The Physiologic Effects of Noninvasive Ventilation

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Summary

The physiologic effects of noninvasive ventilation (NIV) on work of breathing (WOB) and breathing pattern, respiratory-system mechanics, and hemodynamic function were examined via a literature review of clinical studies done between 1990 and 2008. Forty-one relevant studies were found; the majority examined patients with chronic obstructive pulmonary disease, whereas some also included patients with restrictive chest-wall disease or acute hypoxic respiratory failure. NIV reduced WOB in direct proportion to the level of inspiratory pressure-assist, and also by the ability of applied positive end-expiratory pressure (PEEP) to counter intrinsic PEEP. In general an inspiratory pressure-support level of 15 cm H₂O and a PEEP of 5 cm H₂O reduced most measures of WOB and inspiratory effort toward normal. When set to the same level of inspiratory pressure-assist, both pressure-support ventilation and proportional-assist ventilation effected comparable reductions in WOB. At high levels of inspiratory pressure-assist, NIV consistently increased dynamic lung compliance and tidal volume, and improved arterial blood gases. The hemodynamic effects of NIV are dependent upon the interplay between the type of mask, the level of inspiratory pressure-assist and PEEP, and the disease state. In general, patients with chronic obstructive pulmonary disease have a higher tendency toward decreased cardiac output at high levels of inspiratory pressure-assist, compared to those with acute lung injury. Key words: noninvasive ventilation, work of breathing, respiratory-system mechanics, pressure-support ventilation, proportional-assist ventilation, breathing pattern. [Respir Care 2009;54(1):102–114. © 2009 Daedalus Enterprises]
Introduction

The goals of mechanical noninvasive ventilation (NIV) are the same as mechanical ventilation accomplished through tracheal intubation, namely ensuring the adequacy of pulmonary gas exchange and normalizing/minimizing patient work of breathing (WOB). In patients with cardiovascular-pulmonary or neurologic disease, mechanical ventilation improves gas exchange primarily through tidal volume (VT) augmentation and guaranteeing adequate alveolar ventilation. By enhancing VT, mechanical ventilation, particularly when used with positive end-expiratory pressure (PEEP), may improve respiratory-system compliance by recruitment and stabilization of collapsed alveoli and improved aeration of under-ventilated alveoli. Depending upon a number of factors, mechanical augmentation of VT reduces the intensity and duration of inspiratory muscle contractions, thus lowering patient WOB. However, positive-pressure ventilation has potentially deleterious effects, primarily reduced venous return, decreased cardiac output, and systemic hypoperfusion.5-7

The primary focus of this paper concerns the physiologic effects of NIV on WOB, breathing pattern, respiratory-system mechanics, and hemodynamic function. Within this context, the effects of NIV on pulmonary gas-exchange function were also reviewed. Physiologic studies on respiratory-system mechanics and measurements of WOB cannot be done in patients with acute cardiogenic pulmonary edema, for obvious safety reasons. Thus, a large amount of physiologic evidence is missing from one of the major patient cohorts for whom this therapy is used. In consequence, we have limited our review to studies primarily done on patients with other forms of pulmonary disease, from whom in-depth physiologic data are available. The exception to this delimitation has been the hemodynamic effects of NIV. Nonetheless, at the end of this review we discuss evidence from some studies in patients with acute cardiogenic pulmonary edema, to provide a wider, albeit limited, perspective on the effects of NIV in that patient population.

Primary materials for this review were obtained first by conducting a PubMed search with the terms “noninvasive ventilation” and “noninvasive positive-pressure ventilation,” delimited to human studies between 1990 and 2008. Each abstract was reviewed for reported data on WOB, breathing effort, ventilatory pattern, respiratory-system mechanics, and hemodynamics. The reference section of each paper was reviewed to obtain pertinent publications not found in the PubMed search. Mean reported data were abstracted to quantify, in aggregate, the relative effects of NIV compared to unassisted spontaneous breathing.

Work of Breathing

Forty-one relevant studies were found that investigated the effects of NIV on WOB and breathing effort. The majority of these studies were done in patients with chronic obstructive pulmonary disease (COPD).5-9,10,12,13,15,16,20,22,25,28-30,33,38,44,46,47 whereas some also included patients with restrictive chest-wall disease,8,14,19,27,29,34,42 acute hypoxic respiratory failure,22,34 obesity hypoventilation syndrome,11,24 or acute cardiogenic pulmonary edema.17,18,36,37,40 Others studied the effects of NIV in patients with cystic fibrosis, or postoperative acute hypoxic respiratory failure. Duchenne muscular dystrophy, and acute lung injury (ALI).43 Four studies investigated the effects of NIV in normal subjects.32,39,45,49

All the studies were prospective. The majority were designed as randomized presentation, crossover studies that compared various combinations of ventilator modes, such as continuous positive airway pressure (CPAP), pressure-support ventilation (PSV), bi-level positive airway pressure (BiPAP), proportional-assist ventilation (PAV), and volume-control ventilation (VCV). The studies were conducted in various environments: 39% in laboratories;10,12,19,21,23-25,27,32,33,38,39,41,45,47 39% in intensive care units,9,15,17,22,26,28,31,37,40,43,44 59% in emergency department,18,36 or hospital wards;13,14,35 and 22% in rehabilitation centers,29,30,34,42,46 or patients’ homes.1,11,16,20,48 Likewise, the variables measured often differed between studies, and included WOB, diaphragmatic electromyography, oxygen consumption, resting energy expenditure, exercise tolerance, and dyspnea.

