Introduction

Mechanical ventilation plays a key role in current medical practices. Its use in intensive care units, emergency departments and operating rooms has advanced the ability of medical professionals to treat compromises to the respiratory system. The first use of a mechanical means to ventilate humans began in the sixteenth century, but did not gain popularity among the medical community. In the 1920’s Philip Drinker developed an artificial ventilation apparatus using the concept of negative pressure to mimic the normal physiology of breathing. This device came to be known as the iron lung and was used extensively in the 1950s to treat respiratory failure during the polio epidemic [1]. Ventilators using positive pressure have since replaced the iron lung and are able to operate in several different modes depending on the application and needs of the patient.

The use of mechanical ventilation by anesthesiologists during surgical procedures has become a necessity and allows more extensive life-saving operations to be performed. Early experience with positive pressure ventilation was complicated by severe barotrauma due to large tidal volumes. Another hypothesized consequence of mechanical ventilation, although it has never been well established, is the development of atelectasis from low tidal volumes. Anesthesiologists must therefore set respiratory rate and tidal volume in such a manner as to avoid the extremes of barotrauma and alveolar collapse.

During general anesthesia, respiratory rates are set significantly lower and tidal volumes are set significantly higher than the respiratory rate and tidal volume of a conscious, non-anesthetized person at rest [4,5]. Anesthetists typically use tidal volumes of approximately 10-12ml/kg and adjust the respiratory rate to achieve an end-tidal CO$_2$ level of 38-40mmHg. Large tidal volumes are used in order to prevent atelectasis, however clinical studies attempting to show that large tidal volumes prevent atelectasis have produced mixed results [2,3]. Even considering this, large tidal volumes have remained popular among anesthetists [4].
A recent study conducted with patients admitted to intensive care with acute lung injury or acute respiratory distress syndrome looked at the effects of lower tidal volume during mechanical ventilation. The outcomes of patients ventilated at 12ml/kg were compared to patients ventilated with 6ml/kg. After enrolling 861 patients, it was concluded that there was a significant decrease in mortality with patients ventilated at the lower tidal volumes and a decrease in days with ventilator use. It is hypothesized that a similar outcome may be the result of using lower tidal volumes during anesthesia.

Setting respiratory rate and tidal volume during mechanical ventilation has been based largely on clinical judgement. Modification of these settings based on individual patient requirements has been ill defined and comes largely from experience and historical studies of mechanical ventilation. Mechanical ventilation is set to provide adequate oxygen supply and to remove CO$_2$ from the lungs. Because of the of the clinical judgement involved in making adjustments to ventilator settings, there is wide range of tidal volumes and respiratory rates that are used to provide the same gross alveolar ventilation.

Previous studies have suggested that by evaluation of respiratory system mechanics, tidal volumes and respiratory rates could be set to minimize the amount of work performed on the respiratory system tissue [6,7]. By minimizing the work performed by the ventilator on the respiratory system, while maintaining acceptable alveolar ventilation, it is hypothesized that the pulmonary tissue will sustain a minimum amount of damage.

To determine the amount of work done on the respiratory system, it is necessary to analyze the forces present during ventilation. During spontaneous breathing the muscles of the respiratory system apply the force which generates the pressure necessary to cause a change in volume. Thus the muscles are performing all of the work. However in mechanical ventilation either a combination of the ventilator and the respiratory muscles are performing the work or the ventilator is performing all of the work itself. When a patient is sedated under general anesthesia the later is usually the case and the work performed by the respiratory muscles is negligible.
Thus all work performed on the pulmonary tissue is performed by the ventilator. So by minimizing the work of the ventilator, work on the pulmonary tissue is minimized, which in turn minimizes tissue damage.

Derivation of the work of breathing as defined by Otis and Mead is shown in Appendix A. The rate of work is defined by equation 1.

\[ W = \frac{1}{2C} \left( \frac{\dot{V}_A}{f} + V_d \right)^2 + \frac{1}{4} R \pi^2 \left( \dot{V}_A + fV_d \right)^2 \]  

(1)

Where:

- \( C = \) Compliance (ml/cmH\(_2\)O)
- \( \dot{V}_A = \) Gross Alveolar Volume (ml/sec)
- \( V_d = \) Series Deadspace Volume (ml)
- \( R = \) Resistance (cmH\(_2\)O/ml/sec)
- \( f = \) Breathing Frequency

In a clinical setting, the work of breathing or respiratory work is referred to in terms of work per minute or work per liter. The rate of work or work per minute is also commonly known as power. Work per liter is calculated by dividing work per minute by the minute ventilation.

