ELSEVIER

respiratoryMEDICINE

Effect of sleep on patient/ventilator asynchrony in patients undergoing chronic non-invasive mechanical ventilation ☆

Francesco Fanfulla[a],*, Anna Eugenia Taurino[a], Nadia D'Artavilla Lupo[a], Rossella Trentin[a], Carolyn D'Ambrosio[b], Stefano Nava[c]

[a]*Divisione di Pneumologia, Istituto Scientifico di Montescano and Pavia, Italy*
[b]*Tufts University School of Medicine, Boston, MA 02111, USA*
[c]*Fondazione S. Maugeri, IRCCS, Pavia, Italy*

Summary
Background: Patients who require home non-invasive ventilation (NIV) during sleep normally have the ventilation settings adjusted empirically during daytime wakefulness. However, patient-ventilator asynchrony may occur during sleep. To detect the incidence of ineffective efforts (IE) during the sleep compared to wakefulness, we studied 48 patients already enrolled in a long-term home NIV programme.
Methods: We evaluated arterial blood gases, breathing pattern during spontaneous breathing (SB) and ventilation during wakefulness. In addition, we assessed the breathing pattern and oxygen gas exchange during night-time NIV.
Results: Daytime NIV significantly improved blood gases compared to SB (PaO_2 $_{NIV}$ 10.2 ± 1.95 kPa vs PaO_2 $_{SB}$ 8 ± 1.37, $p < 0.001$; $PaCO_2$ $_{NIV}$ 5.75 ± 1.08 kPa, vs $PaCO_2$ $_{SB}$ 6.5 ± 1.25, $p < 0.001$). The IE index was higher during sleep compared to wakefulness (48 ± 39.5 events/h versus 0 ± 0). The IE index was correlated with the time spent with SaO_2 $< 90\%$ ($r = 0.39$, $p < 0.01$), but not with ventilator parameters, underlying disease, ventilation mode or type of mask. Eight patients had an IE index > 100 events/h; these patients had a faster respiratory rate, required a higher level of inspiratory assistance and had poor gas exchange during sleep.

Conclusions: We conclude that IE to breath are common during nocturnal NIV and that they may be associated with desaturations even in patients who are considered compliant and effectively treated.

Introduction

Non-invasive ventilation (NIV) is widely used as a treatment for chronic hypercapnic respiratory failure, especially when nocturnal hypoventilation is suspected. Possible mechanisms of hypoventilation that may benefit from the application of NIV are impairment of respiratory muscles, alterations in gas exchange, and abnormalities of the central respiratory drive.[1] The use of NIV in patients affected by chronic obstructive pulmonary disorders (COPD) is still controversial. While most of the studies performed in restrictive thoracic disorders (RTD) and neuromuscular diseases suggests that it alleviates symptoms of chronic hypoventilation and may prolong survival.[2–7] Pressure support ventilation (PSV), with or without some level of external positive end-expiratory airway pressure (PEEPe), is the most common mode of providing ventilatory assistance in the home setting. Usually, the ventilatory parameters are set based on arterial blood gases and patient's tolerance. However, during wakefulness, this has been shown to be accompanied by patient-ventilator asynchrony, especially during sleep.[8–10]

Ineffective efforts (IE) are the most common causes of asynchrony and may cause suboptimal ventilation during sleep, when profound modifications in the recruitment of respiratory muscles can occur.[9] Patient/ventilator asynchronies during the night are very rarely assessed in the clinical practice, due to technical problems, lack of knowledge by the physicians and because they may be imperceptible to the patient.[11] We postulated that IE may occur during sleep even in patients already accustomed to NIV. Therefore, we determine in this study the incidence of asynchronies during sleep in a group of patients already receiving home long-term PSV programme due to sleep hypoventilation or chronic hypercapnic respiratory failure.

Patients

Forty-eight patients (age 56.8 ± 13.3 yr) were studied when they were admitted to hospital in a phase of clinical stability for a scheduled control of their respiratory function and for a respiratory rehabilitation trial. Nocturnal polygraphy or polysomnography in our hospital is a standard evaluation for all the patients receiving nocturnal mechanical ventilation.

Clinical stability was defined as a lack of hospital admissions and exacerbations requiring supplemental medical therapy and no variations in levels of arterial blood gases (i.e., no changes $>5\%$ in pH, $PaCO_2$, and PaO_2) or ventilator settings in the 3 months preceding the study.

Eighteen patients were affected by COPD and 30 by RTD (12 patients with obesity-hypoventilation syndrome and 18 with kyphoscoliosis). They were all already established on long term (>6 months) NIV at night-time, but none of the patients was fully ventilator-dependent.