Spontaneous Work of Breathing in Chronic Respiratory Disease

Data from several studies reveal highly elevated spontaneous WOB in patients with chronic lung disease, as evidenced by substantial negative deflections in both esophageal pressure (ΔPeo) and transdiaphragmatic pressure (ΔPdi), which typically reached 14–16 cm H2O (Table 1). When these studies are analyzed together, the mean pressure-time product (PTP) of the inspiratory muscles, which is the mechanical correlate of inspiratory muscle oxygen consumption, commonly reached values of 260 cm H2O·s/min, whereas the reported mean PTP of the diaphragm was usually higher (350 cm H2O·s/min). Likewise, mean WOB was approximately 1.23 J/L, whereas the power output of the inspiratory muscles (W) was 13.7 J/min. Mean values for dynamic intrinsic PEEP (PEEPi) (the lowest alveolar pressure that must be overcome by the inspiratory muscles to initiate inspiratory gas flow) typically exceeded 3 cm H2O and sometimes 5 cm H2O in critically ill patients. By comparison, normal subjects entered into NIV
studies\textsuperscript{39,45,49} had a mean $\Delta P_{es}$ of 5 cm H$_2$O, WOB of 0.36–0.47 J/L, W˙ of 7.5 J/min, and PTP of 113–134 cm H$_2$O/s/min at baseline.

### Overall Effectiveness of NIV

In patients with diverse etiologies and severity of pulmonary disease, NIV uniformly reduced inspiratory effort (Table 2). At NIV settings that provided maximal efficacy, mean $\Delta P_{es}$ was reduced 8–15 cm H$_2$O (50%–76%),\textsuperscript{14,22,27,31} and mean $\Delta P_{di}$ was reduced 5–10 cm H$_2$O (42%–62%).\textsuperscript{9,12,17,32,36,40,47,48} The reduction in PTP ranged from 127 cm H$_2$O/s/min to 345 cm H$_2$O/s/min, which represents a decline of 20%–78%.\textsuperscript{9,12,15,22,24,27,28,30,31,33,34,37,41,43,44,47,48} Across all the studies, the average decline in PTP with NIV was 189 cm H$_2$O s/min (55%), compared to unassisted spontaneous breathing. Likewise, both WOB and W were reduced 0.27–1.3 J/L (31%–69%)\textsuperscript{22,31,37,39,43} and 5.4–10.2 J/min (30%–59%),\textsuperscript{22,33,37,43} respectively. Overall, maximal levels of NIV produced an approximate 60% reduction in measures of WOB and patient effort (Table 3). In 8 of 9 studies NIV reduced mean dyspnea scores by 29%–67%,\textsuperscript{11,13,16–19,23,25,36} NIV caused substantial reductions in mean diaphragmatic electromyography (EMG di), ranging from 17% to 93%,\textsuperscript{8–12,16,22,28,34,36} which signifies decreased inspiratory effort. In patients with COPD or restrictive chest-wall disease, maximal reduction in EMG di was reached at mean inspiratory pressure-assist values of 13 cm H$_2$O and 17 cm H$_2$O, respectively.\textsuperscript{8} The time course for reduction in both inspiratory efforts and EMG di activity was 5–6 breaths.

### Endurance, Muscle Strength, and Spirometry

In 4 studies that measured exercise tolerance as an indirect assessment of inspiratory muscle function, endurance was increased 14%–95%.\textsuperscript{16,20,22,48} In other studies, maximal inspiratory pressure increased 37% (11 cm H$_2$O)\textsuperscript{17} and vital capacity increased 10%\textsuperscript{48} following NIV. Yet not all studies found that NIV improved muscular strength\textsuperscript{16} or spirometry.\textsuperscript{11,17,20}

### Table 1. Baseline Measurements of Breathing Effort and Work-Related Variables During Unsupported Spontaneous Breathing in Patients With Chronic Pulmonary Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>$\Delta P_{es}$ (cm H$_2$O)</th>
<th>$\Delta P_{di}$ (cm H$_2$O)</th>
<th>PTP (cm H$_2$O $\cdot$ s/min)</th>
<th>PTP$_{di}$ (cm H$_2$O $\cdot$ s/min)</th>
<th>WOB (J/L)</th>
<th>W (J/min)</th>
<th>PEEPi (cm H$_2$O)</th>
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</thead>
<tbody>
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<td>13</td>
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<td>Elliott\textsuperscript{14}</td>
<td>13</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
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<td>ND</td>
<td>432</td>
<td>ND</td>
<td>ND</td>
<td>5.6</td>
</tr>
<tr>
<td>Girault\textsuperscript{22}</td>
<td>21</td>
<td>ND</td>
<td>364$^*$</td>
<td>ND</td>
<td>1.89</td>
<td>17.1</td>
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<td>O’Donoghue\textsuperscript{38}</td>
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<td>ND</td>
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<tr>
<td>Prinianakis\textsuperscript{44}</td>
<td>ND</td>
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<td>Pogg\textsuperscript{47}</td>
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<tr>
<td>Average</td>
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<td>353</td>
<td>1.23</td>
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<tr>
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<td>110</td>
<td>ND</td>
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<td>0</td>
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</table>

$^*$ Estimated from data

$^\dagger$ Normocapnia

$^\ddagger$ Hypercapnia

$\Delta P_{es}$ = inspiratory change in esophageal pressure

$\Delta P_{di}$ = inspiratory change in transdiaphragmatic pressure

PTP = pressure-time product of the inspiratory muscles, derived from esophageal pressure

PTP$_{di}$ = transdiaphragmatic pressure-time product

WOB = work of breathing

W = power output of the respiratory muscles.

