Work of Breathing and Airway Occlusion Pressure during Assist-Mode Mechanical Ventilation*

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We determined the effect of varying ventilator tidal volume (VT) and inspiratory flow (V) on the inspiratory muscle work (WI) during assist-mode mechanical ventilation (AMV) in four healthy subjects. In another four subjects, under constant chemoreceptor input, we determined the responses of neuromuscular output as assessed by the mouth occlusion pressure (P<sub>0.1</sub>) to alteration in WI. During AMV, the inspiratory work of breathing is partitioned between WI and ventilator work. With a constant ventilator trigger sensitivity, we calculated WI (joules/L of volume) as the difference between the area subtended by the airway pressure-inspiratory volume curves and the ordinate of the assisted breaths subtracted from that of the controlled breaths at ventilator V of 40, 60 and 80 L/min and ventilator VT of 100, 125 and 150 percent spontaneous breathing VT. At all ventilator settings, WI was less than inspiratory muscle work of spontaneous breathing (SB) and was a function of both ventilator VT and V (<p<0.05), but ventilator V has more effect on WI. Under isocapnia and hyperoxia, we measured P<sub>0.1</sub> and WI during AMV at ventilator VT of 125 percent of spontaneous breathing VT and ventilator V of 60, 80 and 100 L/min. End-expiratory lung volume remained constant. P<sub>0.1</sub> during AMV was similar to that of the SB. Although WI decreased with increasing ventilator V, P<sub>0.1</sub> did not decrease significantly. We conclude that during AMV, both ventilator V and to a less extent ventilator VT determine W. In healthy subjects changes in WI do not affect P<sub>0.1</sub>.

During assist-mode mechanical ventilation (AMV), when the ventilator delivers a set tidal volume (VT) at a set inspiratory flow (V), inspiratory external work of breathing is partitioned between the work performed by the inspiratory muscles (WI) and the ventilator. The ventilator is "pushing" gas while the inspiratory muscles are "pulling" gas. The magnitude of work performed by inspiratory muscles depends on factors related both to the subject (respiratory center output, respiratory system compliance and resistance) and the ventilator settings. Previous studies have shown that both ventilator trigger sensitivity and ventilator V influence WI. When the trigger sensitivity is low, the inspiratory muscles have to work harder to start inspiration. On the other hand, as the ventilator V increases, the inspiratory muscles work less.

In contrast to the interaction between both ventilator trigger sensitivity and V, little is known concerning the interaction between ventilator V and VT on WI. In patients on AMV, Flick et al<sup>4</sup> showed that the volume at which phasic diaphragmatic electrical activity (EMG<sub>d</sub>) ceases was similar to the spontaneous breathing VT and was not affected by varying ventilator V or VT. This suggests that at a low ventilator V and a high ventilator VT, EMG<sub>d</sub> duration lengthens, (inspiratory muscles contract longer). When anesthetized dogs were ventilated with a high ventilator VT (20 ml/kg), the duration of EMG<sub>d</sub> was similar to that of spontaneous breathing, but the effect of ventilator V was not systematically studied. Although the interaction between ventilator V and VT on EMG<sub>d</sub> has been studied,<sup>1,4</sup> there was no information on the effect of varying ventilator V and VT on WI. From these studies,<sup>1,4</sup> it is unclear to what extent ventilator VT affects WI.

Depending on the ventilator settings, AMV can unload inspiratory work. Because a decrease in neuromuscular output as measured by the mouth occlusion pressure 0.1 s from the onset of inspiration (P<sub>0.1</sub>) occurs with resistive unloading when healthy subjects breathe a helium-oxygen gas mixture,<sup>4</sup> one would also expect that P<sub>0.1</sub> would decrease during AMV. The decrease of P<sub>0.1</sub> during AMV, however, could also be attributed to the decrease in arterial CO₂ tension (PaCO₂).<sup>7</sup> By maintaining chemoreceptor inputs constant, (under hyperoxic and isocapnic conditions during AMV), the response of P<sub>0.1</sub> to alteration in WI could be assessed.

