Anesthesiology
69:29–35, 1988

Optimization of Respiratory Muscle Relaxation during Mechanical Ventilation

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The authors calculated the active work of inspiration (Wp) and the inspiratory muscle pressure-time product ($\int$ Pmus · dt) in seven patients undergoing mechanical ventilation (MV). This was done by comparing the areas under the inflation pressure-volume and inflation pressure-time curves generated when the patient was contributing to the work of ventilation with those following sedation, when inspiratory muscle activity was absent (defined as absence of diaphragmatic EMG activity and of palpable accessory muscle contraction). Inspiratory muscle inactivity could be predicted by the observation of a smooth rise in inflation pressure that was highly reproducible from breath to breath. Relaxation was present without sedation during MV in the control mode with inspiratory flow rates above 65 l/min. In the assist mode (AMV), both Wp and $\int$ Pmus · dt were significantly ($P < 0.05$) greater than in the control (CMV) mode. Reducing trigger sensitivity during AMV further increased Wp and $\int$ Pmus · dt ($P < 0.05$). During AMV and CMV Wp and $\int$ Pmus · dt decreased with increasing rate of inspiratory flow delivered by the ventilator. With AMV at low trigger sensitivity and low flow rates, Wp approached 65% of the total inspiratory work. The authors conclude that inspiratory muscle activity can be substantial during MV, particularly during AMV at low trigger sensitivity and flow. Monitoring of inflation pressure is a simple means of determining the degree of inspiratory muscle rest during MV. (Key words: Ventilation, mechanical: work of breathing. Muscle, respiratory: work of breathing.)

PROVIDING REST FOR the respiratory muscles, thus allowing recovery from fatigue, is one of the putative benefits of mechanical ventilation.[1] If valid, it would be useful to have a simple means of monitoring the degree of inspiratory muscle relaxation so that appropriate ventilatory parameters can be selected. This paper presents a simple, non-invasive method for accomplishing this.

During positive pressure mechanical ventilation, the ventilator and the respiratory muscles behave as two pumps hydraulically in series. If the muscles are completely relaxed, the ventilator must develop all of the pressure required to overcome the elastic, flow-resistive and inertial properties of the lungs and chest wall in order to inflate the respiratory system. This is the pressure difference across the respiratory system Prs, and it is easily measured; it is the pressure at the airway opening, usually an endotracheal tube, relative to the pressure at the body surface, which is usually atmospheric. If inspiratory muscle contraction supplies all the pressure required to inflate the system, Prs is zero. If Prs becomes negative, the mechanical ventilator is hindering the muscles during inflation of the lung. The relationship between the pressure developed by the ventilator and that developed by the muscles is given by

$$\text{Pinf} = \text{Prs} + \text{Pmus},$$

where Pinf is the pressure required to inflate the respiratory system and Pmus is the pressure developed by the respiratory muscles.

With the muscles completely relaxed, Prs = Pinf. If one can measure Prs during relaxation to obtain Pinf, then Pmus during situations when muscular relaxation is incomplete can be quantified as Pinf − Prs. This is true to the extent that tidal volume, flow, and chest wall shape are similar during the relaxed and unrelaxed inflations. We have measured Prs during relaxation during positive pressure ventilation in patients requiring ventilatory support, and also when the patients own muscles were contributing to inflation. By subtracting Prs during these breaths from Pinf measured as Prs during relaxation, we have quantified the pressure-time product of the respiratory muscles[2] and (along with the measurement of lung volume change) the work of breathing.[3,4]

The inspiratory muscle pressure-time product and inspiratory work of breathing during both machine-initiated (CMV) and patient-initiated (AMV) mechanical ventilation were measured, and the effects of changes in ventilatory parameters were explored.

