This is possible because the sudden loss of PEEP allows atelectasis to rapidly occur causing lung de-recruitment and poorer gas exchange.
The ARDSNet Protocol set standards for acceptable pH to be maintained between 7.30-7.45 by setting a respiratory rate (RR) by matching the patient’s minute ventilation (V_E) but limiting the RR to a maximum of 35 breaths per minute (bpm). If pH < 7.30, “the following rules were followed for the management of acidosis: if pH = 7.15 to 7.30, RR should be increased until pH > 7.30 or PaCO2 < 25 mmHg (maximum RR = 35 bpm); if pH < 7.15, RR should be increased to 35 bpm; and if pH remains < 7.15, V_TPW should be increased by 1 ml/Kg until pH > 7.15 (maximum V_TPW = 8 ml/Kg)” (Pomprapa et al., 2014, p. 3). For respiratory alkalosis with a pH > 7.45 a recommended decrease of RR by step-wise -5 bpm until pH drops below 7.45 is achieved. This protocol allows for permissive hypercapnia in its approach.

The protocol stresses checking P_Plat pressures every 4 hours while maintaining P_Plat ≤ 30 cmH2O utilizing an inspiratory hold of 0.5 seconds x 5 breaths and using the average result for the correct number. “If P_Plat > 30 cmH2O, tidal volume per weight (V_TPW) may be decreased by 1 ml/Kg with the minimum value of 4 ml/Kg and if P_Plat < 25 cmH2O and V_TPW < 6 ml/Kg, V_TPW may be increased by 1 ml/Kg until P_Plat > 25 cmH2O or V_TPW = 6 ml/Kg” (Pomprapa et al., 2014, p. 3).

Oxygenation goals for the ARDSNet Protocol call for P_aO2 between 55-80 mmHg or SpO2 between 88-95%. A PEEP ladder is implemented for oxygenation by adjusting both PEEP and F_I/O2 which states PEEP to be set at +5 cmH2O for F_I/O2 of 30-40%. PEEP should be increased to +8 cmH2O for an F_I/O2 of 40-50% and increased to 10 cmH2O for an F_I/O2 between 50-70%. PEEP pressures of +12-16 may be used for F_I/O2’s between 70-90% and PEEP pressure of +18-24 cmH2O for F_I/O2 of 100% (Pomprapa et al., 2014, p. 3).

Since using these ventilation strategies in hospitals since 2000, mortality from ARDS dropped to 31% from just under 40% vs using a V_TPW of 12 ml/Kg (Pomprapa et al., 2014).
ARDSNet Protocol has shown to be the cornerstone for mechanical ventilation treatment for the ARDS intensive care patient. The pH value, oxygenation, and plateau pressure are the primary measurement goals of the protocol. The focal point of the ARDSNet Protocol is $V_{TPW}$ goal of 6 ml/Kg with variability of ± 2 ml/Kg. Protecting alveoli by keeping low $V_T$’s inhibits VLI but may also lead to some decreases in alveoli that are open. Utilizing the PEEP ladder is necessary to keep the lung from de-recruiting during this process.

Alveolar Recruitment for ARDS Trial (ART)

The Alveolar Recruitment for ARDS Trial (ART) was designed to be the most comprehensive study to date involving 80 hospitals around the world (ART, 2012). Its measurement goal is to measure whether there is improvement to the 28 day survival rate of ARDS patients vs. ARDSNet Protocol patients. This on-going study is attempting to compare whether a strategy of alveolar recruitment maneuvers which involves optimum PEEP levels and PP is comparable, better, or worse than the ARDSNet Protocol.