PEEPi = intrinsic positive end-expiratory pressure (dynamic)

ND = no data reported
Relative Effects of Support Level

Determining the efficacy of NIV requires differentiating the effects of CPAP from those of inspiratory support on WOB. Positive-pressure inspiratory support reduces WOB by supplying a greater proportion of transpulmonary pressure during inspiration (the “push-pull” effect).\(^5^1\) In contrast, applying PEEP reduces WOB by 2 mechanisms: first, by counterbalancing PEEPi and thereby reducing the threshold load to inspiration;\(^5^2\) second, by increasing respiratory-system compliance and thereby reducing the elastic load to inspiration.\(^5^3\)

Seven studies examined the effects of varying the inspiratory support level and/or the addition of PEEP to NIV on WOB.\(^1^2,1^5,3^3,4^3,4^6\) or dyspnea.\(^1^8,2^3\) Another study examined the effects of CPAP alone.\(^3^8\) In patients with COPD and chronic hypercapnia studied in the laboratory setting, Nava et al\(^1^2\) found that increasing the pressure support from 10 cm H\(_2\)O to 20 cm H\(_2\)O caused additional decrease in mean \(\Delta P_{\text{di}}\) of 4.5–5.9 cm H\(_2\)O (35%–46%) and further reduced PTP\(_{\text{di}}\) by 50%–65%. Applying 5 cm H\(_2\)O PEEP had an additive effect; it significantly reduced EMG\(_{\text{di}}\).

Studying patients with COPD classified as either normocapnic or hypercapnic, Vanpee et al\(^3^3\) found that stepwise application of pressure support in 5-cm H\(_2\)O increments between 5–20 cm H\(_2\)O progressively reduced both PTP\(_{\text{di}}\) and W, despite increasing dynamic PEEPi, which rose by as much as 3 cm H\(_2\)O (Fig. 1). Whereas pressure support of 5 cm H\(_2\)O caused only minor reductions (3%–6%) in PTP\(_{\text{di}}\) and W, further incremental steps of 5 cm H\(_2\)O were associated with substantial reductions of approximately 15%–20% at each step. While keeping peak inspiratory pressure constant, adding PEEP of 5 cm H\(_2\)O and 10 cm H\(_2\)O generally caused a greater decrease in PTP\(_{\text{di}}\) than did the same level of peak inspiratory pressure without PEEP (Fig. 2). However, 10 cm H\(_2\)O of pressure support with PEEP of 10 cm H\(_2\)O was less effective in reducing inspiratory muscle work load than was using a higher pressure-support level of 15–20 cm H\(_2\)O with either no PEEP or 5 cm H\(_2\)O of PEEP.

Similarly, Appendini et al\(^1^5\) found that combining PEEP of 5 cm H\(_2\)O with pressure support of 10 cm H\(_2\)O reduced PTP\(_{\text{di}}\) more (229 cm H\(_2\)O \(\cdot\) s/min, 53%) than either pressure support of 10 cm H\(_2\)O (110 cm H\(_2\)O \(\cdot\) s/min, 22%) or

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**Table 2.** Measurements of Breathing Effort and Work-Related Variables During NIV Set at Maximum Inspiratory Support in Patients With Chronic Pulmonary Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>(\Delta P_{\text{es}}) (cm H(_2)O)</th>
<th>(\Delta P_{\text{di}}) (cm H(_2)O)</th>
<th>PTP (cm H(_2)O (\cdot) s/min)</th>
<th>PTP(_{\text{di}}) (cm H(_2)O (\cdot) s/min)</th>
<th>WOB (J/L)</th>
<th>W (J/min)</th>
<th>Max PS (cm H(_2)O)</th>
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<tr>
<td>Nava(^{1^2})</td>
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<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>15</td>
</tr>
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<td>ND</td>
<td>203</td>
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<td>ND</td>
<td>10</td>
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<tr>
<td>Girault(^{2^2})</td>
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<tr>
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<td>ND</td>
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<td>ND</td>
<td>12</td>
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<tr>
<td>Porta(^{2^7})</td>
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<td>ND</td>
<td>96</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>16</td>
</tr>
<tr>
<td>Polese(^{2^8})</td>
<td>9</td>
<td>11</td>
<td>195</td>
<td>218</td>
<td>ND</td>
<td>ND</td>
<td>14</td>
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<td>Vitacca(^{3^0})</td>
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<td>ND</td>
<td>126</td>
<td>ND</td>
<td>ND</td>
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<td>ND</td>
<td>1.61</td>
<td>35</td>
<td>17</td>
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<td>Vanpee(^{3^3\uparrow})</td>
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<td>ND</td>
<td>114</td>
<td>ND</td>
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<td>20</td>
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<tr>
<td>Vanpee(^{3^3\downarrow})</td>
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<td>ND</td>
<td>ND</td>
<td>84</td>
<td>ND</td>
<td>1.5</td>
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<td>Porta(^{3^4})</td>
<td>6.8</td>
<td>7.6</td>
<td>106</td>
<td>ND</td>
<td>ND</td>
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<td>Racca(^{4^9})</td>
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<td>Average</td>
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<td>115</td>
<td>0.65</td>
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</table>