Rationale

During spontaneous ventilation, the work of inspiration can be calculated in the standard manner by integrating the pressure developed across the respiratory system over the change in lung volume during lung inflation.[5] Similarly, by measuring the area contained in the inflation pressure-volume curve during positive pressure ventilation, the work done by the ventilator on the respiratory system during inflation of the lungs may

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Received from the Montreal Chest Hospital Centre and the Meakins-Christie Laboratories, McGill University, Montreal, Quebec, Canada. Accepted for publication February 11, 1988.

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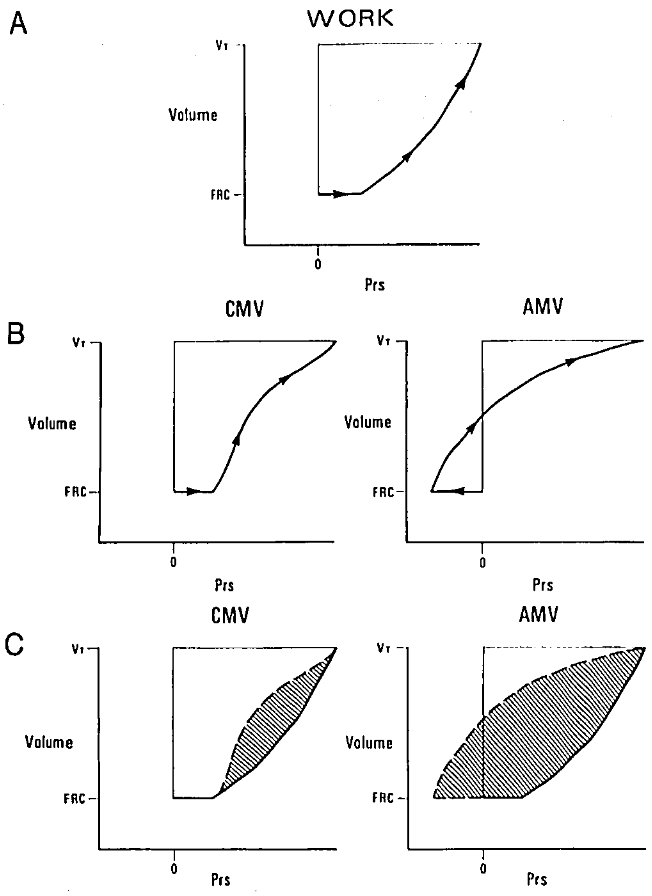

FIG. 1. Subtraction of the area subtended by the inflation pressure (Prs)-volume curve in the presence of inspiratory muscle activity (panel B) from that recorded during passive inflation (panel A) yields the work of inspiration performed by the patient (shaded area, panel C).

be calculated. When the patient makes no respiratory effort, this area (∫ Prs • dV, where dV is the change in lung volume) gives the total work of inflating the respiratory system, and this work is performed entirely by the ventilator (fig. 1A). When the inspiratory muscles are active, the area contained in the curve still gives the work performed by the ventilator, but this is no longer the total work (fig. 1B). The difference between these areas yields the work done on the lungs and chest wall by the patient's respiratory muscles (fig. 1C). Comparison of these curves is valid if they are generated during ventilation under identical conditions of inspiratory flow, tidal volume, and respiratory frequency, and provided that the mechanical properties of the respiratory system remain unchanged.

In an analogous manner, the area under the transrespiratory system pressure-time curve when the patient is contributing to the energy of inspiration may be subtracted from that generated in the absence of respiratory muscle activity to yield the pressure-time product of the inspiratory muscles (∫ Pmus • dt) (fig. 2).

