Mechanism of Relief of Tachypnea During Pressure Support Ventilation*

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Pressure support ventilation (PSV) provides a range of ventilatory support from partial respiratory muscle unloading, where inspiratory work is shared between the patient and the mechanical ventilator, to total respiratory muscle unloading, where inspiratory work is performed solely by the ventilator. This study is designed to determine if minimizing work fully accounts for relief of tachypnea during PSV. We examined respiratory parameters over a range of PSV that includes the crossover from partial to total respiratory muscle unloading. Eight studies were obtained on seven intubated patients in respiratory failure. Ventilation, occlusion pressure (P0.1), and patient inspiratory work (WOBinsp) were measured while PSV was varied. In all patients, WOBinsp decreased as PSV increased. The level of PSV where WOBinsp was minimized was identified; this marked the crossover from partial to total respiratory muscle unloading. Frequency decreased with increasing PSV but remained elevated (range, 22 to 38 breaths/min) at the crossover. Frequency was normalized only at PSV levels 131 to 193% of the levels of pressure at the crossover. Tidal volume (Vt) changed little during partial support and averaged 5.9 mL/kg at the crossover. Vt increased only on PSV providing total unloading. Six of seven patients exhibited increasing static compliance with increasing Vt suggesting alveolar recruitment. P0.1 tracked WOBinsp over the entire range of PSV (r=0.95, p<0.001). The normalization of frequency observed above the crossover coincided with increasing Vt rather than decreasing work. These observations suggest that reflexes resulting from increased Vt and/or alveolar recruitment may have contributed to the normalization of frequency.

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Key words: occlusion pressure; pressure support ventilation; pulmonary stretch receptors; respiratory insufficiency; work of breathing

Abbreviations: Cdy,rs=dynamic compliance of the respiratory system; Cst,rs=static compliance of the respiratory system; f=respiratory frequency; P0.1=occlusion pressure at 100 ms; PEEP=positive end-expiratory pressure; P/̅T̅CO2=end-tidal carbon dioxide tension; PSV=pressure support ventilation; VT=minute ventilation; Vt=tidal volume; WOBinsp=inspiratory work (of breathing)

Pressure support ventilation (PSV) provides a range of ventilatory support from partial respiratory muscle unloading, where inspiratory work is shared between the patient and the mechanical ventilator, to total respiratory muscle unloading, where inspiratory work is performed solely by the ventilator. Relief of tachypnea is commonly used as a guide to optimizing pressure support. A proposed mechanism for the relief of tachypnea with pressure support is that the reduced frequency results from reduction of excessive work. MacIntyre and Leatherman showed that respiratory rate was returned to normal in most patients at high levels of pressure support. These levels of pressure support were chosen to deliver high tidal volumes (Vts) to assure total unloading and, therefore, were above the level of pressure support at the crossover from partial to total respiratory muscle unloading. Because the response to pressure support at the crossover was not evaluated in their study, it is unclear if respiratory rate returned to normal when work first was minimized. Other authors have demonstrated a poor relationship between respiratory rate and directly measured patient work. The present study is designed to determine if minimizing work fully accounts for relief of tachypnea, by examining respiratory parameters over a wide range of pressure support that includes the crossover from partial to total respiratory muscle unloading.

Materials and Methods

Eight studies were obtained on seven intubated patients in respiratory failure. Patients were not necessarily designated by the clinical management team as candidates for weaning from mechanical ventilatory support. Patient characteristics are shown in Table 1. Inclusion criteria were as follows: hemodynamic stability manifested by systolic BP greater than 90 mm Hg without the use of IV
pressors; sinus rhythm on ECG monitoring; and respiratory frequency greater than 35 breaths per minute during spontaneous breathing. All patients were studied while they were in a semisupine position and pressure support was delivered by a mechanical ventilator (Puritan Bennett 7200 ventilator; Puritan-Bennett; Carlsbad, Calif.). For all studies, triggering sensitivity was set to 0.5 cm H₂O and positive end-expiratory pressure (PEEP) was set to zero. The internal diameter of the endotracheal tubes used during the study ranged from 7.5 to 8.5 mm.

The protocol involved measurement of respiratory frequency (f), Vt, minute ventilation (Ve), end-tidal carbon dioxide tension (Pet CO₂), respiratory drive as assessed by occlusion pressure at 100 ms (P0.1), and patient inspiratory work (WOBinsp). The level of pressure support was varied from the lowest pressure tolerated, to levels above the point of total respiratory muscle unloading. The lowest level of pressure support tolerated was defined as the pressure that did not result in hypotension, hypertension, tachycardia, oxygen saturation less than 90%, cardiac arrhythmia, or patient discomfort.