A separate study by De Matos et.al (2012) was to fully study “the open-lung hypothesis”. De Matos et.al showed, through the use of lung CT scanning, that most alveolar lung tissue can be recruited at an acceptable risk thereby ultimately providing better lung protection by breaching the ceiling of $P_{PLAT}$ of 30cm/H2O by reaching a lung opening $P_{PLAT}$ of approximately 59.6 cm/H2O and a mean PEEP titrated after a maximal recruitment strategy (MRS) of 24.6 cm/H2O (De Matos et al., 2012). During MRS maneuvers, a stepwise approach was taken to increase PEEP levels up to 45 cm/H2o and a maximal $P_{PLAT}$ of 60 cm/H2O which far exceeds most lung protective ventilation strategies. This was performed concurrent with CT imaging so visualization of the newly recruited lung tissue could be assessed as to what pressures it takes to obtain massive recruitment. In 51 patients, mean $P_aO2/FiO2$ ratio increased from 125 to 300
after MRS and remained above 300 for the next seven days. They showed that at minimum PEEP levels 53% of lung tissue was non-aerated and that number was reduced to 8% at maximum PEEP and titrated PEEP to 45 cm/H2O. This conclusion runs counter to an older study which utilized a RM of 35-40 cm/H2O for 30 seconds and found an increase in oxygenation to be small and transient (The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network [NHLBI], 2004).

PEEP

In surgical patients without ARDS, general anesthesia caused the sigh reflex people normally have to dissipate while rapid onset of atelectasis occurred in all patients (Hartland, Newell, & Damico, 2015). Atelectasis has been defined by The American Heritage® Medical Dictionary (2007) as “the absence of gas from all or part of the lung, due to failure of expansion of the alveoli.” A major cause of atelectasis results from loss of surfactant which stabilizes alveoli by decreasing the surface tension of the alveoli. Lack of surfactant causes a loss of surface area available to be involved in gas exchange and the subsequent collapse of the alveoli. There are many documented adverse events that occur from contracting atelectasis. Pneumonia has a definite link to atelectasis in the form of a secondary and/or nosocomial infection as well as subsequent increases in health care costs from its complications.

There are reasons to believe it is possible to fully recruit lungs and reverse hypoxemia in ARDS. Recruitment of dependent lungs refers to the intentional increase in trans-pulmonary pressures to re-open collapsed alveoli, i.e. PEEP 40 cmH2O x 40 seconds (Fan, Needham, & Stewart, 2005). There are several different methods of RM’s which can range from optimal PEEP, optimal PEEP + extended sigh, and sustained inflation (SI) 40cm H2O for 40 seconds as well as a progressive or step-wise increase of PEEP up to 40 cmH2O (Guerin et al., 2011). A
study by Borges et.al (2006) utilized inspiratory pressure increases by 5 cmH2O up to 60 cm H2O to achieve a $P_{aO_2} + P_{aCO_2} \geq 400$ mm Hg (Borges et al., 2006). They were able to utilize CT scans and continuous monitoring and showed that 24 of 26 patients were able to keep an open lung for the duration of treatment due to this recruitment strategy without any incidence of barotrauma reported. The study also reiterates the strong relationship between the amount of un-recruited lung tissue and hypoxemia. The Borges et.al (2006) study utilized an open lung approach (OLA) which applied 40 cmH2O PEEP for 40 seconds then PEEP was adjusted to the lower inflection point + 2 cmH2O in keeping with a $V_T$ of 6 ml/Kg. Then a maximum recruitment strategy was applied of PEEP +25 cmH2O and a pressure control driving pressure of 15 cmH2O to produce peak airway pressures of 40 cm H2O then held for 4 minutes. After this, PEEP was increased to 30 cmH2O for two minutes then a two minute resting phase at 25 cmH2O before increasing to Peep + 35 cmH2O and repeating the cycle until peak pressures reached 60 cmH2O. The authors suggest that temporarily breaching lung protective pressures in order to obtain OLA and full recruitment may provide far more benefit than risk. Similar findings suggesting step-wise or progressive RM offered greater lung recruitment and oxygenation while negative effects associated with VLI were significantly lower as compared to SI (Guerin et al., 2011).