Materials and Methods

SUBJECTS

Ten patients in the Intensive Care Unit of the Montreal Chest Hospital Centre for treatment of respiratory failure consented to participate in this study. Progressive hyperinflation at low inspiratory flow rates prevented completion of the protocol in two patients. One patient developed excessive inflation pressure (>60 cm H_2O) at the highest inspiratory flow rate. These patients were excluded. Of the remaining seven patients, five had chronic airflow limitation, one had pulmonary fibrosis, and one developed postoperative respiratory failure after surgery for bronchogenic carcinoma. Their minute ventilation ranged from 8.6 to 12.3 l/min, and maximum inspiratory pressures from 14 to 26 cm H_2O. All patients had recovered from the acute phase of the respiratory illness that had precipitated respiratory failure, and had no other active medical problems. All developed clinical signs of respiratory muscle fatigue (rapid shallow breathing, respiratory alternans, and abdominal paradox[6]) between 35 min and 6 h after discontinuing ventilatory support, and had, therefore, been started on a program of respiratory muscle training. This consisted of intervals of spontaneous ventilation, continued until clinical signs of respiratory muscle fatigue occurred, separated by intervals in which respiratory muscle rest was achieved by ventilation in the CMV mode with settings adjusted by monitoring the inflation pressure tracing for signs of inspiratory muscle contribution. The cycle was repeated one to three times per day, depending on the length of the spontaneous ventilation intervals with at least 12 h of complete rest overnight. Measurements for this study were performed following 24 h of complete rest, and no patient exhibited clinical signs of respiratory muscle fatigue at the time of study. Three patients (No. 4, 5, and 7) had undergone tracheostomies (No. 8 Portex cuffed tracheostomy tubes), while the remaining patients were intubated orotracheally with 7½–9-mm internal diameter endotracheal tubes.

APPARATUS

The patients were studied while in the supine position, their lungs being ventilated using a volume cycled ventilator (Bennett MA-1 or MA-2). Prs was measured using a differential pressure transducer (Validyne MP 45 ± 100 cm H_2O) recording the pressure in the endotracheal tube relative to atmospheric pressure. A pneumotachygraph (Fleisch No. 3) and differential pressure transducer (HP 270 ± 4 cm H_2O) were used to measure flow through the endotracheal tube, and this signal was integrated to yield volume (V).

Electromyographic (EMG) activity of the diaphragm was recorded from an esophageal electrode[7] through a preamplifier (DISA 15 C 01). All signals were recorded using a strip chart recorder (HP 7758B). Prs and V were plotted simultaneously on an X-Y recorder (HP 7046A). The areas under the Prs-V and Prs-time curves were measured planimetrically using a graphics tablet (HP 9111A).

VENTILATION SETTINGS

During all studies, tidal volume (V_T) was set at 12 ml/kg and inspired oxygen concentration was adjusted to maintain the arterial oxygen saturation greater than 90%. No patient was receiving positive end expiratory pressure.

The inspiratory flow ($\dot{V}$) delivered by the ventilator was set by adjusting the "Peak Flow Rate" setting, as is done in clinical practice. Twenty-five liters/minute was the lowest flow rate most patients could tolerate without developing excessive limitation of expiratory time and progressive hyperinflation. Sixty-five liters/minute was the highest flow some patients with severe chronic airflow limitation could tolerate without developing excessive inflation pressures. Sixty-five liters/minute was also the inspiratory flow rate at which the work of inspiration performed by the patient during CMV was essentially zero. This range included those inspiratory flow rates in clinical use at the Montreal Chest Hospital Centre at the time of the study.

The inspiratory effort required to initiate inspiration during AMV was set by adjusting the "Sensitivity" setting on the ventilator, so that the airway pressure signal registered the desired negative deflection prior to the onset of inspiratory flow. In studies with the ventilator operating in the AMV mode, mandatory respiratory rate was set at 0 per minute so that the patient was required to initiate each breath by making an inspiratory effort. The patients were thus free to choose whatever respiratory frequency they wished. The respiratory frequency used when the ventilator was operating in the CMV mode was that chosen by the patients during ventilation in the AMV mode at the same inspiratory flow setting. This varied less than 10% across the range of $\dot{V}$s studied, and no change in this parameter reached statistical significance. Altering the trigger sensitivity setting did not influence the respiratory rate chosen during AMV.

All measurements were made following a 5–10-min accommodation period during each condition, when the patients had achieved a stable breathing pattern.