The point of total unloading was defined as the level of pressure support at which patient work was minimized. This point was identified by noting the level of PSV where the negative deflection of esophageal pressure was not sustained after the triggering of inspiration. The choice of this point was confirmed statistically using breakpoint regression on work and pressure support. The work-pressure support curve was subdivided into two consecutive sections such that the explained sum of squares was maximized by separate least squares linear regression lines. Additional measurements of all parameters were made at two to three levels of PSV above the point of total unloading. Patients were maintained at each level of PSV for 4 to 10 min. Data for analysis were obtained from periods of stable ventilation and were averaged over 30-s intervals.

Airway and esophageal pressures were measured with strain gauge transducers (Physio-Dyne; Amityville, NY). Airway pressure was measured at the mouth. Esophageal pressure was measured using an esophageal balloon positioned in the distal third of the esophagus. Airflow was measured utilizing a heated pneumotachograph (model 3700; Hans Rudolph Inc; Kansas City, Mo) connected to a differential pressure transducer and digital integrator (P.K. Morgan; Andover, Mass). These signals were digitized and recorded at 50 Hz by a computer (Modular Instruments, Malvern, Pa). Using custom software, Vt was derived from the integration of instantaneous flow rates, f and Vt were calculated from Vt and the duration of each breath; 30-s averages were then derived. Examination of the esophageal pressure traces confirmed the absence of respiratory efforts that failed to trigger the mechanical ventilator. P0.1 was measured at random intervals by occluding the inspiratory and expiratory circuits of the ventilator with inflatable shutoff valves (series 9340 shutoff valves; Hans Rudolph Inc). Patient inspiratory work was calculated for each breath by integrating the product of esophageal pressure referenced to end-expiratory pressure and instantaneous flow over inspiration, as is shown in the shaded area in Figure 1. This represents the total resistive work (airways plus breathing apparatus) and the portion of elastic work performed on the lungs. Data for patient inspiratory work per

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**Table 1—Characteristics of Patients**
minute (power of breathing) were then calculated by multiplying patient work per breath by f.

In one patient, the protocol was repeated (utilizing the BiCore Monitoring Systems CP-100; Irvine, Calif). This allowed for the calculation of total work by including an estimate of the portion of elastic work performed on the chest wall based on a measurement of chest wall compliance. Chest wall compliance was measured during volume-controlled mechanical ventilation while the patient was relaxed and not exerting a spontaneous respiratory effort as indicated by the esophageal pressure tracing. The static compliance of the chest wall was calculated as \( V_r \) divided by the difference between esophageal pressure during an end-inspiratory plateau and esophageal pressure at end-expiration.

At the conclusion of the study, each patient was given volume-assisted mechanical ventilation to measure dynamic and static compliance of the respiratory system \( C_{dyn,rs} \) and \( C_{stat,rs} \) over the range of \( V_r \)s noted during the study. \( C_{dyn,rs} \) was calculated as \( V_r \) divided by the difference between end-inspiratory airway pressure and end-expiratory alveolar pressure. For the calculation of static compliance, inspiratory flow was interrupted at end-inspiration to allow for equilibration of mouth pressure to alveolar pressure. \( C_{stat,rs} \) was calculated as \( V_r \) divided by the difference between end-inspiratory alveolar pressure and alveolar pressure at end-expiration. End-expiratory alveolar pressure was measured as the negative deflection in esophageal pressure from the onset of inspiratory effort to the point of zero flow. Two patients in whom end-expiratory alveolar pressure was not measured were excluded from this analysis.

This study was approved by the institutional review boards of New York University Medical Center and the Health and Hospitals Corporation of New York City. All patients, or their surrogates, signed informed consent prior to entering the study.

### RESULTS

Figure 2 (left) illustrates patient WOBInsp over the range of pressure support studied for each of the eight studies. Patient WOBInsp was high (range, 6.4 to 31.8 J/min) in all subjects at the lowest level of pressure support tolerated (range, 0 to 27 cm H2O). Patient WOBInsp decreased as pressure support was increased. For each study, a critical level of pressure support where patient WOBInsp was minimized was identified. Patient WOBInsp became essentially zero at this point and remained unchanged with further increases in pressure support. Therefore, this critical level of pressure support marks the crossover point (0) from partial to total muscle unloading. Right: patient WOBInsp is replotted against a normalized pressure support. All pressure support values were normalized such that the value at the crossover point in each study was assigned a value of 100%. At levels of pressure support below 100%, patients shared the inspiratory work with the ventilator and were therefore receiving partial support. At levels of pressure above 100%, patient WOBInsp was essentially zero indicating total respiratory muscle unloading. The minimization of patient WOBInsp at the crossover point is illustrated for each study by the plateau of patient WOBInsp seen at pressures beyond the crossover point.
To provide a common reference, all pressure support values were normalized such that the value at the crossover point in each study was assigned a value of 100%. At levels of pressure support below 100%, patients shared the inspiratory work with the ventilator and were therefore receiving partial support. At levels of pressure above 100%, patient WOBinsp was essentially zero indicating total respiratory muscle unloading. This is illustrated in Figure 2 (right) that replots patient WOBinsp against this normalized pressure support axis. The minimization of patient WOBinsp at the crossover point is illustrated for each study by the plateau of patient work seen at pressures beyond the crossover point. Figure 3 examines the relationship of patient WOBinsp to pressure support in one patient when elastic work performed on the chest wall work is included. At each level of pressure support that provided partial support, total WOBinsp (including chest wall work) was greater than measures of WOBinsp that excluded chest wall work. However, the crossover point from partial to total respiratory muscle unloading was not affected.

