The Physiologic Effects of Noninvasive Ventilation

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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 H_2O and a PEEP of 5 cm H_2O 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.

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Mr Kallet presented a version of this paper at the 42nd RESPIRATORY CARE Journal Conference, "Noninvasive Ventilation in Acute Care: Controversies and Emerging Concepts," held March 7-9, 2008, in Cancún, México.

The authors report no conflicts of interest related to the content of this paper.

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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 cardiopulmonary or neurologic disease, mechanical ventilation improves gas exchange primarily through tidal volume (V_T) augmentation and guaranteeing adequate alveolar ventilation.[1] By enhancing V_T, 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.[2] Depending upon a number of factors, mechanical augmentation of V_T reduces the intensity and duration of inspiratory muscle contractions, thus lowering patient WOB.[3,4] 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.[8-49] The majority of these studies were done in patients with chronic obstructive pulmonary disease (COPD),[9,10,12,13,15,16,20,22,25,28-30,33,38,44,46,47,49] whereas some also included patients with restrictive chest-wall disease,[8,14,19,27,29,34,42] acute hypoxic respiratory failure,[22,31] 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,[35] postoperative acute hypoxic respiratory failure,[26] Duchenne muscular dystrophy,[48] 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).[8,10,14,15,18,19,22-26,29,31,33-35,39,42,43,45,47] 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] emergency departments,[18,36] or hospital wards;[13,14,35] and 22% in rehabilitation centers,[29,30,34,42,46] or patients' homes.[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[9,14,15,22,24,27,28,30,33,34,37,38,44,46,47] reveal highly elevated spontaneous WOB in patients with chronic lung disease, as evidenced by substantial negative deflections in both esophageal pressure (ΔP_{es}) and transdiaphragmatic pressure (ΔP_{di}), which typically reached 14–16 cm H_2O (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,[50] commonly reached values of 260 cm $H_2O \cdot s$/min, whereas the reported mean PTP of the diaphragm was usually higher (350 cm $H_2O \cdot s$/min). Likewise, mean WOB was approximately 1.23 J/L, whereas the power output of the inspiratory muscles ($\dot{W}$) 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 H_2O and sometimes 5 cm H_2O in critically ill patients.[9,15,22] By comparison, normal subjects entered into NIV

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

Study	ΔP_{es} (cm H_2O)	ΔP_{di} (cm H_2O)	PTP (cm $H_2O \cdot$ s/min)	PTP_{di} (cm $H_2O \cdot$ s/min)	WOB (J/L)	$\dot{W}$ (J/min)	PEEPi (cm H_2O)
Brochard[9]	ND	19	ND	428	ND	ND	5.2
Nava[12]	12	13	ND	ND	ND	ND	2.7
Elliott[14]	13	ND	ND	ND	ND	ND	ND
Appendini[15]	ND	20	ND	432	ND	ND	5.6
Girault[22]	21	ND	364*	ND	1.89	17.1	4.5
Pankow[24]	ND	ND	ND	480	ND	ND	ND
Porta[27]	14	ND	240	ND	ND	ND	1.6
Polese[28]	ND	19	ND	361	ND	ND	2.6
Vitacca[30]	13	15	ND	347	ND	ND	3.2
Vanpee[33]†	ND	ND	ND	618	0.73	17.9	4.2
Vanpee[33]‡	ND	ND	ND	234	1.03	6.2	2.7
Porta[34]	13	14	218	249	ND	ND	2.7
Lellouche[37]	15	ND	268	ND	1.27	ND	0.6
O'Donoghue[38]	ND	16	ND	240	ND	ND	ND
Prinianakis[44]	ND	9	203	206	ND	ND	2.8
Poggi[47]	ND	ND	ND	292	ND	ND	2.2
Average	14.4	15.6	260	353	1.23	13.7	3.1
Normal	5	6	110	ND	0.5	5	0