STUDY SEQUENCE

AMV. With the ventilator operating in the AMV mode, set to deliver the prescribed tidal volume in response to a fall in airway pressure of 2 cm H_2O, recordings were made at each of five different inspiratory flow rates; 25, 35, 45, 55, and 65 l/min. Samples of blood for gas analysis were drawn from the patients' indwelling arterial catheters during the first and last conditions (25 and 65 l/min).

The sensitivity setting was then adjusted so that inspiratory flow was initiated in response to a fall in airway pressure of 5 cm H_2O. Recordings were made at each of three different inspiratory flow rates, 35, 45, and 55 l/min.

CMV. Measurements were made with the ventilator operating in the CMV mode at each of five different inspiratory flow rates; 25, 35, 45, 55, and 65 l/min. Arterial blood samples for gas analysis were drawn during the first and last conditions (25 and 65 l/min).

PASSIVE INFLATION CURVES

To record the inspiratory Prs-V and Prs-time curves in the absence of respiratory muscle activity, measurements were made with the ventilator operating in the CMV mode following sedation with diazepam (10–20 mg intravenously with supplementary doses as needed to maintain respiratory muscle inactivity). Respiratory muscle inactivity was defined as the absence of EMG activity of the diaphragm (as detected by an esophageal electrode) and the absence of palpable contraction of the scalene or sternomastoid muscles. Separate curves were generated for each set of ventilatory parameters studied during identical conditions of respiratory rate, tidal volume, and flow rate.

ANALYSIS

The Prs-V and Prs-time curves were recorded for 12 consecutive breaths during each condition. For each breath in this series, the areas contained in the Prs-V and Prs-time curves, with respect to the end-expiratory volume and pressure, were then measured planimetrically. The work per breath done by the patient was calculated by subtracting the area under the Prs-V curve recorded in the presence of inspiratory muscle activity from that obtained during passive inflation at identical ventilator settings (fig. 1). The rate of inspiratory work (power) performed during AMV and CMV at each set of ventilatory parameters was calculated and expressed in terms of work per minute by multiplying the mean work per breath by the respiratory frequency recorded for that condition. The inspiratory muscle pressure-time product was determined by subtracting the mean area under the Prs-time curve in the presence of inspiratory muscle activity from that during the corresponding passive inflation curve (fig. 2).

The statistical significance of all observed differences was determined using an analysis of variance for multiple measures and a paired *t* test. Significance was inferred if $P < 0.05$.

Results

In the absence of inspiratory muscle activity, the Prs-time curves are characterized by a smooth rise and are highly reproducible from breath to breath (fig. 2A). In contrast, when the respiratory muscles become active, the curves are not smooth and vary from breath to breath. During CMV, they generally contract after the onset of inspiratory flow, and their contraction reaches peak intensity near the middle of inspiration, resulting in scooping of the inflation pressure curves (fig. 2B). During AMV, the respiratory muscles contract in order to initiate inspiratory flow, causing Prs to become negative, and they continue to contract throughout a large portion of the mechanically delivered breath. In practice, it is easy to determine muscle inactivity by simple inspection. The pressure time curves are highly reproducible from breath to breath, and Prs never becomes negative and is always concave to the time axis.

INFLUENCE OF PEAK FLOW SETTING

The relationship between inspiratory flow rate and the patients' work of inspiration (Wp) and inspiratory muscle pressure-time product ($\int$ Pmus · dt) is illustrated in figure 3. At all inspiratory flow rates studied, both Wp and $\int$ Pmus · dt are significantly ($P < 0.05$) greater during ventilation in the AMV than in the CMV mode.