Prone Positioning

Prone Positioning (PP) is considered a RM by itself and also may lead to greater success of other RM’s instituted (Pelosi, Gama de Abreu, & Rocco, 2010). PP itself can redistribute ventilation, increase end-expiratory lung volumes, and change regional blood volume and perfusion (Pelosi, Gama de Abreu, & Rocco, 2010). PP was found to have significantly reduced
ARDS mortality in the era of lung protective ventilation that utilizes low Vₜ’s (Beitler et al., 2014). Guerin et al (2011) found that utilizing prone positioning cut the risk of death in half.

A study by Rival et al. (2011) investigated the combined effect of PP and RM’s to improve oxygenation. Sixteen patients were ventilated for six hours in supine position (SP) and six hours in PP while utilizing a 35, 40 and 45 cmH2O PIP for 30 seconds each. Once reaching a PIP of 45 cmH2O a 30 second end-inspiratory pause was utilized. The findings were when an extended sigh during PP was utilized, a marked improvement in oxygenation was noted and when combination RM and PP were used, this led to the highest increases in PaO2/FiO2 (PF) ratio (Rival et al., 2011). Rival et al. (2011) were able to demonstrate that increases in PaO2 were transient in SP but sustainable in PP. PF ratio increased from 98.3 to 165.6 mmHg and plateau pressures decreased after each RM and during the entire PP period (Rival et al., 2011).

High Frequency Oscillation Ventilation (HFOV)

HFOV is a ventilation technique that utilizes high frequencies (3-15 Hz) and small Vₜ’s (1-4 ml/Kg) to provide excellent lung protection and constant alveolar recruitment (Sud et al., 2010). HFOV has been linked with improved oxygenation in several studies but more studies are underway which may find out if ARDS mortality is decreased vs. conventional low Vₜ strategies. A significant study on whether early implementation of HFOV increased survival rates of ARDS patients was stopped less than half way through randomization due to a 12% increase in mortality in the HFOV group vs. conventional ventilation with higher levels of PEEP (Ferguson et al., 2013). The negative to HFOV is due to the fact that neuromuscular blockade and heavy sedation are usually required for adult patients to adequately tolerate because spontaneous breathing is not effectively accommodated (Daoud, Farag, & Chatburn, 2012).
Typically HFOV is utilized as a rescue or salvage therapy for those ARDS patients not tolerating conventional ventilation due to refractory hypoxemia.

APRV/Bi-Level

Another modern way to recruit alveoli as part of an open lung approach to treating ARDS is through the use of APRV or Bi-Level mode of ventilation. APRV was shown to improve oxygenation, end-organ blood flow, cardiac performance, and pulmonary blood flow as well as having a positive effect on lung recruitment and pulmonary vasoconstriction (Maung & Kaplan, 2011). APRV applied early on in ALI is able to maintain alveolar surfactant and improve oxygenation when compared to traditional volume lung protective ventilation strategies (Kollisch-Singule et al., 2015). Kollisch-Singule et al., (2015) also concluded that despite APRV having greater $P_{PLAT}$ pressures and increased tidal volumes compared to lung protective volume ventilation, trans-pulmonary pressures remained the same. These modes incorporate higher levels of PEEP than conventional mechanical ventilation. Bi-Level typically utilizes a 1:1 I:E ratio at a high PEEP ($P_{High}$) (determined by $P_{PLAT}$, usually less than 35 cmH2O) and low PEEP ($P_{Low}$) (determined by PEEP on conventional ventilator settings). The difference in this mode of ventilation is that the patient can spontaneously breath at both high and low PEEP level and pressure support (PS) (determined by Delta P) is dialed into the ventilator for all spontaneous breaths. The shifting from $P_{High}$ to $P_{Low}$ is called the release phase and is where most of the CO$_2$ is expelled from the bloodstream without the loss of PEEP which prevent alveolar de-recruitment.