* Estimated from data
† Normocapnia
‡ Hypercapnia
ΔP_{es} = inspiratory change in esophageal pressure
ΔP_{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
$\dot{W}$ = power output of the respiratory muscles.
PEEPi = intrinsic positive end-expiratory pressure (dynamic)
ND = no data reported

studies[39,45,49] had a mean ΔP_{es} of 5 cm H_2O, WOB of 0.36–0.47 J/L, $\dot{W}$ of 7.5 J/min, and PTP of 113–134 cm $H_2O \cdot$ 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 ΔP_{es} was reduced 8–15 cm H_2O (50%–76%),[14,22,27,31] and mean ΔP_{di} was reduced 5–10 cm H_2O (42%–62%).[9,12,17,30,32,36,40,47,48] The reduction in PTP ranged from 127 cm $H_2O \cdot$ s/min to 345 cm $H_2O \cdot$ s/min, which represents a decline of 20%–78%.[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 $H_2O \cdot$ s/min (55%), compared to unassisted spontaneous breathing. Likewise, both WOB and $\dot{W}$ were reduced 0.27–1.3 J/L (31%–69%)[22,31,37,39,43] and 5.4–10.2 J/min (30%–59%),[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%.[11,13,16-19,23,25,36]

NIV caused substantial reductions in mean diaphragmatic electromyography (EMG_{di}), ranging from 17% to 93%,[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_2O and 17 cm H_2O, respectively.[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%.[16,20,22,48] In other studies, maximal inspiratory pressure increased 37% (11 cm H_2O)[17] and vital capacity increased 10%[48] following NIV. Yet not all studies found that NIV improved muscular strength[16] or spirometry.[11,17,20]

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

Study	ΔP_{es} (cm H_2O)	ΔP_{di} (cm H_2O)	PTP (cm $H_2O \cdot$ s/min)	PTP_{di} (cm $H_2O \cdot$ s/min)	WOB (J/L)	$\dot{W}$ (J/min)	Max PS (cm H_2O)
Nava[12]	3.7	4.96	ND	ND	ND	ND	15
Appendini[15]	ND	11.4	ND	203	ND	ND	10
Girault[22]	9.8	ND	169*	ND	0.85	9.4	17
Pankow[24]	ND	ND	ND	128	ND	ND	12
Porta[27]	6	ND	96	ND	ND	ND	16
Polese[28]	9	11	195	218	ND	ND	14
Vitacca[30]	5.5	7	ND	126	ND	ND	16
Wysocki[31]	12	ND	287	ND	1.61	35	17
Vanpee[33]†	ND	ND	ND	114	ND	8.6	20
Vanpee[33]‡	ND	ND	ND	84	ND	1.5	20
Porta[34]	6.8	7.6	106	97	ND	ND	12
Lellouche[37]	5.7	ND	112	ND	0.56	7.3	15
L'Her[43]	ND	5.4	100	115	0.44	7.7	15
Prinianakis[44]	ND	4.2	93	79	ND	ND	14
Wysocki[45]	3	ND	42	ND	0.13	2.8	9
Vittaca[46]	ND	ND	ND	107	ND	ND	16
Racca[49]	ND	ND	ND	84	ND	ND	15
Average	6.8	7.4	138	115	0.65	10.1	15.1

* Estimated from data
† Normocapnia
‡ Hypercapnia
NIV = noninvasive ventilation
ΔP_{es} = inspiratory change in esophageal pressure
ΔP_{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
$\dot{W}$ = power output of the respiratory muscles
PS = pressure support
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).[51] In contrast, applying PEEP reduces WOB by 2 mechanisms: first, by counterbalancing PEEPi and thereby reducing the threshold load to inspiration;[52] second, by increasing respiratory-system compliance and thereby reducing the elastic load to inspiration.[53]

Seven studies examined the effects of varying the inspiratory support level and/or the addition of PEEP to NIV on WOB[12,15,33,43,46] or dyspnea.[18,23] Another study examined the effects of CPAP alone.[38] In patients with COPD and chronic hypercapnia studied in the laboratory setting, Nava et al[12] found that increasing the pressure support from 10 cm H_2O to 20 cm H_2O caused additional decrease in mean ΔP_{di} of 4.5–5.9 cm H_2O (35%–46%) and further reduced PTP_{di} by 50%–65%. Applying 5 cm H_2O PEEP had an additive effect; it significantly reduced EMG_{di}.

Studying patients with COPD classified as either normocapnic or hypercapnic, Vanpee et al[33] found that stepwise application of pressure support in 5-cm H_2O increments between 5–20 cm H_2O progressively reduced both PTP_{di} and $\dot{W}$, despite increasing dynamic PEEPi, which rose by as much as 3 cm H_2O (Fig. 1). Whereas pressure support of 5 cm H_2O caused only minor reductions (3%–6%) in PTP_{di} and $\dot{W}$, further incremental steps of 5 cm H_2O were associated with substantial reductions of approximately 15%–20% at each step. While keeping peak inspiratory pressure constant, adding PEEP of 5 cm H_2O and 10 cm H_2O generally caused a greater decrease in PTP_{di} than did the same level of peak inspiratory pressure without PEEP (Fig. 2). However, 10 cm H_2O of pressure support with PEEP of 10 cm H_2O was less effective in reducing inspiratory muscle work load than was using a higher pressure-support level of 15–20 cm H_2O with either no PEEP or 5 cm H_2O of PEEP.