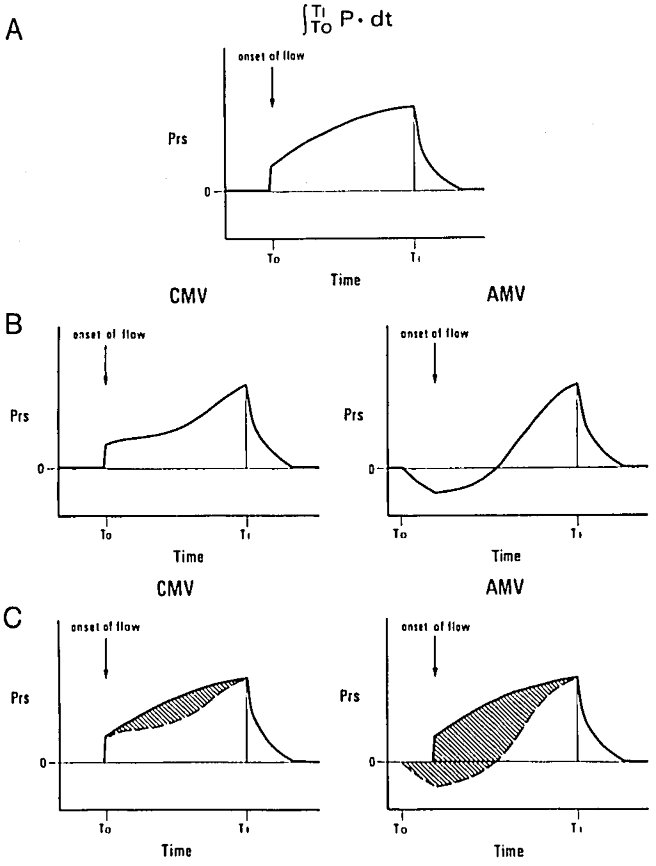

FIG. 2. Subtraction of the area subtended by the inflation pressure (Prs)-time curve in the presence of inspiratory muscle activity (panel B) from that recorded during passive inflation (panel A) yields the pressure-time product ($\int$ P · dt) of the inspiratory muscles.

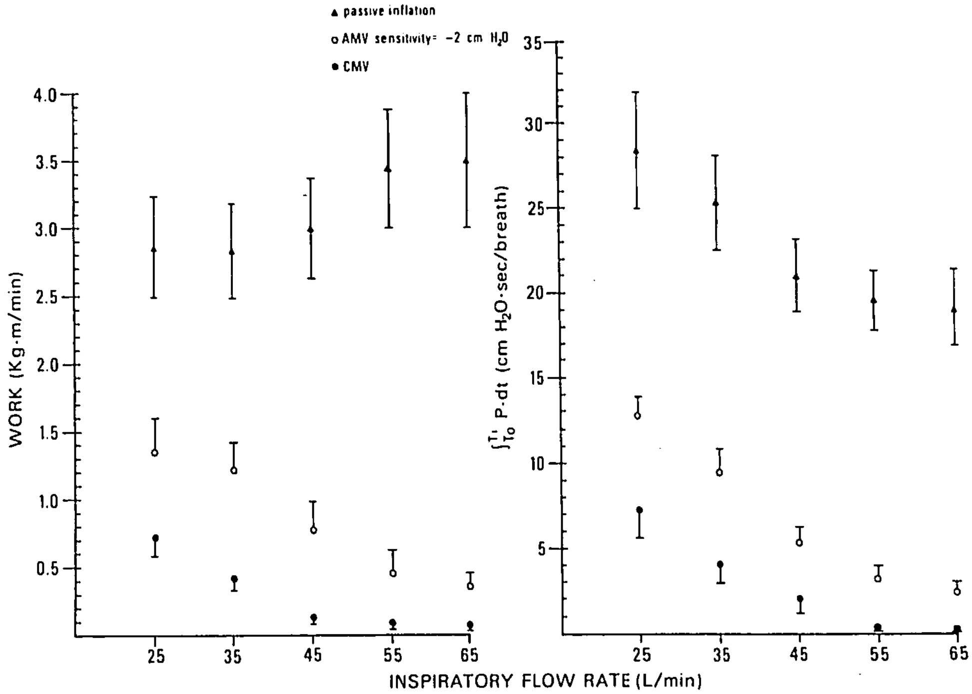

FIG. 3. The influence of inspiratory flow rate on inspiratory work of breathing and inspiratory muscle pressure-time product during CMV (closed circles) and AMV (open circles). The areas under the Prs-volume and Prs-time curves during passive inflation are plotted above for comparison. Values represent mean ± standard error.