In this study we determined: 1) the effects of varying ventilator V and VT on external inspiratory muscles work (WI) while trigger sensitivity was held constant,
and 2) the $P_{a1}$ responses to mechanical unloading during AMV in healthy subjects under hyperoxic and isocapnic conditions.

**Materials and Methods**

Eight healthy volunteers free of respiratory symptoms (seven physicians and a respiratory therapist), participated in the study. This study consisted of two protocols; four subjects participated in each. All subjects signed a written informed consent form approved by the Long Beach VA Human Experimentation Committee.

Prior to the study, the subjects were instructed to relax. To distract them from the surrounding environment, throughout the experiment they listened to classical music using ear phones.

**Protocol 1. The Effect of Varying Ventilator $V$ and VT Settings on WI**

Following 10 min of spontaneous breathing, in the seated position, the subjects were connected through a mouthpiece to the ventilator (MA-1, Bennett Respiration Products, Los Angeles). The inspired gas was humidified and end-tidal $P_{ETCO_2}$ (PECO2) was continuously monitored. The ventilator trigger sensitivity was set at $-1$ to $-2$ cmH2O with no back-up ventilator rate. Nine ventilator $V$-VT settings were applied in random order. This consisted of a ventilator $V$ of 40, 60 and 80 L/min, combined with a ventilator VT of 100, 125 and 150 percent of VT during spontaneous breathing. Each ventilator setting was maintained for 10 min after a stable PECO2 had been reached. At the end of these 10 min spontaneous breathing (SB), AMV settings, the WI, ventilatory variables, lung resistance (RI), dynamic lung compliance and end-expiratory transpulmonary pressure (Ptp-exp) reflecting changes in functional residual capacity (FRC) were measured and/or calculated.

**Protocol 2. $P_{a1}$ Responses to Alteration in WI**

To minimize the effect of chemoreceptor inputs on $P_{a1}$, the study was conducted under isocapnic conditions and the inspired oxygen concentration ($F_{IO_2}$) was maintained at 30 percent. To maintain isocapnia during AMV as during spontaneous breathing (PETCO2 constant $\pm 1$ mm Hg), CO2 was bled into the humidified inspired gas as needed. The ventilator trigger sensitivity was also set at $-1$ to $-2$ cmH2O with no ventilator back-up rate. The ventilator $V$ was set at 60, 80 and 100 L/min, and the ventilator VT was set only at 125 percent of the spontaneous breathing VT. Following 10 min of spontaneous breathing, the 3 ventilator V- VT settings were applied randomly and maintained for 10 min of isocapnic breathing. At the end of these periods, $P_{a1}$, WI, ventilatory variables, Ptp-exp and PECO2 were measured.

In both protocols, for measurement of WI (see below), a controlled breath of the same ventilator VT and V settings was interposed manually (by pressing the manual button on the ventilator) in between the assisted breaths as soon as expiratory flow returned to zero (Fig 1) to minimize changes in respiratory system compliance and resistance. At least three controlled breaths were delivered randomly. Although the expiratory time preceding the controlled breath was somewhat shortened (Fig 1), no significant change in FRC occurred as evidenced by the similar magnitude of Ptp-exp of the controlled and the preceding assisted breaths ($1.84 \pm 0.27$ cmH2O and $1.62 \pm 0.28$ cmH2O; $\pm SE$, respectively). During the controlled breath, the ventilator performs the entire work. This assumption can only be made if the inspiratory muscles are inactive. Our method lacked the electromyographic measurement of the inspiratory muscles. Yet, we believe that our assumption was reasonable since the coefficients of variation of the work measured during the three controlled breaths at varying ventilator $V$ and VT setting were low—7 to 12 percent. This suggests that the subjects were relaxed and the ventilator assumed the entire work. Furthermore, Flick and associates1 did not detect EMG in patients on controlled mechanical ventilation. Marini et al2 also demonstrated that the work during the controlled breaths in unsedated critically ill patients was similar to that during paralysis. These observations suggest that during the controlled breaths the inspiratory muscles are inactive and the ventilator performs the work.