Similarly, Appendini et al[15] found that combining PEEP of 5 cm H_2O with pressure support of 10 cm H_2O reduced PTP_{di} more (229 cm $H_2O \cdot$ s/min, 53%) than either pressure support of 10 cm H_2O (110 cm $H_2O \cdot$ s/min, 22%) or

Table 3. Summary of Effects of Maximum Inspiratory Support During NIV on Breathing Effort and Work-Related Variables in Patients With Chronic Pulmonary Disease

First Author	Outcome
Nava[12]	69% ↓ ΔP_{es}, 62% ↓ ΔP_{di}
Appendini[15]	43% ↓ ΔP_{di}, 53% ↓ PTP_{di}
Girault[22]	53% ↓ ΔP_{es}, 45% ↓ $\dot{W}$, 74% ↓ PTP
Pankow[24]	73% ↓ PTP_{di}
Porta[27]	57% ↓ ΔP_{es}, 60% ↓ PTP
Polese[28]	42% ↓ ΔP_{di}, 40% ↓ PTP_{di}
Vitacca[30]	53% ↓ ΔP_{di}, 64% ↓ PTP_{di}
Vanpee[33†]	82% ↓ PTP_{di}
Porta[34]	46% ↓ ΔP_{di}, 48% ↓ ΔP_{es}, 51% ↓ PTP, 61% ↓ PTP_{di}
Lellouche[37]	62% ↓ ΔP_{es}, 58% ↓ PTP, 56% ↓ WOB
Prinianakis[44]	53% ↓ ΔP_{di}, 54% ↓ PTP, 62% ↓ PTP_{di}
Average	46% ↓ ΔP_{di}, 50% ↓ ΔP_{es}, 59% ↓ PTP, 62% ↓ PTP_{di}, 56% ↓ WOB

† Normocapnia
NIV = noninvasive ventilation
ΔP_{es} = inspiratory change in esophageal pressure
ΔP_{di} = inspiratory change in transdiaphragmatic pressure
PTP_{di} = transdiaphragmatic pressure-time product
$\dot{W}$ = power output of the respiratory muscles
PTP = pressure-time product of the inspiratory muscles derived from esophageal pressure
WOB = work of breathing

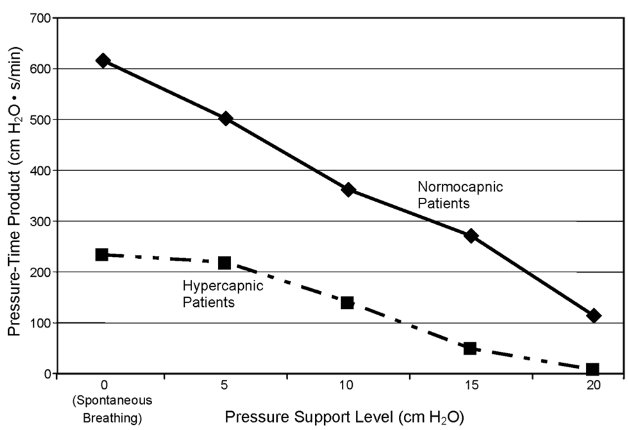

Fig. 1. Differential effects of increasing pressure support on inspiratory pressure-time-product in patients with normocapnic and hypercapnic chronic obstructive pulmonary disease. (From data in Reference 33.)