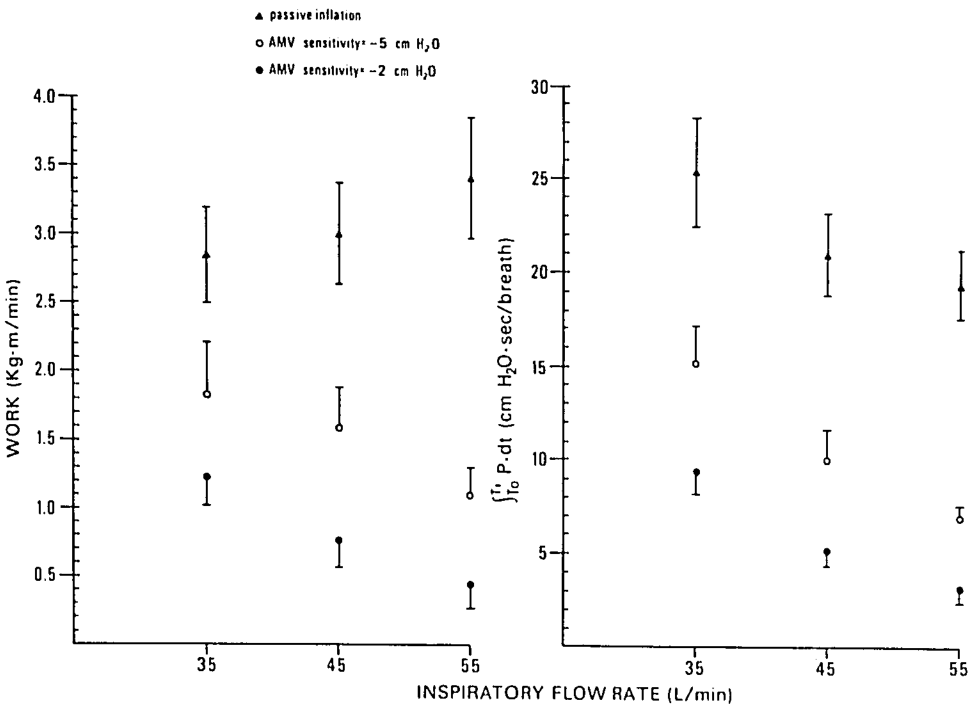

FIG. 4. The influence of changing the sensitivity setting from −2 cm H_2O (closed circles) to −5 cm H_2O (open circles) on the inspiratory work of breathing and inspiratory muscle pressure-time product during ventilation in the AMV mode. Values represent mean ± standard error.

During both CMV and AMV, as the inspiratory flow was decreased, there was an increase in Wp and in ∫ Pmus·dt. During ventilation in the CMV mode, Wp and ∫ Pmus·dt were essentially zero above an inspiratory flow rate of 65 l/min.

INFLUENCE OF SENSITIVITY SETTING

The effect of increasing the magnitude of the inspiratory effort required to initiate inspiration during AMV is illustrated in figure 3. At all inspiratory flow settings studied, increasing the fall in airway pressure required to initiate inspiration from 2 to 5 cm H_2O resulted in a significant ($P < 0.05$) increase in Wp and Pmus·dt (fig. 4). Neither the mode of mechanical ventilation nor the inspiratory flow rate significantly influenced Pa_{O_2} (which ranged from 74.5 ± 7.8 SD mmHg during AMV at 65 l/min to 75.6 ± 8.4 SD mmHg during CMV at 25 l/min) Pa_{CO_2} (which ranged from 40.1 ± 3.7 SD during AMV at 65 l/min to 37.6 ± 3.2 SD during AMV at 25 l/min, and *p*H which ranged from 7.41 ± 0.06 SD during AMV at 65 l/min to 7.44 ± 0.06 during CMV at 25 l/min and AMV at 25 l/min.