The breathing circuit consisted of a mouthpiece, a heated pneumotachograph (No 2, Fleisch, Lausanne, Switzerland) connected to a differential pressure transducer (MP45, $\pm 2$ cmH2O, Validyne Corp, Northridge, CA) to measure flow and a one-way valve (No 2600, Hans Rudolph, Kansas City, MO). The ventilator inspiratory and expiratory tubings were connected to the inspiratory and expiratory ports of the Hans Rudolph valve, respectively. The resistance of the circuit (excluding the ventilator tubings) was 2.0 cmH2O/L/s at a flow of 1 L/s. The calibration factors were similar when the pneumotachograph was calibrated with both air and 30 percent oxygen. The dead space of the circuit was 95 ml. Airway pressure (Paw) was measured through a port mounted on the mouthpiece using a differential pressure transducer (MP45, $\pm 50$ cmH2O, Validyne Corp, Northridge, CA).

Occlusion pressure was measured on the first attempted spontaneous breath against the occlusion. The inspiratory line was occluded during the preceding exhalation with a noise- and vibration-free pneumatic valve. At least three measurements separated by an interval of not less than 15 s of AMV were obtained, and the mean values were used for analysis. Ptp-exp was obtained by subtracting Pes from Paw at the end of expiration. Pes was measured with an esophageal balloon filled with 0.6 ml of air, connected to another differential pressure transducer (MP45, $\pm 50$ cmH2O, Validyne Corp, Northridge, CA) using a standard technique.

Volume was obtained by integrating the flow signal (8815A, Hewlett Packard, Waltham, MA). Respiratory frequency was calculated from the flow signal. Minute ventilation (Vt) was calculated as the product of volume and frequency. Lung resistance (RI, resistance of the airways and lung tissues) during AMV was calculated using the isovolume method, by taking the ratio of changes in Pes subtracted from Paw and changes in Vt at mid inspiratory and expiratory lung volumes. Dynamic lung compliance (Clv) was calculated as the ratio of change in lung volume and change in Pes subtracted from Paw at points of zero flow. PECO2 was measured from another port mounted on the mouthpiece using an infrared CO2 analyzer (Beckman LB2, Sensormedics, Anaheim, CA). All measured variables were recorded on an 8-channel recorder (Hewlett Packard 7750B).

An average of 10 breaths were analyzed for Ptp-exp, RI, Clv, ventilatory variables and PECO2.

**Figure 1. Analog tracing of a controlled breath (C) interposed between the assisted breaths (A) of a representative subject during assist-mode mechanical ventilation. Paw = airway pressure, Pes = esophageal pressure, V = air flow, VT = tidal volume.**
Measurement of Work during Spontaneous Breathing

The total inspiratory work during spontaneous breathing was measured using the Campbell diagram as the area subtended between the inspired volume-Paw and the static volume-pressure curve of the chest wall. The latter was obtained using the published data of normal subjects.

Data and Statistical Analysis

Means and standard error for each variable were calculated unless otherwise indicated. Analysis of variance was used for comparing means. If the F value was significant, the least significant difference between means was calculated. Regression analysis was used when applicable. Probability values < 0.05 were considered significant.

RESULTS

Table 1 shows the subjects' characteristics, resting VT, VE and WI. Resting WI was within the reported values of healthy subjects. At all ventilator V-VT settings during AMV, WI was significantly lower than that during spontaneous breathing. Mean highest value of WI during AMV was 0.32 joules/L (Fig 3) vs 0.05 joules/L during spontaneous breathing (Table 1).

Effects of Varying Ventilator V and VT on WI

Higher ventilator V-VT settings increased VE significantly (p < 0.05, Fig 3). This resulted in a proportionate decrease in PetCO₂. Figure 3 shows that for a given ventilator VT, VE was higher at ventilator V of 60 and 80 L/min as compared to at 40 L/min. When ventilator flow was held constant, VE was greater at 125 and 150 percent VT in comparison to 100 percent VT; except at ventilator V of 40 L/min, VE was significantly higher at 150 percent VT only. The ensuing hypocapnia might decrease respiratory center output and consequently decreases WI. However, during assisted ventilation there were no significant correlations between VE (r = -0.137) or PetCO₂ (r = 0.139) and WI.