Home ventilatory programme

The criteria used to determine the need of home NIV were: $PaCO_2 \geqslant 6.65$ kPa, pH>7.34 breathing room air, and/or polygraphic signs of nocturnal hypoventilation with daytime symptoms. Nocturnal hypoventilation was defined as the presence of tonic, profound desaturations occurring mainly during REM sleep and with a more than 10% of total sleep time spent with $SaO_2 <90\%$. Blood gases recorded at the time of enrolment in the home nPSV programme and the duration of the NIV are summarized in Table 1. Patients with diagnosis of obstructive sleep apnea as demonstrated by polysomnography performed at enrolment in home ventilatory programme were excluded from the study.

Thirty-six patients received NIV in spontaneous/time (S/T) mode with a back-up respiratory rate of 12.2 ± 1.5 bpm while the reminder received NIV in spontaneous mode. In the whole group of patients, the inspiratory positive pressure (IPAP) was 14.8 ± 3.11 cmH$_2$O and the expiratory positive pressure (EPAP) was 6 ± 1.9 cmH$_2$O. Oxygen therapy was added to the NIV in order to achieve a $SaO_2 >92\%$. NIV was provided by a portable ventilators and delivered through different types of mask, according to patient's preference (Table 1). Compliance to NIV was assessed by means of patient's reports and by ventilator's hour counter.

Protocols

All the patients received a night study using an 8-channel polygraphy (Embletta X-trace, Medcare–Iceland). The equipment provided simultaneous measurements of mask pressure, body position, thoracic and abdominal movements, airflow derived from the pressure signal, SaO_2 and pulse rate. Respiratory movements were recorded using a

Table 1 Underlying disease, duration of NIV, daytime data on gas exchange at the time of initiation the home NIV program.

Underlying disease (COPD/OHS/KS)	18/12/18
Duration of NIV (months)	18.1 ± 14.9
Mask (nasal/oro-nasal/pillows)	35/11/2
PaO_2 (kPa)	8.04 ± 1.14
$PaCO_2$ (kPa)	6.7 ± 0.96
pH	7.39 ± 0.02
TIB_{90} (% of recording time)	45.4 ± 27.5

TIB_{90}, time of recordings with $SaO_2 <90\%$ (% of total recording time); NIV, non-invasive ventilation; COPD, chronic obstructive pulmonary disorders; KS, kyphoscoliosis; OHS, obesity-hypoventilation syndrome.

plethysmographic method (X-trace, Medcare, Iceland). The breathing pattern was analysed considering a 5-min epoch, and simultaneously reading the traces for mask pressure, airflow, thoracic and abdominal movements, the sum of thoracic and abdominal efforts, body position, SaO_2 and pulse rate. IE were identified as the presence of a respiratory movement recorded with respiratory inductive plethysmography and/or a positive deflection in expiratory flow without a concomitant breath delivered by the ventilator, as previously described.[9]

We measured IE, expressed both as the IE index (number of IE/h) and as the percentage of total breaths; the mean respiratory rate during the period of synchronized NIV (RRsync); the patient's mean respiratory rate (including IE) during dyssynchronized NIV (RRdyssync); the effective respiratory rate (RReff), defined as the number of breaths delivered by the ventilator (RRdyssync minus IE), and the time in bed (TIB$_{90}$) spent with $SaO_2 < 90\%$.

The protocol of the study was approved by the scientific committee of our institution. The Ethical Committee commented that the approval was waived since the patients at hospital admission must sign or not, the consent that their medical records and "routine" examinations may be used for research proposals. We have analysed only records of patients who agreed to sign.

Statistical analysis

Results are presented as mean and standard deviation. The Kolmogorov–Smirnov statistic with a Lilliefors significance level and Shapiro–Wilk tests were used to test the normality of distribution of IE in all patients.

Differences in anthropometric or physiological data between COPD and RTD patients were assessed by one-way ANOVA. Paired t-tests were used to assess differences in physiological data between the period of synchronized and dyssynchronized ventilation. The relationships between variables were evaluated by Pearson's product–moment correlation coefficient.

All the analyses were performed using the STATISTICA/W statistical package (Tulsa, OK, USA), and a p value < 0.05 was considered statistically significant.

Results

At home, no patients reported intolerance during NIV or complaints related to the occurrence of IE during sleep. Compliance to NIV was good in all patients: 33 patients used ventilator for all the night while the remaining 15 used ventilator at least 5 h/night.

Daytime data

Table 2 reports the data on gas exchange during spontaneous breathing and during mechanical ventilation. No statistically significant differences were found between COPD, OHS and KS patients in age, gas exchange during spontaneous breathing, gas exchange during mechanical ventilation, levels of IPAP; EPAP was higher in OHS groups in comparisons with COPD or KS patients. Gas exchange improved similarly during NIV in all patients, independently of underlying

Table 2 Age, ventilatory parameters and gas exchange data during spontaneous breathing (SB) and during daytime NIV, recorded at the time of the present study, separately for COPD, OHS and RTD patients.