Discussion

For the purposes of this study, inspiratory muscle inactivity was defined as the absence of diaphragmatic EMG activity and absence of palpable contraction of the other inspiratory muscle groups. We achieved these conditions, either through sedation or ventilation in the CMV mode, at inspiratory flow rates of 65 l/min.

Although the aim of this paper is to describe a method suitable for monitoring the contributions of the patients' muscles to breathing during positive pressure ventilation in an intensive care unit, rather than to determine optimal ventilator settings, some conclusions can be drawn about the influence of ventilator settings on the patients' respiratory muscle activity.

The total work of passive inflation in our patients was similar to the work of breathing previously reported in patients with respiratory failure.[8] During CMV at the lowest flow rate studied (25 l/min), 25% of this work was being performed by the patients, and this decreased with increasing inspiratory flow rate until the patients' contribution was insignificant at 65 l/min. During AMV, inspiratory muscle activity was greater at all inspiratory flow rates than during CMV. Wp and ∫ Pmus·dt increased with decreasing inspiratory flow and, as would be expected, with decreasing trigger sensitivity. The highest mean value for Wp recorded during AMV was approximately 60% of the work of passive inflation and, in some cases, the patients' inspiratory efforts resulted in a calculated active work greater than that required for passive inflation. Under the most optimal conditions studied with the ventilator operating in the AMV mode ($\dot{V}$ = 65 l/min and trigger sensitivity = −2 cm H_2O), the patients were performing 10.5% of the work of inflation (0.4 ± 0.1 [SE] kg·m/min), an amount similar to the work of breathing required of normal subjects at rest.[9]

During ventilation in the AMV mode, initial inspiratory efforts are made without corresponding volume changes. Thus, the effort of generating the initial triggering pressure will not result in an increase in the calculated work (Wp). That Wp did increase in our patients reflects the increased inspiratory muscle activity that occurred during the time when volume was changing; that is, once activated, the inspiratory muscles do not stop contracting with the onset of inspiratory flow, but continue to contract throughout the ensuing inspiration. Since Wp does not reflect the inspiratory effort required to initiate inspiration, the inspiratory muscle pressure-time product ($\int$ Pmus • dt) may more accurately reflect the energy expenditure of the respiratory muscles under these conditions.

It is important to the validity of our measurements of Wp that sedation not significantly increase the work of passive inflation, as this may lead to an overestimation of the patients' work of breathing. The dynamic compliance of the respiratory system (Cdyn) was determined in our patients by dividing the measured tidal volume by Prs at the point of zero flow after the end of inspiration. Measurements of Cdyn were made before and after sedation when the ventilator was operating in the CMV mode, set to deliver the prescribed tidal volume (12 ml/kg) at an inspiratory flow of 45 l/min. Under these conditions, contraction of the inspiratory muscles had ceased prior to the end of inspiration, thus allowing comparison with the post-sedation measurement. As no significant change in Cdyn occurred in our patients following sedation (30.2 ± 6.9 *vs.* 28.9 ± 6.4 ml/cm H_2O), we feel that this assumption is reasonable.

Our method may underestimate the degree of respiratory muscle activity, because the minimum work of inflation occurs when the chest wall and abdomen are displaced along their relaxed pressure-volume relationships.[10] Distortion of the rib cage and abdomen from their relaxation characteristics by the inspiratory muscles will result in a higher work of inflation than that required under conditions of passive inflation. The magnitude of these effects is unknown. On the other hand, any so-called "intrinsic peep" is included in our pressure measurements during relaxation. It is contained in the increase in pressure that occurs before any change in volume (fig. 1). The pressure the inspiratory muscles must generate to overcome "intrinsic peep" is thus included in our estimates.