For a given ventilator VT, WI was significantly lower with higher ventilator V. However, when ventilator V

Table 1—Subjects' Characteristics, Tidal Volume, Minute Ventilation and Inspiratory Muscle Work During Spontaneous Breathing

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age, y</th>
<th>Weight, kg</th>
<th>FVC, % pred</th>
<th>FEV₁, % pred</th>
<th>VT, L</th>
<th>VE, L/min</th>
<th>WI, Joules/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>31</td>
<td>84.1</td>
<td>94.5</td>
<td>98.4</td>
<td>.882</td>
<td>11.1</td>
<td>.662</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>41</td>
<td>86.4</td>
<td>111.7</td>
<td>97.2</td>
<td>.956</td>
<td>10.4</td>
<td>.573</td>
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<tr>
<td>3</td>
<td>M</td>
<td>25</td>
<td>68.2</td>
<td>105.7</td>
<td>101.6</td>
<td>1.165</td>
<td>13.4</td>
<td>.634</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>28</td>
<td>86.2</td>
<td>86.2</td>
<td>88.6</td>
<td>.755</td>
<td>8.2</td>
<td>.660</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>31.2</td>
<td>81.8</td>
<td>99.5</td>
<td>96.5</td>
<td>.940</td>
<td>10.8</td>
<td>.630</td>
</tr>
<tr>
<td>± SD</td>
<td></td>
<td>6.9</td>
<td>9.3</td>
<td>11.4</td>
<td>5.6</td>
<td>.172</td>
<td>2.1</td>
<td>.040</td>
</tr>
</tbody>
</table>

FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 s; VT = tidal volume; VE = minute ventilation; WI = inspiratory muscle work.
was held constant, WI decreased significantly with 150 percent VT, but only when ventilator \( \dot{V} \) was set at 80 L/min. In fact, with a ventilator \( \dot{V} \) of 40 L/min, WI was greater at 150 percent VT than when ventilator VT was set at 125 percent VT.

During AMV, Rl did not decrease significantly as compared to that during spontaneous breathing. Similarly, Rl or Clsp did not change significantly on any of the ventilator \( \dot{V} \)-VT settings.

P\(_{0.1}\) Responses to Alteration in WI

The increased VE with increasing ventilator \( \dot{V} \) resulted in a decrease in P\(_{\text{T-CO}}\). The administration of CO\(_2\) to the inspired gas to maintain isocapnia augmented VE further (\( p < 0.01 \)). This was primarily due to the increase in frequency (f), with a mean of 11.3, 13.7 and 14.5 breaths/min at ventilator \( \dot{V} \) of 60, 80, 100 L/min. Occlusion pressure during SB was 1.5±0.2 cmH\(_2\)O (± SE), which did not differ significantly from those during AMV. Despite a significant reduction in WI with increasing ventilator \( \dot{V} \), P\(_{0.1}\) did not change significantly (Fig 4). P\(_{\text{tp-exp}}\) was unchanged at different ventilator \( \dot{V} \) settings (at ventilator \( \dot{V} \) of 60, 80 and 100 L/min: 2.3±0.7, 2.4±1.5, and 2.2±1.3 cmH\(_2\)O, ± SE; respectively), suggesting that end-expiratory lung volumes remained constant.

**DISCUSSION**

Our results show that in healthy subjects, AMV decreased WI per liter of volume. The reduction in WI was a function of both the ventilator \( \dot{V} \) and to a lesser

**FIGURE 3.** The subjects’ inspiratory muscle work (WI) and minute ventilation (VE) at varying ventilator inspiratory flow and volume settings. VT = spontaneous breathing tidal volume. Comparison between different ventilator inspiratory flows for a given ventilator volume setting (analysis of variance): *p<0.001 compared to 40 L/min (WI) and VE); †p<0.01 compared to 40 L/min (WI and VE); ‡p<0.05 compared to 60 L/min (VT), compared to 40 L/min (VE). Comparison between different ventilator volumes for a given ventilator inspiratory flow setting (analysis of variance): *p<0.001 compared to 100% and 150% VT (WI); †p<0.02 compared to 100% VT (WI and VE).