The left panel of Figure 4 relates f to increasing pressure support. Frequency ranged from 29 to 49
breaths/min at the lowest levels of pressure support tolerated. Frequency decreased with increasing pressure support. However, at the crossover point, frequency remained elevated (range, 22 to 38 breaths/min). This occurred despite minimization of patient WOBinsp. Frequency was normalized (<20 breaths/min) at pressure support levels 131 to 193% of the level of pressure at the crossover point. This was well into the range of total respiratory muscle unloading and represented pressure support levels as high as 65 cm H₂O.

The right panel of Figure 4 relates Vt to increasing pressure support. Vt ranged from 3.2 to 9.3 mL/kg (5.2±1.8 mL/kg, mean±SD) at the lowest levels of pressure support tolerated. Vt changed little during partial support and averaged 5.9±3.2 mL/kg at the crossover point. With further increases in pressure support to levels above the crossover to total unloading, Vt increased in accord with the increasing inflation pressure.

The changes in frequency and Vt that occurred with increasing levels of pressure support resulted in no consistent changes in either Ve or PetCO₂. Ve at the lowest levels of pressure support was 10.8±1.9 L/min (mean±SD), and at the highest levels of pressure support, Ve was 10.4±3.0 L/min (t=0.45; p=NS). PetCO₂ at the lowest levels of pressure support was 37.1±9.0 mm Hg (mean±SD), and at the highest levels of pressure support, PetCO₂ was 34.2±6.8 mm Hg (t=1.47; p=NS).

Figure 5 relates the Cstrs to the passive increase in Vt that occurred between the crossover point and the highest level of pressure support studied. Measurements were available for five patients. All five patients exhibited increasing compliance with the increase in Vt suggesting alveolar recruitment.

The relationship between respiratory drive, as assessed by P0.1, and patient WOBinsp is illustrated in
Figure 6. P0.1 tracked patient work over the entire range of pressure support studied (r=0.95, p<0.0001). Thus, P0.1 was minimized at the crossover point and remained stable with increasing inflation pressures. The further decrease of frequency to normal observed above the crossover was not associated with a further decrease in respiratory drive as assessed by P0.1.

**DISCUSSION**

This study extends prior observations on the effect of pressure support on ventilatory pattern. This was accomplished by direct measurements of both patient work of breathing and respiratory drive over a wide range of pressure support levels, including pressures above and below the crossover from partial to total respiratory muscle unloading. The results show that although f decreased with decreasing patient WOBinsp, minimizing work did not fully account for relief of tachypnea. Frequency remained elevated at the crossover from partial to total unloading and decreased to normal only at higher levels of pressure support.

The normalization of frequency observed at pressure support levels above the crossover coincided with increasing Vt. Because patient work was already minimized, the increase in Vt was likely due to passive inflation as a consequence of total respiratory muscle unloading. In addition, static compliance increased concomitant with the increase in Vt suggesting alveolar recruitment. These observations suggest that reflexes resulting from increased Vt and/or alveolar recruitment may have contributed to the reduction of frequency at pressure support levels above the crossover to total unloading.