* Estimated from data
\(\uparrow\) Normocapnia
\(\downarrow\) Hypercapnia
NIV = noninvasive ventilation
\(\Delta P_{\text{es}}\) = inspiratory change in esophageal pressure
\(\Delta P_{\text{di}}\) = inspiratory change in transdiaphragmatic pressure
PTP = pressure-time product of the inspiratory muscles derived from esophageal pressure
PTP\(_{\text{di}}\) = transdiaphragmatic pressure-time product
WOB = work of breathing
W = power output of the respiratory muscles
PS = pressure support
ND = no data reported
CPAP of 5 cm H2O (83 cm H2O · s/min or 19%) in critically ill patients with COPD. Dolmage and Goldstein23 found that the combination of PAV with PEEP of 5 cm H2O improved exercise endurance time by 95% in patients with COPD, compared to either CPAP of 5 cm H2O (26%) or PAV without PEEP (8%).

Noninvasive CPAP alone was found to reduce inspiratory work load in patients with COPD. O'Donoghue et al.38 reported that stepwise application of CPAP up to 10 cm H2O caused a progressive reduction in mean dynamic PEEPi by approximately 69% (2 cm H2O), whereas both mean PTPdi and ΔPdi decreased by 53% and 48%, respectively (approximately 130 cm H2O · s/min and 9 cm H2O). However, these improvements were offset by a substantial (1.1 L) increase in mean end-expiratory lung volume.

Vitacca et al.46 partitioned the inspiratory work load to assess the fraction required to overcome dynamic PEEPi, and then assessed the effects of applied PEEP set to patient comfort versus maximal physiologic effect (defined as a
40%–90% reduction in PTPdi). During unassisted spontaneous breathing, dynamic PEEPi accounted for 38% of PTPdi (6.7 cm H2O/s per breath). The mean PEEP set to achieve patient comfort and physiologic improvement were similar (3.6 cm H2O vs 3.1 cm H2O, respectively) which resulted in 29% and 20% reductions in the inspiratory work associated with overcoming dynamic PEEPi.

In patients with ALI, L’Her et al43 reported that CPAP of 10 cm H2O reduced PTP by a relatively modest 16% (40 cm H2O / s/min). In contrast, pressure support of 10–15 cm H2O in combination with PEEP of 5–10 cm H2O reduced PTP by over 50% (133–142 cm H2O / s/min) (Fig. 3). Mehta et al18 reported that BiPAP with 15 cm H2O inspiratory support and 5 cm H2O PEEP improved dyspnea scores more than CPAP of 10 cm H2O (62% vs 46%, respectively).

Relative Effects of NIV Mode

Nine studies14,22,25,31,34,35,42,45,47 have compared the relative effectiveness of different modes in reducing WOB during NIV. Seven of these studies compared PAV to PSV.25,31,34,35,42,45,47 In patients with COPD, studied in a laboratory setting, Bianchi et al25 found comparable reductions in dyspnea scores, of approximately 30%, with similar increases in exercise endurance. Among hospitalized patients with cystic fibrosis, when PSV and PAV were set to achieve the same level of inspiratory support, Serra et al35 found that peak EMGdi was reduced by similar magnitudes (14%–17%, respectively).

Winck et al42 studied dyspnea and quality of sleep in patients with COPD or restrictive chest disease in a rehabilitation unit. Again, both PSV and PAV were set to achieve the same levels of peak inspiratory support and PEEP. Neither magnitude of dyspnea nor quality of sleep was different between the modes, although PAV resulted in less drying of the mouth and nose. Other studies31,45,47 also found no statistically significant difference between PSV and PAV in reducing PTP, WOB, or ΔPesp when the modes were adjusted to achieve the same or similar levels of inspiratory support. Interestingly, Wysocki et al31 reported better patient comfort with PAV, despite finding no difference in any of the work-related variables. This was associated with increased Vt variability during PAV and attributed to PAV’s greater responsiveness to patient demand.31 That PAV was no more effective than PSV in reducing patient work-related variables might be explained by the fact that PAV was set to a single measurement of pulmonary resistance and elastance, This limitation may soon be overcome, as very recent advances in PAV technology provide ongoing determination of pulmonary resistance and elastance, and thus will allow inspiratory support to adjust continuously to changes in both patient effort and pulmonary mechanics. Nonetheless, it is important to emphasize that these studies were brief time-series with crossover designs, so it is unlikely that pulmonary mechanics changed markedly during the studies.

In a laboratory study, Elliott et al14 compared VCV to BiPAP in patients with clinically stable COPD. Both modes were set to achieve patient comfort. Although both modes significantly reduced PTP by a relatively modest 16% (40 cm H2O / s/min), there was little difference in ΔPesp between modes (9.5 cm H2O vs 8.8 cm H2O, respectively). In patients with COPD and acute hypoxemic respiratory failure, Girault et al22 reported that VCV reduced WOB and PTP more than did PSV (0.58 J/L vs 0.85 J/L, and 71 cm H2O / s/min vs 144 cm H2O / s/min, respectively). The differences in WOB were probably explained by the fact that inspiratory time was significantly shorter and mean inspiratory flow was significantly higher during VCV.