APRV operates the same as Bi-Level except APRV utilizes inverse I:E ratio of up to 8:1 is utilized causing the time spent at $P_{High}$ (up to 4 seconds) to be much greater than the release phase ($P_{Low}$) for exhalation. $P_{Low}$ can be set to 0 and be as short as 0.5 seconds. APRV also
allows the patient to spontaneously breathe at both levels of PEEP. Spontaneous breathing PS breaths typically accounts for 10-30% of the APRV $V_E$ thus improving trans-pulmonary pressure with a reduction in dead space and this was shown to improve ventilation/perfusion (V/Q) matching (Daoud et al., 2012). The $P_{High}$ and a short release or time at low pressure ($T_{Low}$) has been shown to reduce alveolar microstrain (Kollisch-Singule et al., 2014).

The theory behind APRV is to keep an open lung at end expiration which reduces VLI from shearing the alveoli during mechanical ventilation (Sabino, Holowaychuk, & Bateman, 2013).

Weaning from APRV has been described by a “drop and stretch method” where the gradual reduction in $P_{High}$ (drop) and increasing time at high PEEP ($T_{High}$) (stretch) until continuous positive airway pressure (CPAP) is achieved as part of a spontaneous breathing trial (Daoud et al., 2012).

ECMO

Extracorporeal membrane oxygenation (ECMO) is the act of providing life support to pulmonary and cardiac failure patients via two catheters and an oxygenator. The first catheter extracts venous blood and returns the blood through a second catheter after the blood has flowed through an oxygenator. This method greatly decreases the workload of the heart and lungs. ECMO has had many successes in the neonatal intensive care unit however adult studies have not shown great success in improving survival rates in ARDS. It is often utilized as a treatment of last resort when all other attempts at conventional ventilation have failed and refractory hypoxemia remains a central issue. More studies are needed pertaining to the utilization of ECMO in various stages of ARDS while using modes such as Bi-level/APRV after an RM has
been performed. This could show a possible improvement in the treatment of refractory hypoxemia that occurs in severe ARDS.

Inhaled Nitric Oxide (INO)

Inhalation of low amounts of INO is known to cause pulmonary vessel vasodilation. INO has been shown to dilate the vessels located in open and ventilated sections of lung tissue while creating a shift in pulmonary blood flow away from non-ventilated sections and decreasing the right-to-left shunt (Rossaint et al., 1995). A decrease in right-to-left shunting by a shift in pulmonary blood flow toward ventilated areas of lung improves oxygenation by increasing the partial pressure of oxygen (PaO2) and reducing pulmonary artery pressure (PAP).

The Rossaint et al. 1995 determined while INO had a positive effect on PaO2 and PAP, it failed at reducing pulmonary hypertension and failed to effect pulmonary gas exchange in severe ARDS patients. There has not been any studies which have been able to show an improvement in survival rates of severe ARDS patients from INO therapy.

Inhaling high amounts of INO can be toxic and lethal by causing severe pulmonary edema and methemoglobinemia (Rossaint et al., 1995). Inhaling low concentrations of ≤ 40ppm of nitric oxide has not been shown to be toxic to the lungs.

Discussion

The universal adoption of the ARDSNet Protocol in 2000 as a lung protective measure for mechanically ventilated patients has reduced mortality by nearly 9% (Pomprapa et al., 2014). Further reductions in mortality are potentially achieved by reducing atelectrauma through the use of an open lung technique and recruitment maneuvers but more comprehensive studies still remain to be researched. Atelectrauma on a ventilator is akin to atelectasis after surgery so one
could surmise the same negative effects are possible such as increases in pneumonia, hypoxemia, and longer, more difficult and lengthy stays in the hospital at an exponentially increased cost.

PP is considered a recruitment maneuver by itself so the potential of near full lung recruitment when combined with an open-lung mode such as Bi-Level or APRV would logically make sense for the recruitment of dependent lung regions of the lung and sustaining these open alveoli. None of the studies reported an increase in barotrauma or adverse lung events while utilizing RM involving higher levels of PEEP vs. traditional volume ventilation.