The respiratory rate in breaths per minute (BPM) that results in the minimum work of breathing is defined by equation 2.

\[ RR = 30 \sqrt{1 + \frac{4 \pi^2 RC \dot{V}_A}{V_d} - 1} \]  

(2)
Where the units of alveolar ventilation are ml/min, of deadspace are ml, of resistance are cmH₂O/L/sec and of compliance are mL/cmH₂O.

By knowing respiratory rate, tidal volume can be determined from the following expression:

\[
V_T = \frac{V_A}{RR} + V_d
\]  

Thus the respiratory rate required to minimize work is a function of the resistance and compliance of the respiratory system. The product of the resistance and compliance gives the time constant of the respiratory system. This time constant is a measure of how quickly the respiratory system can respond when a change in pressure is applied to it. As resistance or compliance increases, so does the time constant. This increase in response time causes a decrease in respiratory rate. Thus the respiratory rate required for minimal work is inversely related to the time constant of the respiratory system.

Preliminary Study

In a preliminary retrospective study done in this lab, the ventilator settings set by anesthetists were compared to the ventilator settings that would be suggested using the minimum work model described previously. Data was collected from 31 patients undergoing general anesthesia for a coronary artery bypass graft (CABG) procedure.

Each patient underwent an intravenous induction of anesthesia followed by tracheal intubation and initiation of mechanical ventilation with tidal volumes and respiratory rates selected by the anesthetist. Data was collected for five-minutes prior to skin incision.
Using airway pressure, CO₂, and flow sensors, placed in the breathing circuit between the endotracheal tube and the anesthetic circuit, tidal volume, respiratory rate, respiratory system compliance and resistance, and series airway deadspace were monitored. A personal computer recorded these variables. Using the equations derived previously, the optimal respiratory rate and tidal volume needed to minimize the work done by the ventilator on pulmonary tissue and maintain the same gross alveolar ventilation were calculated. The results of this study are shown in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Actual Values Mean ± SD</th>
<th>Target Values Mean ± SD</th>
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<tbody>
<tr>
<td>Tidal Volume (ml/kg)</td>
<td>8.9 ± 1.9</td>
<td>5.25 ± 1.28</td>
</tr>
<tr>
<td>Respiratory Rate (breaths/min)</td>
<td>9.7 ± 1.4</td>
<td>19.3 ± 3.5</td>
</tr>
<tr>
<td>Work of Breathing (Joules/min)</td>
<td>6.85 ± 1.4</td>
<td>4.57 ± 2.11</td>
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In all patients enrolled in the study, the minimum work algorithm suggested a higher respiratory rate and a lower tidal volume than was set by the anesthesiologist. Compared to the actual ventilator settings, the target settings suggested by the minimum work model propose a 40.7% decrease in tidal volume and a 100.4% increase in respiratory rate. This would result in 31.4% decrease in the work done by the ventilator. This shows a significant difference in the ventilator settings set by anesthetists and those suggested by the minimum work of breathing model.

The data from this preliminary study suggested that ventilator settings would change when optimized to reduce the work done on pulmonary tissue. However, this study did not show
any of the physiologic effects that minimization of the work of breathing has on patients. In the following study, the settings suggested by the minimum work model will be used to ventilate patients enrolled in the study. Blood gases will be measured and compared to baseline values. It is hypothesized that there will be no significant difference in arterial oxygen partial pressure ($P_AO_2$) or arterial carbon dioxide partial pressure ($P_AC0_2$), when using the work of breathing algorithm to determine respiratory rate and tidal volume.
Methods

The Institutional Review Board at the University of Utah approved the study protocol. Each patient enrolled in the study was thoroughly informed about the study protocol and had the opportunity to ask questions about the procedure. After being informed about the study, each participant signed a written consent form. Data was collected from 18 patients undergoing general anesthesia for a variety of different surgical procedures at the Veterans Affairs (VA) Hospital in Salt Lake City, Utah. All of the necessary approval was obtained from the VA Research Approval Board before the study began. The study protocol excluded patients less than 18 years of age, patients who were prisoners, and pregnant or nursing women. Each patient enrolled in the study was previously scheduled for the placement of an arterial line during the surgery.

An effort was made to enroll patients with varying respiratory system physiologies, from healthy lungs to patients with chronic obstructive pulmonary disease. Smokers were also enrolled in the study. By having a wide variation of lung physiologies in the sample group, the hypothesis and the work of breathing model can be validated over a larger range of resistance and compliance values.