Patient Comfort Versus Optimization of Respiratory Muscle Function

Despite the findings of Girault et al22 that inspiratory work load was substantially reduced with VCV, paradoxically there was greater discomfort with VCV than with PSV. Other studies30,44 have reported similar findings, whereby ventilator adjustments that optimize inspiratory muscle function do not necessarily maximize comfort. Prinianakis et al44 found that PSV with a rapid pressurization rate (pressure-rise time) of 200 cm H2O/s produced the greatest reduction in PTPdi (62%) and ΔPesp (54%), but also the poorest patient tolerance and largest mask leaks.

Vitacca et al30 reported discrepancies between BiPAP set to optimize WOB and settings chosen by patients to maximize comfort. Although the mean differences in inspiratory support and PEEP between physiologic comfort were small (approximately 1 cm H2O), directional prefer-
ences differed considerably between patients. For example, in 39% of patients the physiologic level of inspiratory support exceeded the level chosen for comfort, whereas in 52% of patients the physiologic level of inspiratory support was less than the comfort level. Similarly, in 30% of patients the physiologic level of PEEP exceeded the level chosen for comfort, whereas in 56% of patients the inverse was true.

In a subsequent study by Vitacca et al.\textsuperscript{41} various combinations of increasing pressure support and PEEP produced a linear improvement in respiratory drive, breathing pattern, and oxygen saturation. However, patient comfort followed a U-shaped curve, wherein there was greater discomfort at both the lowest and highest levels of support. The zone of maximal comfort occurred either at a PEEP of 5 cm H\textsubscript{2}O with pressure support of 5–10 cm H\textsubscript{2}O, or at zero PEEP with pressure support of 15 cm H\textsubscript{2}O (Fig. 4). Although there was a wide discrepancy among individuals in the pressure-support settings that maximized comfort, approximately half of the patients chose a pressure support of 10–15 cm H\textsubscript{2}O, whereas a third chose a pressure support of 20 cm H\textsubscript{2}O. Decreasing comfort with higher pressure support was explained partly by patient-ventilator discoordination from more uncaptured efforts. Because the majority of patients were diagnosed with either COPD or neuromuscular disease, this finding is not surprising, as it has been documented frequently during invasive mechanical ventilation with pressure support.\textsuperscript{54–56}

As mentioned above, Vitacca et al.\textsuperscript{46} found small differences in external PEEP applied to reduce the work associated with dynamic PEEPi, based upon physiologic settings versus patient comfort. Interestingly, the distribution of applied PEEP set to patient comfort was much wider than that set to optimize patient work.

**Effects of Mask Interface**

Navalesi et al.\textsuperscript{29} compared the effects of different patient interfaces (nasal mask, nasal plugs, and face mask) on breathing pattern and tolerance of NIV. They reported that, despite better VT and peak flow with a face mask, patients favored nasal masks. An important complication associated with long-term NIV is skin breakdown and discomfort,\textsuperscript{57} which in one report accounted for approximately 18\% of therapeutic failures.\textsuperscript{17} As a result, a helmet NIV interface was developed. By necessity, these helmets have a large internal volume (12–15 L). This results in a substantial compressible volume,\textsuperscript{49} which probably interferes with circuit pressurization, trigger sensitivity, and WOB.

A laboratory study with normal subjects found no significant difference in WOB between CPAP delivered via large or small helmet versus face mask.\textsuperscript{39} In contrast, WOB during PSV with a face mask was reduced to near-zero and the mean time to reach the pressure-support level was 330 ms, whereas with either the large or small helmet, WOB (0.12 J/L and 0.13 J/L, respectively) and the time to reach the pressure-support level (1,020 ms and 960 ms, respectively) were significantly higher. When the NIV helmet was compared to a face mask during PSV, as resistive loads of 15 cm H\textsubscript{2}O/L/s and 29 cm H\textsubscript{2}O/L/s were applied, the helmet was associated with substantially higher PTP di (270 cm H\textsubscript{2}O · s/min and 149 cm H\textsubscript{2}O · s/min, respectively), partial pressure of end-tidal carbon dioxide (associated with rebreathing), dyspnea score, and pressurization delay.\textsuperscript{49} These results suggest caution when considering a helmet interface, particularly those with severe acute hypercapnia, when a rapid increase in alveolar ventilation is required.

**Humidification Devices**

Although the upper airway is not bypassed during NIV, prolonged delivery of dry gas at high flow may exceed the ability of these anatomic structures to provide adequate humidification. Therefore, supplemental humidification
has been recommended during NIV.\textsuperscript{58} Yet the choice of humidification device during NIV substantially impacts WOB. For example, a heat-and-moisture exchanger, compared to a heated humidifier, during NIV is associated with significantly higher WOB (0.66 J/L vs 0.36 J/L) and W (15.5 J/min vs 8.4 J/min).\textsuperscript{57}

**Breathing Pattern**

Twenty-one studies that measured WOB during NIV also evaluated changes in breathing pattern.\textsuperscript{9,10,12-15,22,27,29-31} The inspiratory pressures that produced maximal reductions in inspiratory work load were associated with a mean \( V_T \) increase of approximately 230 mL (47%). The response of respiratory frequency to NIV was varied. In most studies,\textsuperscript{9,10,12-15,22,27,29-31} mean respiratory frequency decreased by 6 breaths/min (22%), whereas in 2 studies\textsuperscript{28,34} mean respiratory frequency did not change. In 3 laboratory studies, done primarily with normal subjects, respiratory frequency increased slightly, by 2–3 breaths/min.\textsuperscript{32,33,45} Despite the general decrease in respiratory frequency, mean minute ventilation increased by 3 L/min (31%). When PAV was compared to PSV, there was no difference in respiratory frequency or \( V_T \), but there was more variability in \( V_T \) during PAV.\textsuperscript{31}