There are many studies about individual RM’s, PP, and PEEP with regard to alveolar recruitment. There is a need for more comprehensive studies to be performed utilizing combined approaches to keeping an open lung and reducing mortality. The difficulty in obtaining more comprehensive studies is that much of what is learned in the visual sense, is obtained under computerized tomography (CT) scanning. Performing such studies and RM’s under CT scanning is both cost prohibitive and poses a risk to the patient in the form of radiation. The rest of what is learned is through the use of calculations such as $P_aO_2/F_iO_2$ ratios, PCWP, and PAP.

There is also a need to compare APRV against Bi-Level ventilation. APRV has a shorter release phase than Bi-Level and often sets $P_{Low}$ at 0 cmH20 with reliance on auto PEEP due to the short $T_{Low}$ to keep alveolar de-recruitment from taking place. Bi-Level adopts slightly higher $P_{Low}$ and slightly longer $T_{Low}$ so that there is closer to a 1:1 I:E ratio and no reliance on auto PEEP to maintain recruited alveoli during the release phase. The question needing answered here is if the loss of delivered PEEP at $P_{Low}$ at 0 cmH20 translates into spikes in $PcO2$ and drops in $PO2$ as suggested in the Pomprada et al. (2014)? Is reliance on auto-PEEP at $P_{Low}$ at 0 cmH20 enough to maintain an open lung?
PEEP is instrumental in maintaining a patent, open alveoli in ARDS. Evidence of this is proven in the ARDSNet Protocol when each pig suffered marked increases in PcO2 and decreases in PO2 for 30 minutes after being disconnected from the ventilator offering PEEP for just 10 seconds (Pomprapa et al., 2014). This loss of PEEP caused rapid acceleration in the formation of atelectasis which had a lasting effect. A similar comparison to this effect is when chest compressions are stopped during cardiopulmonary resuscitation (CPR), it can take up to 30 seconds to “re-pressurize” the heart and vascular system to achieve maximal perfusion again.

The author hypothesizes step-wise increases in PEEP up to 45 cm H2O and a maximal P_{PLAT} of 60 cm H2O for two minutes each as a safe and effective RM even though this temporarily breaches lung protective limits of standard practice because the benefits of an open-lung outweigh the risks of atelectrauma and hypoxemia. After this strategy was employed on 51 patients, P_{a}O2/F_{i}O2 ratios increased from 150 to over 300 and remained there for the next seven days (De Matos et al., 2012). SI with PEEP of 40 cmH2O for 30 seconds was found to have only minimal and transient effects on increased oxygenation (NHLBI, 2004). The RM using SI probably only recruits lung tissue temporarily and not fully when compared with the step-wise approach.

HFOV is an open lung technique for ventilation but does not allow for spontaneous respirations as does APRV and Bi-Level so it should be used under heavy sedation due to it being uncomfortable. HFOV achieves the desire effect of low volumes and adequate lung recruitment but the lack of the patient being able to take spontaneous breaths is a major drawback that relegates HFOV to serving as primarily a rescue therapy only in ARDS under heavy sedation. The evidence presented by Ferguson et al. (2013) proved that early implementation of HFOV in ARDS actually increased mortality to 47%, up 12% from
conventional ventilation with a mortality of 35%. Other modes of ventilation that allow for spontaneous breathing such as APRV/ Bi-Level should be preferred for patient comfort especially because neither one has been shown to contribute to VLI through their use of high PEEP levels.

Based on this literature review, there is a need for determining whether APRV or Bi-Level is superior and then performing a study based on the use of step-wise PEEP RM’s along with PP while ventilating a patient in better determined mode to establish a further reduction in mortality in ARDS patients.

It would seem a logical assertion that recruiting as much lung as possible through methods that by themselves have been shown to not cause adverse barotrauma effects is a benefit which should be fully explored in a comprehensive study. Higher levels of PEEP have not shown to cause any sort of VLI as compared to simply ventilating a patient with tidal volumes at >8 cmH2O. The constant overstretching of alveoli causes barotrauma that has not been noted with sustained PEEP which keeps the alveoli open hence the “open lung” technique. More PEEP is much safer for lungs than more volume. Higher levels of PEEP also recruit more lung tissue and decrease atelectrauma and atelectasis especially when implemented following an adequate RM.