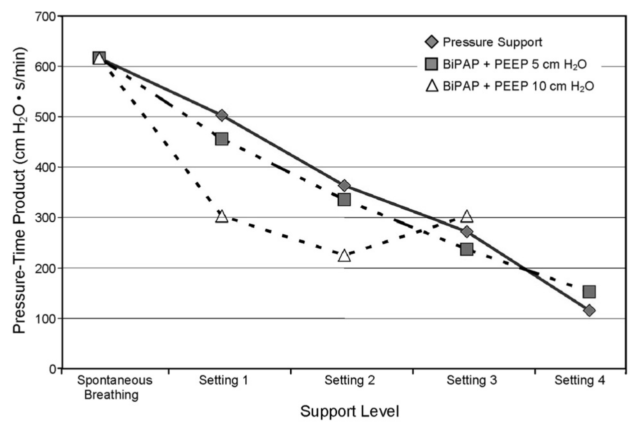

Fig. 2. Effect of increasing ventilatory support in pressure-support and bi-level positive-pressure ventilation (BiPAP) on inspiratory pressure-time-product in patients with chronic obstructive pulmonary disease. Setting 1 through Setting 4 refer to ventilator settings where pressure support was increased in 5 cm H_2O increments from 5–20 cm H_2O without positive end-expiratory pressure (PEEP), whereas during BiPAP inspiratory support was added in 5 cm H_2O increments above a PEEP of either 5 cm H_2O or 10 cm H_2O to a peak pressure of 20 cm H_2O. (From data in Reference 33.)

CPAP of 5 cm H_2O (83 cm $H_2O \cdot$ s/min or 19%) in critically ill patients with COPD. Dolmage and Goldstein[23] found that the combination of PAV with PEEP of 5 cm H_2O improved exercise endurance time by 95% in patients with COPD, compared to either CPAP of 5 cm H_2O (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 H_2O caused a progressive reduction in mean dynamic PEEPi by approximately 69% (2 cm H_2O), whereas both mean PTP_{di} and ΔP_{di} decreased by 53% and 48%, respectively (approximately 130 cm $H_2O \cdot$ s/min and 9 cm H_2O). 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

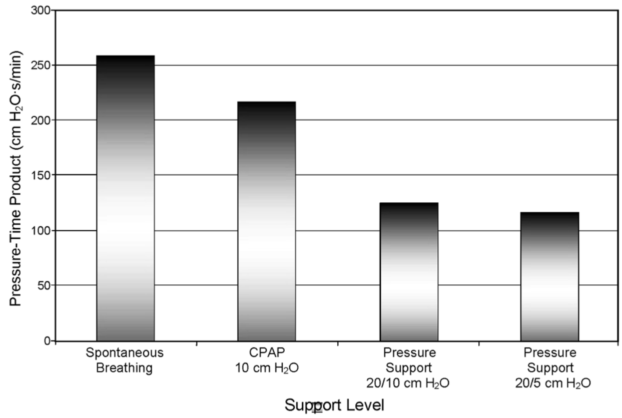

Fig. 3. Effects of noninvasive ventilation on pressure-time product of the inspiratory muscles in patients with acute lung injury. (From data in Reference 43.)

40%–90% reduction in PTP_{di}). During unassisted spontaneous breathing, dynamic PEEPi accounted for 38% of PTP_{di} (6.7 cm H_2O/s per breath). The mean PEEP set to achieve patient comfort and physiologic improvement were similar (3.6 cm H_2O vs 3.1 cm H_2O, respectively) which resulted in 29% and 20% reductions in the inspiratory work associated with overcoming dynamic PEEPi.

In patients with ALI, L'Her et al[43] reported that CPAP of 10 cm H_2O reduced PTP by a relatively modest 16% (40 cm $H_2O \cdot$ s/min). In contrast, pressure support of 10–15 cm H_2O in combination with PEEP of 5–10 cm H_2O reduced PTP by over 50% (133–142 cm $H_2O \cdot$ s/min) (Fig. 3). Mehta et al[18] reported that BiPAP with 15 cm H_2O inspiratory support and 5 cm H_2O PEEP improved dyspnea scores more than CPAP of 10 cm H_2O (62% vs 46%, respectively).

Relative Effects of NIV Mode

Nine studies[14,22,25,31,34,35,42,45,47] 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 al[25] 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 al[35] found that peak EMG_{di} was reduced by similar magnitudes (14%–17%, respectively).