**FIGURE 4.** Inspiratory muscle work (WI), airway occlusion pressure (P\(_{0.1}\)), minute ventilation (VE) with constant end tidal P\(_{\text{CO}}\) at 125% spontaneous breathing tidal volume and different ventilator inspiratory flow settings. *p<0.01 compared to 60 L/min (WI and VE); †p<0.02 compared to 80 L/min (WI) and 60 L/min (VE).
extent, ventilator VT. While maintaining chemoreceptor inputs constant and stable end-expiratory lung volume, mechanical unloading using AMF failed to decrease $P_{o_1}$.

**Effect of Varying Ventilator $\dot{V}\cdot$VT settings on WI**

During AMV, respiratory center output, inspiratory muscle strength, and the ventilatory settings determine inspiratory muscle work. In our study, the contribution of a fall in respiratory center output consequent to hypocapnia on the reduction in WI, if any, did not appear to be significant. This was supported by the observation that WI remained unchanged at ventilator $\dot{V}$ of 40 L/min - 150 percent VT as compared to 40 L/min-100 percent VT setting, despite a significant increase in $\dot{V}e$ in the former (Fig 3). Furthermore, in the second protocol, when respiratory chemical inputs were held constant, WI still decreased significantly. Maximum inspiratory pressure, an index of inspiratory muscle strength, was not measured in our study. However, there was no reason to believe that our healthy subjects had decreased inspiratory muscle strength.

At varying ventilator $\dot{V}$ and VT settings, RL and $C_{L_{pv}}$ did not change significantly. Ayres et al. also showed that RL of healthy subjects did not change with increasing flow rate during intermittent positive pressure breathing. Although those authors found decreases in $C_{L_{pv}}$, with increasing flow rates (0.3 to 0.8 L/s), others did not despite using a flow rate of 1.5 L/s and peak pressures of 5, 10 and 15 cmH$_2$O. The discrepancy between the results of those studies was difficult to explain; nevertheless in our study, lung mechanics remained unchanged during AMV. The relaxation of the subject will certainly alter chest wall elastance and affect WI. Previous studies demonstrated that when the subjects were relaxed during intermittent positive pressure breathing, WI diminished, but exceeded that of spontaneous breathing when they were unable to follow instructions. Our subjects were specifically instructed to relax and they were distracted from the surrounding environment. They appeared to be able to relax as shown by the stability of the airway pressures tracing (Fig 1). Undoubtedly, this partly explains the decrease in WI in our subjects during AMV.

The effect of high ventilator $\dot{V}$ on WI are consistent with previous studies. At all ventilator $\dot{V}$ settings, ventilator $\dot{V}$ was set higher than $\dot{V}$ of the spontaneous breathing; therefore, it is not surprising that WI was less during AMV. The higher the ventilator $\dot{V}$, the less inspiratory muscle work. In addition, our study demonstrated that the highest ventilator $\dot{V}$ (80 L/min) and VT (150 percent spontaneous breathing VT) setting appeared to decrease WI most (Fig 3). It is possible that the decrease in WI was primarily due to the effect of the high ventilator $\dot{V}$ alone. Yet, when ventilator $\dot{V}$ was held constant at 80 L/min, WI decreased significantly at ventilator VT of 150 percent as compared to 100 percent spontaneous breathing VT. This suggests that a high ventilator VT decreases WI, provided that it is properly matched by the ventilator $\dot{V}$. On the other hand, a high ventilator VT matched by an inappropriately low ventilator $\dot{V}$ (150 percent VT-40 L/min) resulted in an increased WI as compared to a low ventilator VT (100 percent VT) with the same ventilator $\dot{V}$ (Fig 3), thereby offsetting the effect of high ventilator VT in decreasing WI. Since during AMV, inspiratory flow is a square wave, a high ventilator VT with an inappropriately low ventilator $\dot{V}$ results in prolongation of inspiratory time. We have observed that during AMV diaphragmatic electrical activity persisted throughout inspiration to early expiration in patients with acute respiratory failure (unpublished observation). With respect to this observation, the prolonged inspiratory time increases the duration the inspiratory muscles have to contract and therefore increases WI.