Each patient underwent an intravenous induction of anesthesia, which included a neuromuscular blockade, followed by tracheal intubation. The use of a neuromuscular blockade ensured that the respiratory muscles were completely relaxed and therefore had no significant part in patient ventilation. Therefore there were no spontaneous breaths from the patient, only mechanical breaths provided by the ventilator. Mechanical ventilation was then initiated and the anesthesiologist selected the tidal volume and respiratory rate they felt was appropriate.

An airway pressure, CO$_2$ and flow sensor (No. 8951-00, Novametrix, Wallingford, CT) was then placed in the breathing circuit between the endotracheal tube and the ventilator breathing circuit. This sensor was connected to a non-invasive cardiac output monitor (NICO) (NICO$_2$, Novametrix, Wallingford, CT), which was connected to a personal computer via a serial
port. The NICO measured and the computer recorded: inspired Tidal Volume, \( (V_T) \), in ml, Respiratory Rate (RR), in breaths per minute (BPM), dynamic inspiratory compliance (C), in ml/cmH\(_2\)O, dynamic inspiratory airway resistance (R), in cmH\(_2\)O/L/sec, and series airway deadspace \( (V_d) \) in ml. The NICO averaged the respiratory rate over eight consecutive breaths. The computer calculated the gross alveolar ventilation that was being delivered to the patient and this same value of gross alveolar ventilation was used in the calculation of optimal tidal volume and respiratory rate. The computer used the work of breathing algorithm described in the introduction to calculate and display the target respiratory rate \( (RR_t) \), the target tidal volume \( (tV_T) \) and the actual and target values for the rate of work \( (WOB_A \text{ and } WOB_T \text{ respectively}) \). Each of the previous parameters was updated and recorded every four seconds.

The ventilator settings set by the anesthesiologist were maintained for at least ten minutes of data collection. This allowed the patient to reach a steady state. A baseline arterial blood sample was then drawn. The anesthetist reviewed the suggested tidal volume and respiratory rate calculated from the minimum work model and, if they felt the changes were safe, set the actual values of respiratory rate and tidal volume to those suggested by the model and added 5 cmH\(_2\)O positive end-expiratory pressure (PEEP).

Because of the non-linearity of the respiratory system, which is not taken into account in the model, the resistance and compliance changed slightly as the respiratory rate and tidal volume were changed significantly. This affected the suggested target values slightly. Thus, up to three adjustments, over a one to two-minute period, was necessary for the system to reach steady-state, where the actual and target values of respiratory rate and tidal volume matched within 10%.

The patient then remained on these new settings for at least ten minutes. This allowed the physiologic response of the patient to adjust to the increase in respiratory rate and decrease in tidal volume and reach a steady-state value. Another arterial blood sample was then drawn. This concluded the study and the anesthesiologist could adjust the ventilator to whatever settings they felt were appropriate.
Results

Of the 18 patients that were enrolled in the study, 14 finished the entire protocol. Of the 14 all were male and 7 were known smokers or had a history of chronic obstructive pulmonary disease (COPD).

In 13 study patients, the minimum work of breathing model suggested a lower tidal volume and higher respiratory rate than was set by the anesthesiologist. In one patient there was no difference in what the minimum work model suggested and what the patient was being ventilated with and thus there was no change in the work of breathing.

Patients were excluded from data analysis if the thoracic cavity was opened before completing the protocol. When the thoracic cavity is open, the mechanics of ventilation is changed due to the change in compliance and viscoelastic resistance. The force caused by the chest wall decreases and therefore the respiratory system becomes more compliant and the resistance decreases. Also there are significant and unpredictable effects on lung mechanics caused by surgical manipulation of the tissue. These changes cause a shift in the work of breathing curve and data before and after opening the thoracic cavity cannot be compared reliably.

<table>
<thead>
<tr>
<th></th>
<th>Before Change</th>
<th>After Change</th>
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<tr>
<td></td>
<td>Mean +/- SD</td>
<td>Max.</td>
</tr>
<tr>
<td>Compliance (ml/cmH2O)</td>
<td>59.71 +/- 17.68</td>
<td>95.64</td>
</tr>
<tr>
<td>Resistance (cmH2O/L/sec)</td>
<td>17.82 +/- 11.23</td>
<td>44.93</td>
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The average and standard deviation of $P_AO_2$, $P_ACO_2$, respiratory rate and tidal volume, before and after the change are shown in Table 3.