The author suggests utilizing RM’s in combination for ARDS patients who have atelectasis with P_{a}O2/F_{I}O2 ratios below 200. Prone positioning should be utilized as well as step-wise PEEP increases up to a maximum PEEP of 45 cmH2O. Following these RM’s, adequate PEEP levels must be maintained to sustain the gains in lung tissue recruited. Temporarily breaching safe plateau pressures of 30cmH2o in an effort to recruit more lung tissue should be considered a safe practice because there were no adverse effects such as pneumothorax
in the studies examined. Utilizing a PEEP ladder per FiO2 requirement as cited in the ARDSNet Protocol can also help to maintain an open lung. Bi-level needs to be studied in this regard because higher PEEP levels are used which achieve this goal all the while allowing a patient to spontaneously breathe at two independent PEEP levels. The spontaneous breathing in Bi-level completely avoids barotrauma from overstretching alveoli because no excessive volume is delivered to the patient while maintaining higher than normal PEEP levels which also avoids atelectrauma.

ECMO should be considered as a salvage therapy when conventional mechanical ventilation and recruitment maneuvers failed to adequately negate hypoxemia problems and PaO2/FiO2 ratios remain below 200.

INO should also be considered as a rescue therapy in an attempt to reduce PAP and improve oxygenation. INO should not be utilized for severe ARDS patients as a routine measure as no improvement in survivor benefit has been shown.

Conclusion

The avoidance of VLI from sheering and over-distending alveoli through the use of targeted VT’s of 6 ml/Kg and PPLAT of ≤ 30 cmH2O has a proven survival benefit to the mechanically ventilated ARDS patient (Neto et al., 2012).

The avoidance of atelectasis through the use of high PEEP levels of up to +18-24 cmH2O for FiO2 of 100% prevents rapid lung de-recruitment and increases functional residual capacity (FRC) (Pomprapa et al., 2014). The open lung approach of step-wise PEEP increases up to levels of 45 cmH2O and maximum PPLAT of 60 cmH2O as part of a MRS, proven by CT imaging, demonstrates massive lung recruitment without reported barotrauma/atelectrauma or VLI (De Matos et al., 2012).
\( \text{P}3\text{O}2/\text{FiO}2 \) ratios were increased up to 59% and \( \text{P}_{\text{plat}} \) decreased following step-wise PEEP increases to 45 cmH2O as a RM along with PP (Rival et al., 2011). Increases in \( \text{PaO}2 \) were sustainable in PP but transient in SP suggesting that PP is an important RM itself (Rival et al., 2011). There has yet to be a proven reduction in mortality through the use of an open-lung technique along with PP but sample sizes are small and trending is promising.

Combination PEEP RM’s along with PP help to reduce atelectasis by recruiting alveoli as part of an open lung approach thereby treating refractory hypoxemia without barotrauma (Guerin et al., 2011).

It is clear from the Ferguson (2013) study that early implementation of HFOV increases mortality by up to 12% vs. conventional low \( V_T \) strategy. HFOV does offer excellent lung protection and continuous alveolar recruitment (Sud et al., 2010). HFOV should be reserved for patients who are failing more conventional approaches and hypoxemia remains a central issue.

APRV/Bi-Level are a form of open lung ventilation which maintains two different continuous positive airway pressures which enables increased alveolar lung recruitment (Sabino et al., 2013). APRB/Bi-level are able to maintain an open lung through the use of PEEP and in-turn maintain alveolar surfactant levels. The maintenance of alveolar surfactant helps stabilize the individual alveoli and prevent its easy collapse. The PEEP is beneficial to maintaining an open lung and has no evidence of barotrauma.
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