Winck et al[42] 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 studies[31,45,47] also found no statistically significant difference between PSV and PAV in reducing PTP, WOB, or ΔP_{es} when the modes were adjusted to achieve the same or similar levels of inspiratory support. Interestingly, Wysocki et al[31] reported better patient comfort with PAV, despite finding no difference in any of the work-related variables. This was associated with increased V_T 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 al[14] compared VCV to BiPAP in patients with clinically stable COPD. Both modes were set to achieve patient comfort. Although both modes significantly reduced ΔP_{es}, compared to unassisted spontaneous breathing (approximately 90% reduction), there was little difference in ΔP_{es} between modes (9.5 cm H_2O vs 8.8 cm H_2O, respectively). In patients with COPD and acute hypoxemic respiratory failure, Girault et al[22] reported that VCV reduced WOB and PTP more than did PSV (0.58 J/L vs 0.85 J/L, and 71 cm $H_2O \cdot$ s/min vs 144 cm $H_2O \cdot$ 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 al[22] that inspiratory work load was substantially reduced with VCV, paradoxically there was greater discomfort with VCV than with PSV. Other studies[30,44] have reported similar findings, whereby ventilator adjustments that optimize inspiratory muscle function do not necessarily maximize comfort. Prinianakis et al[44] found that PSV with a rapid pressurization rate (pressure-rise time) of 200 cm H_2O/s produced the greatest reduction in PTP_{di} (62%) and ΔP_{di} (54%), but also the poorest patient tolerance and largest mask leaks.

Vitacca et al[30] 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 H_2O), directional prefer-

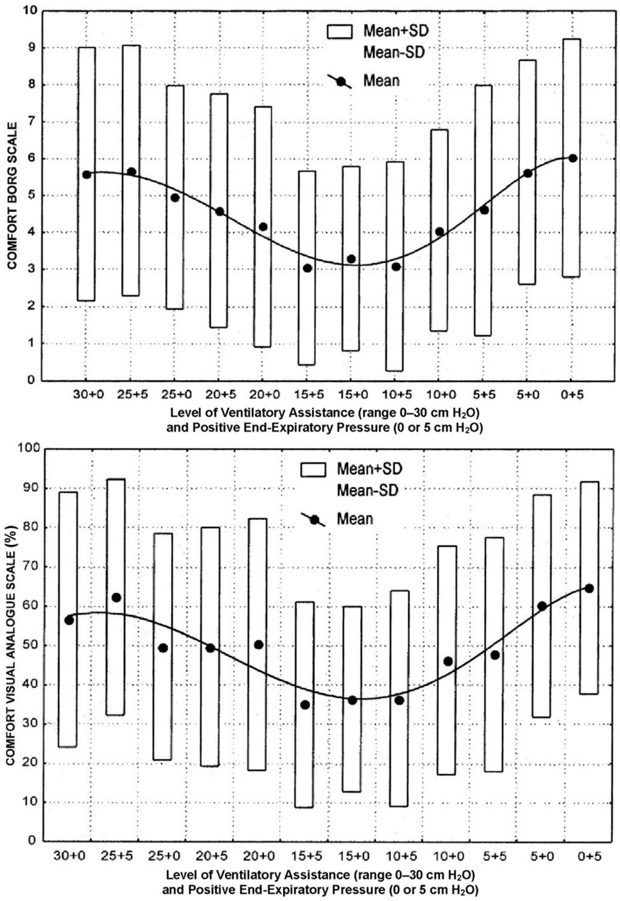

Fig. 4. Subjective comfort at various combinations of inspiratory pressure support and end-expiratory pressure. (Adapted from Reference 41, with permission.)

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[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_2O with pressure support of 5–10 cm H_2O, or at zero PEEP with pressure support of 15 cm H_2O (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_2O, whereas a third chose a pressure support of 20 cm H_2O. 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.[54-56]

As mentioned above, Vitacca et al[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[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 V_T and peak flow with a face mask, patients favored nasal masks. An important complication associated with long-term NIV is skin breakdown and discomfort,[57] which in one report accounted for approximately 18% of therapeutic failures.[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,[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.[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_2O/L/s and 29 cm H_2O/L/s were applied, the helmet was associated with substantially higher PTP_{di} (270 cm $H_2O \cdot$ s/min and 149 cm $H_2O \cdot$ s/min, respectively), partial pressure of end-tidal carbon dioxide (associated with rebreathing), dyspnea score, and pressurization delay.[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.[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 $\dot{W}$ (15.5 J/min vs 8.4 J/min).[37]