<table>
<thead>
<tr>
<th></th>
<th>Before Change</th>
<th>After Change</th>
</tr>
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<tbody>
<tr>
<td>PO2 (mmHg)</td>
<td>312.2 +/- 158.8</td>
<td>268.9 +/- 134</td>
</tr>
<tr>
<td>PCO2 (mmHg)</td>
<td>39.08 +/- 5.69</td>
<td>39.88 +/- 5.86</td>
</tr>
<tr>
<td>Tidal Volume (ml/kg)</td>
<td>9.31 +/- 2.43</td>
<td>6.57 +/- 1.95</td>
</tr>
<tr>
<td>Respiratory Rate (BPM)</td>
<td>8.76 +/- 0.94</td>
<td>14.83 +/- 5.15</td>
</tr>
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Figures 1 through 3 show the average respiratory rate, tidal volume and actual work of breathing, respectively, before and after changes were made to the ventilator for each patient. Figures 4 through 6 show histograms of the average respiratory rate, tidal volume and work of breathing respectively.

The average work done by the ventilator, or the work of breathing, before the setting change was made was 4.75 J/min with a standard deviation of 1.48 J/min. After the ventilator was set to the target values predicted by the minimum work model, the average work of breathing decreased to 4.0 J/min with a standard deviation of 1.34 J/min.

**Statistical Analysis**

The average tidal volume, respiratory rate, $P_AO_2$, $P_ACO_2$, and work of breathing were analyzed before and after the changes to the ventilator were made. The data was analyzed using a Student’s paired two-tail t-test. A p-value of less than 0.05 was considered significant.
There was no significant difference in $P_{A}O_2$ or $P_{A}CO_2$, before and after the ventilator settings were changed. However, there was a significant change in tidal volume, respiratory rate and work of breathing.
Discussion

The most significant finding of this study was that by using the minimum work of breathing algorithm to determine respiratory rate and tidal volume there was no significant change in the concentration of arterial oxygen and carbon dioxide concentrations. This finding suggests that there is no significant amount atelectasis with decreased tidal volumes. This algorithm could be used to set respiratory rate and tidal volume in a way that will minimize the work done on the respiratory system. By using the work of breathing model, anesthetists will have a more precise way to set the ventilator that is based on the respiratory mechanics of the patient.

Another significant finding is that the current practice of anesthesiologists is to set tidal volumes higher and respiratory rates lower than a minimum work model suggests. In order to minimize the work done on the respiratory system this study indicates that anesthetists should decrease tidal volumes and increase respiratory rates from the current conventional settings.

Anesthesiologists caring for mechanically ventilated patients undergoing general anesthesia selected a wide range of tidal volumes, from 6ml/kg to 14ml/kg. In this investigation, only two of the 13 patients were ventilated in the range of 10-12ml/kg. The minimum work model also suggested a wide range of tidal volumes however they were significantly lower, from 3ml/kg to 9.3ml/kg, than what was initially used to ventilate the patient.

Potential Advantages of Minimizing the Work of Breathing

The minimum work model suggests ventilator settings that are optimal for the patient’s particular respiratory system mechanics. By measuring resistance and compliance, the time constant of the respiratory system is determined. The time constant of the lung is a measure of how fast the respiratory system responds to a change in pressure. By basing respiratory rate and tidal volume settings on this parameter, the work done on the tissue can be minimized. In addition, by measuring the deadspace of the respiratory system, the most efficient tidal volumes can be set to attain the desired alveolar ventilation while minimizing work.
Evidence suggests that high tidal volume mechanical ventilation may impair the surfactant production. These deleterious effects of high tidal volume are not seen during low tidal volume ventilation. Faridy et al. presented evidence that three hours of mechanical ventilation impaired the production of alveolar surfactant. Verbrugge et al. showed that the addition of 10cmH\textsubscript{2}O of positive end-expiratory pressure attenuated the deleterious effects of high tidal volume on pulmonary surfactant. Veldhuizen et al. examined the effects of tidal volume and respiratory rate on and tidal volume on the conversion of active surfactant particles into inactive aggregates. The results of his investigation showed that the use of large tidal volumes resulted in increased surfactant inactivation. A subsequent study by the same author suggests that low tidal volume ventilation does not impair surfactant production. A recent study by Franks et al. shows that the negative effects of high tidal volume ventilation are not seen during ventilation at 6ml/kg. These results suggest that the use of small tidal volumes will decrease the impairment of surfactant production. When there is surfactant depletion, high tidal volumes cause the collapse and expansion of alveoli.