The mechanism by which a high ventilator VT decreases WI is not entirely clear. In anesthetized animals, lung inflation inhibits phrenic motoneuron output mediated by phasic vagal stretch receptor stimulation. However, at low volumes (<1.5-2.0 L) this reflex has no influence in conscious humans. It is possible that stimulation of intercostal or diaphragmatic mechanoreceptors through supraspinal and segmental reflexes, respectively, inhibit phrenic motoneuron output accompanied by a generalized decrease in inspiratory muscle activity and a decrease in WI.

$P_{o_1}$, Responses to Alternation in WI

While maintaining chemoreceptor inputs constant and stable end-expiratory lung volume, $P_{o_1}$ did not decrease proportionately during AMV despite a significant decrease in WI with increasing ventilator $\dot{V}$. This is in contrast to findings in patients with respiratory failure. However, our results were consistent with those of Connors and coworkers. They showed that in normal subjects, during AMV, $P_{o_1}$ did not decrease significantly, except when ventilator VT and $\dot{V}$ was doubled from 12 to 24 ml/kg and 50 to 100 L/min (at PetCO$_2$, of 40 mm Hg), respectively. Unfortunately, in that study, WI was not quantitated. It is possible that WI was significantly reduced at that high ventilator VT and $\dot{V}$ settings. A large change in WI is perhaps essential to significantly alter neuromuscular output in subjects with previously normal WI. The failure of $P_{o_1}$ to decrease in response to the decrease in WI appears to contradict our postulated mechanism of phrenic motoneuron output inhibition responsible for the decrease in WI (see above). However, due to our small sample size, we were not able to exclude the possibility
of a type 2 (beta) error.\textsuperscript{25} In addition, under the conditions of our study, to our knowledge phrenic motoneuron output has not been correlated with $P_{a,1}$ to determine whether or not $P_{a,1}$ is a reliable index of respiratory center output. Thus, despite the failure of $P_{a,1}$ to decrease in response to alteration in $W_I$ during assist-mode ventilation, we cannot entirely exclude the possibility that drive was not modulated by $W_I$.

Our measured values of $W_I$ were lower than those of Marini et al\textsuperscript{19} in healthy subjects. This discrepancy might be due to methodologic differences or the relaxation state of the subjects. We did not use cheek support; this could explain the discrepancy between the two studies as peak airway pressure might have been decreased due to the oral compliance. However, we believe that this does not alter our conclusion, since $W_I$ was calculated as the difference between the controlled and the assisted breaths and these were measured under similar conditions.

In summary, during assist-mode mechanical ventilation, in addition to ventilator trigger sensitivity, we have shown that ventilator $V$ and to a lesser extent ventilator $V_T$ determine inspiratory muscle work. While a high ventilator $V_T$ and $V$ decreases $W_I$ most, a high ventilator $V_T$ improperly matched by the ventilator $V$ increases $W_I$. Despite the benefit of both a high ventilator $V$ and $V_T$ in decreasing $W_I$, the higher peak airway pressure generated increases the risk of barotrauma.\textsuperscript{26} In experimental animals, high peak airway pressures have also been shown to cause impairment in lung mechanics and respiratory failure.\textsuperscript{27} Although the latter has not been substantiated in human subjects, in clinical practice a high ventilator $V$ and $V_T$ setting will have to be cautiously applied. Under constant chemoreceptor input and end-expiratory lung volume, $P_{a,1}$ did not decrease proportionately to the reduction in inspiratory muscle work. Whether those responses demonstrated in healthy subjects will be observed in critically ill patients, remains to be determined.

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