	COPD	OHS	KS	p
Age (yrs)	61.3 ± 12.8	53.4 ± 14.6	54.8 ± 12.7	n.s
IPAP (cmH$_2$O)	15.6 ± 2.3	15.3 ± 2.6	13.7 ± 3.8	n.s.
EPAP (cmH$_2$O)	5.8 ± 1.7	7.2 ± 2	5.3 ± 1.6	0.02
PaO_2 SB (kPa)	8.2 ± 1.2	7.99 ± 0.85	8.99 ± 1.42	n.s.
$PaCO_2$ SB (kPa)	5.85 ± 0.5	5.86 ± 0.7	6.28 ± 1.4	n.s.
PaO_2 NIV (kPa)	9.84 ± 2.54	10.33 ± 2.1	10.25 ± 1.08	n.s.
$PaCO_2$ NIV (kPa)	5.6 ± 1.17	5.74 ± 1.09	5.98 ± 1.08	n.s.

IPAP: inspiratory positive pressure. EPAP: expiratory positive pressure.

disease (PaO_2 $_{NIV}$ 10.2 ± 1.95 kPa vs. PaO_2 $_{SB}$ 8 ± 1.37, $p < 0.001$; $PaCO_2$ $_{NIV}$ 5.75 ± 1.08 kPa, vs $PaCO_2$ $_{SB}$ 6.5 ± 1.25, $p < 0.001$).

No patients showed IE during mechanical ventilation in the daytime.

Night data

Table 3 reports data of night studies for all the patients and separately for each underlying disease; no differences were found between them for all the variables considered. During periods of patient/ventilator dyssynchrony, the respiratory rate (Rrdyssync) was statistically significantly higher than that observed during periods of optimal synchrony. The effective respiratory rate was statistically significantly lower than the respiratory rate recorded during synchronized ventilation. Overall, the IE index was not correlated with pressure support, PEEP$_e$, or daytime gas exchange during spontaneous breathing, and was not dependent from underlying disease, ventilation mode or type of mask. On the contrary, a statistically significant correlation was found between IE index and Rrdyssync ($r = 0.34$, $p = 0.019$). Of interest, the power of correlation increased considering only COPD patients ($r = 0.6$; $p = 0.0089$) while disappeared in OHS ($r = 0.18$; $p = $ n.s.) and KS patients ($r = 0.04$ $p = $ n.s.). Furthermore, the IE index in the whole group of patients was statistically significantly correlated with TIB$_{90}$ ($r = 0.39$; $p = 0.006$) (Fig. 1); the degree of correlation increased considering only those patients receiving PSV+O$_2$ therapy ($r = 0.6$; $p < 0.01$). The IE index was not statistically different in patients with the highest and the lowest level of compliance (41.8 ± 38.2 vs. 61.8 ± 40, respectively; ANOVA n.s.).

Fig. 2 shows the distribution of IE in the whole group. Eight patients had an IE index > 100 events/hr (121.1 ± 13.7), corresponding to $> 7\%$ of total breaths (group A). In comparison to patients with an IE index < 100 events/hr (33.4 ± 23.1) (group B), the group A patients had a higher level of pressure support (16.9 ± 2.4 vs. 14.4 ± 3.1 cmH$_2$O, $p < 0.05$), RRsync (19.1 ± 4.9 vs. 16.2 ± 3.2 bpm, $p < 0.05$), and RRdyssync (20.9 ± 5 vs. 18.4 ± 2.6 bpm, $p < 0.05$). In particular, the correlation between IE and RRdyssync was

Table 3 Data obtained during the sleep study for all the patients and separately for those with COPD, OHS and KS.

	Total sample	COPD	OHS	KS	p
Rrsync (bpm)	$16.7 \pm 3.6^{\dagger,*}$	16.5 ± 3.8	18.5 ± 3.5	15.7 ± 3.3	n.s.
Rrdyssync (bpm)	$19.1 \pm 2.9^{\dagger}$	18.9 ± 3.2	20.6 ± 2.3	18.4 ± 2.6	n.s.
Rreff (bpm)	$15.7 \pm 3.3^{*}$	15.2 ± 2.7	17.1 ± 3.8	14.7 ± 3.5	n.s.
IE (n/h)	48 ± 39.5	56 ± 46.1	47 ± 47	40.7 ± 25.1	n.s.
IE (% of total breaths)	4.1 ± 3	4.7 ± 3.9	3.8 ± 3.7	3.8 ± 2.3	n.s.
TIB_{90}	11.1 ± 17.4	15.2 ± 24.3	11.3 ± 13.1	6.9 ± 9.8	n.s.