**Respiratory-System Mechanics**

Because passive ventilation cannot be achieved with most modes used for NIV, lung mechanics must be measured dynamically. As the methods and environment (eg, intensive care unit, rehabilitation center, laboratory) differed considerably between the studies, interpreting the studies’ lung mechanics measurements during NIV is difficult. Furthermore, whereas most of the studies investigated patients with COPD, some studies\textsuperscript{19,27,34} included patients with restrictive chest-wall disease. Seven studies measured dynamic lung compliance or lung resistance,\textsuperscript{15,19,27,28,34,38,47} whereas a larger set of studies measured dynamic PEEPi.\textsuperscript{12,15,19,22,27,28,30,31,33,34,37,38,43,44,46,47} In older normal subjects, dynamic lung compliance is approximately 130 mL/cm H\textsubscript{2}O (range 80–230 mL/cm H\textsubscript{2}O).\textsuperscript{39} In contrast, 4 studies of patients with chronic respiratory failure (primarily COPD) reported a mean dynamic lung compliance of 60–97 mL/cm H\textsubscript{2}O.\textsuperscript{15,28,34,47} In normal subjects, inspiratory lung resistance is approximately 2–4 cm H\textsubscript{2}O/L/s.\textsuperscript{60} In patients with COPD, morbid obesity, or restrictive chest-wall disease, mean inspiratory lung resistance had a range from near-normal (5.5 cm H\textsubscript{2}O/L/s)\textsuperscript{19} to markedly elevated (11.8–18 cm H\textsubscript{2}O/L/s).\textsuperscript{27,28,34,38,47} In those patients, NIV generally significantly increased dynamic lung compliance, by 17%–50%.\textsuperscript{28,34,47} Whereas the reductions in lung resistance were minor and statistically insignificant (4%–6%) in some studies,\textsuperscript{28,34,47} NIV effected substantial reductions (23%–72%) in other studies.\textsuperscript{27,38,47}

During unassisted spontaneous breathing, mean dynamic PEEPi in these studies was 3.4 cm H\textsubscript{2}O.\textsuperscript{12,15,19,22,27,28,30,31,33,34,37,38,43,44,46,47} When external PEEP (usually 5 cm H\textsubscript{2}O) was applied, dynamic PEEPi was reduced by an average of 1.8 cm H\textsubscript{2}O. However, with pressure support of 15 cm H\textsubscript{2}O and zero PEEP, there was an increase in dynamic PEEPi, by an average of 1.8 cm H\textsubscript{2}O.\textsuperscript{33} This is consistent with the findings of Nava et al,\textsuperscript{12} who reported that pressure support of 10 cm H\textsubscript{2}O and 20 cm H\textsubscript{2}O without PEEP increased end-expiratory lung volume. As mentioned above, O’Donoghue et al\textsuperscript{18} also reported substantial increases in end-expiratory lung volume with CPAP up to 10 cm H\textsubscript{2}O.

**Cardiovascular Function**

The hemodynamic effects of NIV vary widely, according to disease state, whether PEEP is used, and by the type of NIV interface. In healthy subjects, applying nasal CPAP of 3–20 cm H\textsubscript{2}O resulted in a pressure-dependent decrease in cardiac index, of 19%–23% (0.8–0.9 L/min/m\textsuperscript{2}), that only became significant once the pressure was \( \geq 15 \) cm H\textsubscript{2}O.\textsuperscript{61} Similarly, in a control group of normal subjects, Philip-Joët et al\textsuperscript{62} found that both CPAP of 10 cm H\textsubscript{2}O and BiPAP of 15/10 cm H\textsubscript{2}O produced 19% decrements in cardiac output (1.1 L/min/m\textsuperscript{2}), whereas mean systemic blood pressure was unchanged. Montner et al\textsuperscript{63} also studied normal subjects and found a significant decrement in cardiac output of 31% (2.3 L/min/m\textsuperscript{2}) at 20 cm H\textsubscript{2}O. However, cardiac depression was modified by the type of mask. CPAP of 15–20 cm H\textsubscript{2}O had no effect on hemodynamic function when a nasal mask was used and the mouth was slightly open. Use of a nasal mask with the mouth closed produced decreases in cardiac output similar to a full-face mask.

Relatively few studies have examined the acute hemodynamic effects of NIV in patients with chronic cardiopulmonary disease.\textsuperscript{62,64-68} In patients with stable hypercapnic COPD undergoing right-heart catheterization, pressure support of 10 cm H\textsubscript{2}O and 20 cm H\textsubscript{2}O caused a slight, insignificant decrease in cardiac output (4%–8%), and systemic oxygen delivery (1%–3%), without a change in systemic arterial blood pressure or heart rate.\textsuperscript{66} However, when PEEP of 5 cm H\textsubscript{2}O was applied with pressure support of 20 cm H\textsubscript{2}O there was a significant decrease in cardiac output (0.9 L/min, 18%) and systemic oxygen delivery (38 mL/min, 13%). Pulmonary arterial occlusion pressure increased significantly (4 mm H\textsubscript{g}, 57%) at pressure support of 20 cm H\textsubscript{2}O, regardless of PEEP, whereas mean pulmonary arterial pressure was unchanged.
In a study of patients with exacerbation of COPD, ventilated with an average pressure support of 12 cm H2O and 3 cm H2O PEEP, there was a significant decrease in cardiac output (0.9 L/min, 13%) and systemic oxygen delivery (79 mL/min, 8%), an insignificant decrease in oxygen consumption (24 mL/min, 9%), a small but significant decrease in mean pulmonary arterial pressure (3 mm Hg, 8%), and an insignificant increase in pulmonary arterial occlusion pressure (2 mm Hg, 17%).