The method used for determination of the inspiratory muscle pressure-time product in this study is subject to the same assumptions as that for measurement of the work of inspiration. For both, comparison of the areas under the curves requires that the flows be identical for the compared breaths. Minor fluctuations in inspiratory flow occurred; however, these fluctuations were brief, thus, the changes in volume that they represent were small. As a result, there was no significant difference in the mean inspiratory flow (V_T/T_I calculated from the measured tidal volume and inspiratory time) between AMV, CMV, or CMV following sedation at any given inspiratory flow setting.

Two studies have previously examined the inspiratory workload during mechanical ventilation.[3,4] In the first of these, Marini *et al.*[3] compared the area under the inflation pressure-volume curves during AMV and CMV modes of mechanical ventilation in normal subjects without endotracheal intubation. They were able to demonstrate an increase in the discrepancy in ventilator work between these two modes (*i.e.*, an increase in the subjects active work of inspiration) with decreasing inspiratory flow rate, decreasing trigger sensitivity, and increasing minute ventilation. In a subsequent report, these authors describe similar measurements in patients with acute respiratory failure of various etiologies.[4] They found the active work of inspiration during patient initiated cycles to be significant. There was no change in the magnitude of the patients' inspiratory work when the inspiratory flow setting was reduced from 100 to 60 l/min. Increasing the patients' minute ventilation through the addition of dead space to the ventilator circuit did enhance the inspiratory work.

In contrast to the above studies, our subjects were chosen to represent patients in whom failure of the neuromuscular apparatus, rather than an acute pulmonary parenchymal process, limited their ability to sustain spontaneous ventilation. Since this group is also that which could potentially benefit most from optimization of respiratory muscle rest, it is important to document the influence of changes in ventilatory parameters on their inspiratory work. Using inspiratory flow rates below the range studied by Marini *et al.*, we were able to document a relationship between inspiratory flow setting and inspiratory work, during both AMV and CMV modes, similar to that observed previously in normal subjects during AMV.[3] Although we confirm and extend the observations of Marini *et al.* on AMV, these authors did not measure patient work during CMV, nor did they measure the pressure-time product. During AMV, this may be more useful than work, because the negative pressure required to trigger the machine is not measured as work, but still represents active muscular effort on the part of the patient. Furthermore, the pressure-time product has the advantages of requiring less equipment to measure and being suitable for monitoring.

During ventilation in the CMV mode, the patients activated their inspiratory muscles after the onset of inspiratory flow, and the magnitude of this contraction reached peak intensity near mid-inspiration; this occurred in the absence of inspiratory efforts between mechanical breaths. These observations suggest that the stimulus for muscle activation arises within an individual breath in response to the imposition of an inappropriate pattern of breathing, rather than due to a generalized stimulation of ventilatory drive. The increased intensity of respiratory muscle contraction, therefore, likely represents an attempt by the patients to restore a more comfortable rate of inspiratory flow.

In patients in whom discontinuation of mechanical ventilation is being contemplated, fatigue of the respiratory muscles may limit their ability to sustain spontaneous ventilation.[6] Programs of alternating rest and exercise can increase the endurance of the respiratory muscles,[11,12] and a similar approach has been successfully applied to patients being weaned from mechanical ventilators.[13,14] The combination of rest and exercise, and the type of exercise required for optimal training of the respiratory muscles, remain to be established. Failure to wean may result from many causes, such as left ventricular failure, hypophosphatemia, etc., that predispose to fatigue by increasing energy demand, decreasing energy supply, or impairing diaphragmatic contractility. Thus, if respiratory muscle fatigue is present when a weaning trial starts, the chance of success is small. It follows that sufficient rest must be provided between exercise intervals so that the electromechanical derangements associated with fatigue may be reversed.

Our results indicate that optimal rest may be achieved by ventilation in the CMV mode at high inspiratory flow rates, and that this can be determined by monitoring the Prs-time curves. Variations in ventilatory demand occur frequently, however, and only continuous attention to the patients' condition and frequent tailoring of ventilatory parameters can be expected to maintain a state of respiratory muscle inactivity for significant periods of time.

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