High shear forces are therefore present between expanded and atelectic regions of the lung. Lachmann describes the effects of high shear forces between expanded and collapsed alveoli with each breath, and recommends ventilation modes that result in minimal airway pressure changes. Such a strategy will reduce ventilator induced lung injury. Thus, another potential advantage of minimizing the work of breathing is that it will result in decreased pulmonary shear forces and thus reduce ventilator induced lung injury.

The use of lower tidal volumes and higher respiratory rates to treat patients with ARDS has been shown to decrease mortality. The ARDS network recommends treating patients with a tidal volume of 6ml/kg. Although this recommendation was developed independent from the work of breathing model, by using the model similar recommendations are suggested. Similar benefits using the work of breathing model for patients undergoing general anesthesia may also be realized.
Potential Disadvantages of the Study

The use of low tidal volumes during general anesthesia has not been accepted due to the potential for atelectasis. It is well established that atelectasis occurs in 85-90% of patients within 5-10 minutes of initiation of mechanical ventilation. This causes decreased lung compliance, increased intrapulmonary shunt and ventilation-perfusion mismatching. Although the exact cause of atelectasis following anesthetic induction is not well understood, it has been related to several factors. The impairment of surfactant and the resulting increase in alveolar surface tension may cause alveolar collapse. Brismar et al. suggests that the relaxation of the diaphragm causes an increased pleural pressure gradient resulting in atelectasis. Strandberg et al., found a significant linear regression between body weight and height and atelectasis and also between the shape of the thorax and atelectasis. Other investigators suggest that the composition of inspired gas plays a role in the formation of atelectasis as well. The role tidal volume plays in post-induction anesthesia is not known, however several investigators have demonstrated that the application of 5-10 cmH\textsubscript{2}O positive end-expiratory pressure reverses anesthesia induced atelectasis. For this reason, the protocol of this study called for the addition of 5 cmH\textsubscript{2}O PEEP when the ventilator changes were made.

The addition of PEEP during mechanical ventilation has several effects on both pulmonary mechanics and cardiac function. The addition of PEEP causes an increase in intrathoracic pressure and a decrease in venous drainage, which can cause a reduction in cardiac output. The addition of positive end-expiratory pressure can also cause a change in pulmonary compliance.

Non-linearity of the work of breathing model

The model used to determine the work of breathing in this study is based on the assumption that the respiratory system is linear. However, airway pressure and airflow can effect
both the resistance and compliance of the respiratory system. The results of the study show that there is a significant decrease in airway resistance after the changes were made to the ventilator. Therefore as the respiratory rate and tidal volume were changed so did the resistance, which caused new values for tidal volume and respiratory rate to be calculated.
Conclusion and Future Work

By using the work of breathing model a respiratory rate and tidal volume can be selected that minimizes the amount of work done on pulmonary tissue by a mechanical ventilator. This study shows that there is no significant difference in blood gas values between contemporary ventilator settings and those suggested by the work of breathing model. In all cases the work of breathing model suggested a decreased tidal volume and increased respiratory rate from those values initially selected by anesthesiologists.

The results of this suggest that there is no adverse effect when compared to contemporary mechanical ventilation. In fact, there may be a significant benefit to decreasing the work done on the respiratory system and pulmonary tissue. As demonstrated by studies done with ARDS patients in the ICU, a decrease in tidal volume and an increase in respiratory rate significantly decreased mortality rates. The decrease in mortality was attributed to decreased stress on the lungs. Although clinical relevance of such a ventilator management strategy is not well defined for patients with a healthy respiratory system, anesthetists may find the work of breathing model to be useful when caring for patients with ARDS.

The previous study shows that there is no harm to patients when the suggested values from the work of breathing model are used for a short-term period. Further study should be conducted to determine the actual effects that work of breathing settings has when applied over a longer period. By applying the settings to patients for a longer period and measuring time to extubation, significant clinical benefit for all patients may be obtained. The amount of injury to the pulmonary tissue could be determined by taking a CT scan of the lungs before and after surgery. By comparing these parameters to a control group more evidence supporting the use of the work of breathing algorithm to determine respiratory rate and tidal volume may be obtained.
Figure 1 - Average Respiratory Rate of Each Subject
Actual Work of Breathing

![Bar chart showing the actual work of breathing before and after a change. The chart is divided into different J/min ranges, and the number of subjects is indicated for each range. The chart includes two bars for each range, one for 'Before Change' and another for 'After Change'.]