In contrast, in patients with acute respiratory failure following lung or liver transplant, NIV had no appreciable effect on hemodynamics. Compared to unsupported spontaneous breathing, neither CPAP of 5 cm H2O nor pressure support of 15 cm H2O with PEEP of 5 cm H2O depressed cardiac index (3.1 L/min/m² vs 2.8 vs 2.9 L/min/m², respectively), pulmonary arterial occlusion pressure (15 mm Hg vs 14 mm Hg vs 15 mm Hg, respectively), or mean systemic arterial blood pressure (85 mm Hg vs 83 mm Hg vs 84 mm Hg, respectively). As ALI is a relatively common cause of respiratory failure following lung or liver transplantation, the lack of hemodynamic effect may be explained by diminished lung compliance and the consequent blunting of positive airway pressure transmission to the pleural space.

In patients with congestive heart failure the hemodynamic effects of NIV are more favorable. In patients with acute decompensation of congestive heart failure, Baratz et al found a mixed response to nasal CPAP. At a mean pressure of 12 cm H2O, over half of the patients had significant increases in cardiac index (0.4 L/min/m² or 16%), systemic oxygen delivery (2 mL/min/kg or 19%), and oxygen consumption (1 mL/min/kg or 30%). As pulmonary arterial occlusion pressure was not significantly changed, the presumed mechanism of increased cardiac function was reduced left-ventricular afterload associated with positive pleural pressure. Patients who did not respond to nasal CPAP showed no signs of depressed hemodynamic function at a slightly lower pressure (10.8 cm H2O). Similarly, Naughton et al reported varied hemodynamic responses to CPAP of 10 cm H2O in patients with congestive heart failure. They observed that ∆PES was significantly greater in patients with congestive heart failure than in normal subjects, which reflects a higher WOB and causes a larger left-ventricular transmural pressure. CPAP reduced both ∆PES and left-ventricular transmural pressure, and, thus, afterload, even though cardiac index did not change. Philip-Joët et al reported that both CPAP of 10 cm H2O and BiPAP of 15/10 cm H2O caused similar reductions in cardiac output (approximately 0.6–0.7 L/min, 16%–18%, respectively), without changes in mean systemic arterial blood pressure.

### Pulmonary Gas-Exchange Function

Eighteen studies in this review reported the short-term effects of NIV on arterial blood gases in patients with pulmonary disease. Across all the studies there was a consistent finding of either significant improvement or a trend toward improvement in arterial blood gases. Overall, at what were deemed to be optimal NIV settings for WOB, the mean arterial pH increased by 0.06, whereas the mean P_{aCO2} decreased by 9 mm Hg, the P_{aO2} increased 8 mm Hg, and the ratio of P_{aO2} to fraction of inspired oxygen (P_{aO2}/F_{IO2}) increased by 27 mm Hg.

### Acute Cardiogenic Pulmonary Edema

As mentioned above, this paper has not included a systematic review of the physiologic effects of NIV in patients with acute cardiogenic pulmonary edema. However, a cursory review of the literature suggests that NIV has similar effects on breathing pattern and gas exchange in patients with acute cardiogenic pulmonary edema as it does in those with COPD, restrictive chest-wall disease, and ALI. Initial studies found that, compared to standard care, 10 cm H2O of CPAP via face mask substantially reduced respiratory frequency (8 breaths/min, 25%) and increased either mean P_{aO2} (17 mm Hg, 30%) or P_{aO2}/F_{IO2} (68 mm Hg, 49%). The response of mean P_{aCO2} and pH were mixed. In hypercapnic patients, noninvasive CPAP significantly reduced P_{aCO2} (12 mm Hg, 21%) and increased mean arterial pH (from 7.18 to 7.28), whereas in normocapnic patients CPAP did not induce hypocapnia. Both studies found that noninvasive CPAP significantly reduced mean heart rate by 9–22 beats/min (8%–19%), whereas systolic arterial blood pressure was significantly reduced in one study (by 21 mm Hg, 15%), and in the other study there was a trend toward reduction (by 17 mm Hg, 10%).

Comparable improvements in breathing pattern and arterial blood gases have been reported in patients with acute cardiogenic pulmonary edema with noninvasive PSV with mean inspiratory/expiratory pressures of 15–21/4–5 cm H2O. In a multicenter randomized controlled trial that compared BiPAP (12/5 cm H2O) to CPAP (8 cm H2O), the 2 modes were equally effective in reducing respiratory frequency, dyspnea, and need for invasive mechanical ventilation, and in improving arterial blood gases.