Breathing Pattern

Twenty-one studies that measured WOB during NIV also evaluated changes in breathing pattern.[9,10,12-15,22,27-36,38,41,44,45] 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,[9,10,12-15,22,27,29-31] mean respiratory frequency decreased by 6 breaths/min (22%), whereas in 2 studies[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.[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.[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[19,27,34] included patients with restrictive chest-wall disease. Seven studies measured dynamic lung compliance or lung resistance,[15,19,27,28,34,38,47] whereas a larger set of studies measured dynamic PEEPi.[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_2O (range 80–230 mL/cm H_2O).[59] In contrast, 4 studies of patients with chronic respiratory failure (primarily COPD) reported a mean dynamic lung compliance of 60–97 mL/cm H_2O.[15,28,34,47] In normal subjects, inspiratory lung resistance is approximately 2–4 cm H_2O/L/s.[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_2O/L/s)[19] to markedly elevated (11.8–18 cm H_2O/L/s).[27,28,34,38,47] In those patients, NIV generally significantly increased dynamic lung compliance, by 17%–50%.[28,34,47] Whereas the reductions in lung resistance were minor and statistically insignificant (4%–6%) in some studies,[28,34] NIV effected substantial reductions (23%–72%) in other studies.[27,38,47]

During unassisted spontaneous breathing, mean dynamic PEEPi in these studies was 3.4 cm H_2O.[12,15,19,22,27,28,30,31,33,34,37,38,43,44,46,47] When external PEEP (usually 5 cm H_2O) was applied, dynamic PEEPi was reduced by an average of 1.8 cm H_2O. However, with pressure support of 15 cm H_2O and zero PEEP, there was an increase in dynamic PEEPi, by an average of 1.8 cm H_2O.[33] This is consistent with the findings of Nava et al,[12] who reported that pressure support of 10 cm H_2O and 20 cm H_2O without PEEP increased end-expiratory lung volume. As mentioned above, O'Donoghue et al[38] also reported substantial increases in end-expiratory lung volume with CPAP up to 10 cm H_2O.

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_2O resulted in a pressure-dependent decrease in cardiac index, of 19%–23% (0.8–0.9 L/min/m^2), that only became significant once the pressure was $\geq$ 15 cm H_2O.[61] Similarly, in a control group of normal subjects, Philip-Joët et al[62] found that both CPAP of 10 cm H_2O and BiPAP of 15/10 cm H_2O produced 19% decrements in cardiac output (1.1 L/min/m^2), whereas mean systemic blood pressure was unchanged. Montner et al[63] also studied normal subjects and found a significant decrement in cardiac output of 31% (2.3 L/min/m^2) at 20 cm H_2O. However, cardiac depression was modified by the type of mask. CPAP of 15–20 cm H_2O 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.[62,64-68] In patients with stable hypercapnic COPD undergoing right-heart catheterization, pressure support of 10 cm H_2O and 20 cm H_2O 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.[66] However, when PEEP of 5 cm H_2O was applied with pressure support of 20 cm H_2O 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 Hg, 57%) at pressure support of 20 cm H_2O, regardless of PEEP, whereas mean pulmonary arterial pressure was unchanged.

In a study of patients with exacerbation of COPD,[67] ventilated with an average pressure support of 12 cm H_2O and 3 cm H_2O 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.[26] Compared to unsupported spontaneous breathing, neither CPAP of 5 cm H_2O nor pressure support of 15 cm H_2O with PEEP of 5 cm H_2O depressed cardiac index (3.1 L/min/m^2 vs 2.8 vs 2.9 L/min/m^2, 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[69] or liver[70] 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.[2]

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[65] found a mixed response to nasal CPAP. At a mean pressure of 12 cm H_2O, over half of the patients had significant increases in cardiac index (0.4 L/min/m^2 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.[71] Patients who did not respond to nasal CPAP showed no signs of depressed hemodynamic function at a slightly lower pressure (10.8 cm H_2O). Similarly, Naughton et al[68] reported varied hemodynamic responses to CPAP of 10 cm H_2O in patients with congestive heart failure. They observed that ΔP_{es} 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 ΔP_{es} and left-ventricular transmural pressure, and, thus, afterload, even though cardiac index did not change. Philip-Joët et al[62] reported that both CPAP of 10 cm H_2O and BiPAP of 15/10 cm H_2O 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,[10,12,1,315,17-19,22,26,28,29,36,37,40,43,44,66,67] whereas 2 other studies have reported on more long-term changes over several days or months in patients receiving domiciliary NIV.[20,42] 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_{aCO_2} decreased by 9 mm Hg, the P_{aO_2} increased 8 mm Hg, and the ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}) 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[72,73] found that, compared to standard care, 10 cm H_2O of CPAP via face mask substantially reduced respiratory frequency (8 breaths/min, 25%) and increased either mean P_{aO_2} (17 mm Hg, 30%) or P_{aO_2}/F_{IO_2} (68 mm Hg, 49%). The response of mean P_{aCO_2} and pH were mixed. In hypercapnic patients, noninvasive CPAP significantly reduced P_{aCO_2} (12 mm Hg, 21%) and increased mean arterial pH (from 7.18 to 7.28),[73] whereas in normocapnic patients CPAP did not induce hypocapnia.[72] 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%),[72] and in the other study there was a trend toward reduction (by 17 mm Hg, 10%).[73]