The mechanism for the decrease in frequency observed above the crossover from partial to total respiratory muscle unloading is of particular physiologic interest as work and drive were already minimized at the crossover. Although it has been suggested that reflex input may contribute to respiratory pattern during changing pressure support, this has not been previously related to the crossover to total unloading. Several lung or chest wall reflexes resulting from increasing Vt may have contributed to the normalization of frequency. These reflexes fall into two categories: stimulation of reflexes that reduce frequency and inhibition of reflexes that increase frequency. Increasing Vt may result in stimulation of slowly adapting stretch receptors (Hering-Breuer reflex) that reduces respiratory rate by lengthening expiratory time. Nilsestuen and coworkers examined the role of these stretch receptors in controlling f in canine lungs collapsed by suction. They observed that f remained elevated until inspiratory airway pressures reached a critical value that resulted in reinflation of lung units collapsed by suction. Bartoli and colleagues showed that this volume-related reflex is very sensitive to small changes in lung volume above and below functional residual capacity. Although slowly adapting stretch receptors are probably inactive in healthy humans at Vrs below 1 L, animal data suggest that the presence of diffuse alveolar disease may sensitize these receptors, thereby increasing their contribution to the control of f. Alternatively, an increase in Vt may result in inhibition of a respiratory rate augmenting reflex. Koller and Ferrer proposed such a reflex mediated by irritant receptors. These are stimulated by alveolar collapse and result in increased respiratory drive and respiratory rate. This mechanism would have contributed to the high respiratory rates noted at low levels of pressure support, and reinflation with recruitment of collapsed lung units would result in slowing of respiratory rate. It is likely that the observed changes in f were mediated by an effect on timing mechanisms, because the influence of these reflexes was not reflected by changes in P0.1.

A purely mechanical explanation may have contributed to the fall in respiratory rate observed at pressure support levels above the crossover: the fall in respiratory rate may have resulted from the obligatory increase in inflation and deflation times required by a larger Vt. However, with the increase in Vt, duty cycle (Tr/TTot) decreased from 0.40 to 0.30±0.06 (mean±SD). This suggests more than adequate expiratory time for respiratory control mechanisms to express themselves, and thus, the mechanical explanation probably does not account for the reduction in frequency observed above the crossover.

There are several additional factors that may influence WOBinsp: dynamic hyperinflation, elastic work performed on the chest wall, and expiratory muscle activity at end-expiration. Dynamic hyperinflation increases WOBinsp due to the presence of intrinsic PEEP which must be overcome in order to initiate subsequent breaths. Although intrinsic PEEP was not measured as part of our protocol, its effects on work of breathing are included in our calculations as both the end-expiratory esophageal pressure and/or the negative deflection of esophageal pressure required to initiate subsequent breaths include a contribution from any intrinsic PEEP present. Elevations in the WOBinsp due to the elastic work performed on the chest wall could have accounted for the persistent tachypnea observed at the crossover. However, in our patient population, there is no reason to assume an elevated chest wall work component. These were patients with respiratory failure due to acute lung injury and not due to chest wall abnormalities. Thus, most of the increased work of breathing was likely due to elastic...
and resistive work performed on the lungs and airways. Lastly, the presence of persistent expiratory muscle activity at end-expiration could have resulted in unmeasured inspiratory work on subsequent breaths. However, in this circumstance, we would have noted variability in measured end-expiratory esophageal pressure, and none was seen.

The clinical implications of this study relate to the application of pressure support when used above and below the pressure at which the respiratory muscles are totally unloaded. If the clinical goal is to exercise the respiratory muscles, then pressure support levels below the crossover are appropriate; if the goal is to rest the respiratory muscles, then pressure support levels above the crossover are appropriate. Thus, it would be clinically useful to have a noninvasive marker of the crossover from partial to total respiratory muscle unloading. Banner and coworkers concluded that only direct measurement of patient WOBinsp reliably identified the crossover. In contrast, McIntyre and Leatherman suggested that total unloading can be assured by levels of pressure support producing high Vrs (10 to 12 mL/kg), but this method does not allow for identification of the crossover. Frequency has been used as a noninvasive marker of the crossover. However, Banner and associates showed that frequency is a poor predictor of patient WOBinsp. Our data confirm that normalization of frequency does not provide a useful clinical marker of the crossover: although normalization of frequency suggested total unloading, persistent tachypnea occurred in the absence of patient work.

Vt may be more useful than f as a marker of the crossover to total unloading. In our study, Vt remained essentially unchanged during partial support and increased at pressure support levels above the crossover to total unloading. This pattern of Vt response to pressure support agrees with the predictions and observations of McIntyre and Leatherman. However, in two of our patients (Fig 4), Vt increased at pressure support levels below the crossover.

P0.1 may provide a reliable noninvasive indicator of the crossover to total respiratory muscle unloading because, in our study, it was directly related to patient WOBinsp. In all patients, P0.1 was minimized at the same pressure support level at which work was minimized. Thus, P0.1, which has been shown to be a useful clinical tool during weaning of patients from mechanical ventilation, may be useful in the application of pressure support.

Our data highlight the complexity of precisely identifying the crossover from partial to total respiratory muscle unloading during PSV. Identification of the crossover has implications for the different clinical situations in which PSV is utilized. Normalization of frequency did not identify the crossover; in contrast, analysis of Vt and/or P0.1 may have been more useful. The observation that minimizing work did not fully account for relief of tachypnea suggests that reflex input may have contributed to the normalization of frequency observed at pressure support levels providing total respiratory muscle unloading.

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