### Summary

From the numerous studies on the physiologic effects of NIV, it is evident that relatively high levels of inspiratory...
pressure-assist markedly reduce patient WOB, inspiratory effort, and dyspnea. Interestingly, when these studies are examined in aggregate, the average level of inspiratory pressure-assist that maximally reduces WOB is 15 cm H₂O, which corresponds to baseline measurements of Pes and Pdi during unassisted breathing (see Table 1). In theory it would seem reasonable to anticipate that this level of mechanical support (in addition to the synergistic effects of PEEP) might reduce patient WOB to near-zero. However, patient WOB and effort remained elevated, but often approximated the upper limits of normal (see Table 2).

This discrepancy between similar levels of patient effort during unassisted breathing and mechanical inspiratory support on the one hand, and the continued patient WOB on the other is more apparent than real. Whenever mean data are used as the basis for discussion, precision is lost in describing the relationship between 2 interacting variables. Furthermore, while the act of breathing is mechanical and quantifiable, it is also a sensory experience acted upon by the subject.

In its classic definitions, dyspnea is an imbalance between breathing effort and chest displacement, whereas the spontaneous breathing pattern represents the patient’s strategy to maintain alveolar ventilation while minimizing WOB by balancing the elastic and resistive forces opposing ventilation. Thus, the breathing pattern adopted by patients with chronic pulmonary disease represents the response to altered respiratory-system mechanics, elevated WOB, and deranged blood gases.

In the studies under review, the primary physiologic effect of NIV was increased VT. NIV improved arterial blood gases as well as improved pulmonary mechanics in
The overwhelming majority of the studies in which it was measured loading effects of PEEPi. Dyspnea was reduced in the effort by the ability of applied PEEP to counter the threshold-pressure possible without placement of an artificial airway.

The inability of NIV to provide complete inspiratory muscle rest is also explained by both technologic and physiologic limitations. First, at an inspiratory pressure of approximately 20 cm H₂O, mask leak becomes more common and is difficult to eliminate. Second, gastric insufflation occurs when airway pressure exceeds the lower esophageal sphincter pressure, which in a healthy adult is approximately 20–25 cm H₂O. However, gastric insufflation can occur at lower airway pressure, particularly in those with neuromuscular disease. Therefore, the possibility for complete unloading of the patient’s inspiratory muscles is constrained by the upper limit of positive inspiratory pressure possible without placement of an artificial airway.

In summary, this review was based primarily upon 41 studies that examined the effects of NIV on breathing effort. The salient findings of this review are summarized below and in Table 4. NIV reduces WOB in direct proportion to the level of inspiratory pressure-assist and also by the ability of applied PEEP to counter the threshold-loading effects of PEEPi. Dyspnea was reduced in the overwhelming majority of the studies in which it was measured. On average, a pressure-support of 15 cm H₂O and a PEEP of 5 cm H₂O reduced most measures of WOB and inspiratory effort toward normal in patients primarily with chronic pulmonary disease. It is worth emphasizing that there is a dissociation between NIV settings that produce maximal physiologic benefit and the settings chosen by patients, and the differences are highly variable between individuals.

When set to the same level of inspiratory pressure-assist, PSV and PAV result in comparable reductions in WOB. However, at higher levels of support, NIV also can significantly reduce cardiac output. NIV consistently increases VT and minute ventilation, whereas respiratory frequency typically decreases. Only a minority of studies attempted to measure respiratory-system mechanics, and most reported an increase in dynamic lung compliance at higher levels of inspiratory pressure-assist. NIV consistently improved arterial blood gases.

REFERENCES


THE PHYSIOLOGIC EFFECTS OF NONINVASIVE VENTILATION

The Physiologic Effects of Noninvasive Ventilation


Discussion

Nava: We always titrate NIV while the patient is awake, and I’m not sure the awake settings give the patient a very nice sleep. I think we need studies of patient-ventilator interaction and gas exchange during sleep.

Kallet: That’s a great point.

Hill: Are you talking about sleep in the acute setting or the long-term setting?

Nava: Acute. We have never reassessed the NIV pressures during sleep. Do you monitor what happens at night with acutely ill patients on NIV?

Gay: Parthasarathy and Tobin studied that. I would say that to some extent we’re forced to recognize this because they develop such terrible periodicity at higher levels of pressure support, so that without a backup rate you’re going to be chasing alarms, especially during sleep.


Kacmarek: I have not seen any studies of sleep quality with NIV.

Nava: My group did one. During the daytime we set the pressure either physiologically or clinically, and at night we checked the sleep quality and found that, in the clinical setting, they had worse sleep with the clinical titration than with the physiologic titration.

Kacmarek: And that was with the NIV delivered via face mask?

Nava: Yes, but they were stable patients: not acute really.

Hill: We’ve been looking at this issue and trying to accumulate patients who are monitored 24 hours, and comparing NIV to invasive ventilation. We’ve had 4 patients so far. It’s very difficult to do this kind of study. There’s a lot of patients who don’t want to do it and the rest are unstable or at risk. And some we wean off right away. But what we have learned—not surprisingly—is that sleep is terribly disrupted in both NIV and invasively ventilated patients. It’s up in the air—which are the best settings. We don’t understand it very well.

Kacmarek: I wonder how much different the disruption is during NIV versus during spontaneous breathing in patients with severe chronic disease. Are we simply unmasking something that exists to a much greater extent than they’re aware of themselves?

Hill: We can’t answer that with the data we have, but it’s clear that even patients who are not being ventilated in the critical care setting have very disrupted sleep, and what additional problems mechanical ventilation adds is not clear, and it’s hard to separate one from the other in this setting.