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 H_2O).[74-76] In a multicenter randomized controlled trial[77] that compared BiPAP (12/5 cm H_2O) to CPAP (8 cm H_2O), 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

Table 4. Summary Findings on the Physiologic Effects of Noninvasive Ventilation

Category	Major Experimental Findings on NIV
Work of breathing	Uniformly decreased inspiratory effort and WOB in patients with diverse etiologies and severity of pulmonary disease. Near-uniform decrease in dyspnea scores At maximum inspiratory support (15 cm H_2O), WOB and patient effort were reduced approximately 60%. Decreased mean diaphragmatic electromyogram 17%–93%. No difference in effectiveness between proportional-assist ventilation and pressure-support ventilation Some studies found improved endurance, inspiratory muscle strength, and spirometry after NIV. NIV settings that minimize WOB and patient effort are not necessarily the settings that maximize patient comfort.
Breathing pattern	Maximal inspiratory support that minimized inspiratory work load increased mean V_T 47%. Respiratory-frequency response to maximal NIV support differed in patients with COPD. Respiratory frequency typically decreased in patients with acute cardiogenic pulmonary edema.
Respiratory-system mechanics	NIV generally increased dynamic lung compliance 17%–50% in patients with COPD, morbid obesity, or restrictive chest-wall disease. During NIV, applied PEEP of 5 cm H_2O decreased dynamic intrinsic PEEP in patients with COPD. High (15 cm H_2O) inspiratory support without applied PEEP tends to increase inspiratory dynamic intrinsic PEEP in patients with COPD.
Cardiovascular function	In healthy subjects, nasal CPAP of $\geq$ 15 cm H_2O decreased cardiac output 20%–30%. In patients with stable COPD, high (10–20 cm H_2O) pressure-support with low (3–5 cm H_2O) PEEP decreased cardiac output approximately 20%. In patients with ALI those NIV levels had negligible effects on cardiac output. In patients with congestive heart failure, NIV often increased cardiac output by decreasing inspiratory effort and left-ventricular afterload.
Pulmonary gas-exchange function	At settings that minimized WOB, NIV typically increased pH an average 0.06, increased P_{aO_2} 8 mm Hg, and decreased P_{aCO_2} 9 mm Hg. NIV typically increased P_{aO_2} in patients with acute cardiogenic pulmonary edema, but only decreased P_{aCO_2} in the subgroup of patients with hypercapnia.

NIV = noninvasive ventilation
WOB = work of breathing
V_T = tidal volume
COPD = chronic obstructive pulmonary disease
PEEP = positive end-expiratory pressure
CPAP = continuous positive airway pressure
ALI = acute lung injury

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 H_2O, which corresponds to baseline measurements of ΔP_{es} and ΔP_{di} 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,[78] 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.[79] 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 V_T. NIV improved arterial blood gases as well as improved pulmonary mechanics in some studies. This may have decreased respiratory drive and thus reduced WOB. Moreover, the application of positive airway pressure directly off-loads the inspiratory muscles, which further decreases respiratory drive. Nonetheless, it is tempting to speculate that unless driven to the brink of exhaustion, patients would probably continue to perform inspiratory work, to achieve a more satisfying breath.

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 H_2O, 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 H_2O.[80] However, gastric insufflation can occur at lower airway pressure, particularly in those with neuromuscular disease.[81] 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 H_2O and a PEEP of 5 cm H_2O 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 V_T 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.

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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.[1] 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.

1. Parthasarathy S, Tobin MJ. Sleep in the intensive care unit. Intensive Care Med 2004;30(2):197-206.

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

Nava: My group did one.[1] 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.

1. Fanfulla F, Delmastro M, Berardinelli A, D'artavilla Lupo N, Nava S. Effects of different ventilator settings on sleep and inspiratory effort in patients with neuromuscular disease. Am J Respir Crit Care Med 2005;172(5):619-624.

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.