Rrsync: mean respiratory rate during the period of synchronized NIV.
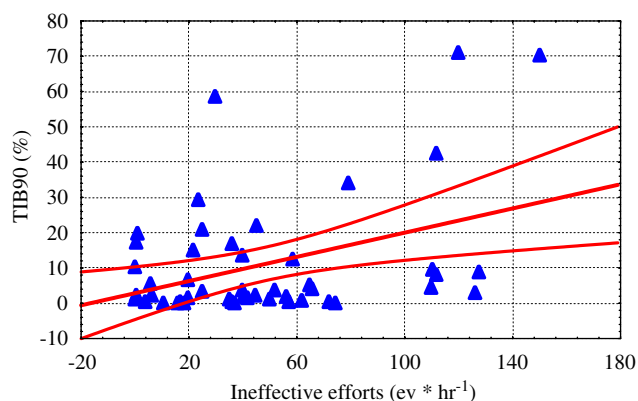Rrdyssync: patient's mean respiratory rate (including IE) during dyssynchronized NIV.
Rreff: effective respiratory rate.
IE: ineffective efforts.
TIB_{90}: time in bed (TIB_{90}) spent with $SaO_2 < 90\%$.
†Differences between Rrsync and Rrdyssync ($p < 0.0001$) for the total sample.
*Differences between Rrsync and Rreff ($p = 0.04$) for the total sample.

Figure 1 Correlation between the IE index and severity of nocturnal gas exchange impairment expressed as time spent with $SaO_2 < 90\%$ (TIB_{90}) in all patients.
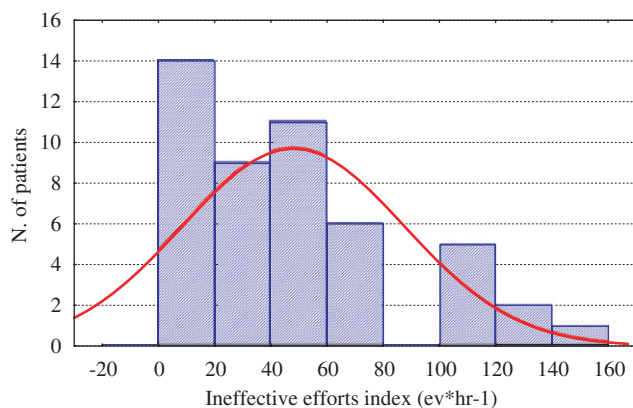
Figure 2 Distribution of the IE index in the whole group of patients. The line represents the normal distribution.

very high in group A patient ($r = .73$; $p = 0.03$) while not significant in group B patient ($r = 0.1$; $p = $ n.s.).

Finally, the development of higher levels of IE was associated with poor oxygen gas exchange during sleep, as demonstrated by a longer TIB_{90} (27 ± 29.6 vs. $7.9 \pm 12\%$ respectively; ANOVA F 9.55, $p < 0.01$). In contrast, during

wakefulness, NIV induced statistically significant improvements of PaO_2 and $PaCO_2$ in both group of patients, with the exception of PaO_2 in group A patients, as reported in Table 4.

The patients enrolled in the present study used different makes of ventilator at home: Respironics Synchrony, ResMed VPAP II-III, Saime Idea VS and ULTRA, Breas PV 102 and Tyco—Puritain-Bennet 425 ST. We did not found any associations between a specific ventilator and the onset of dyssynchrony.

Discussion

This study shows that IE are quite common in patients receiving home NIV during the night but only a small number of patients have a clinically relevant IE index: these patients have poorer nocturnal oxygen gas exchange, despite a good tolerance and compliance. Furthermore, we confirm that the breathing pattern during wakefulness does not predict ventilatory asynchrony while asleep.

A phenomenon of missing or IE has been shown to occur both in ventilator-dependent COPD patients[8] and in others with difficult weaning from ventilator[11] and was attributed to several factors.[12,13] We found that stable patients enrolled in a home NIV programme had a negligible amount of patient/ventilator mismatching during wakefulness. This scenario changed considerably during sleep, when the prevalence of IE became higher, independently of underlying disease or type of ventilation or mask. Patients with the highest IE index are those with a more advanced respiratory failure. Our study confirms the previous report by Vitacca et al. that the diagnosis of COPD is not associated with a higher risk of IE.[11] However, the number of patients who experienced frequent IE was lower than that reported in previous studies.[9,11,14] Our study was conducted on patients in a very stable condition and with a good compliance to NIV, suggesting that the occurrence of I/E may be a "silent" phenomenon, even in patients with the highest level of asynchrony. We did not evaluate patients with poor tolerance to ventilation where the occurrence of IE might be very high, because our aim was to assess the

Table 4 Differences in daytime blood gases during spontaneous breathing and during NIV in the two groups of patients considered.

	PaO_{2SB} (kPa)	PaO_{2NIV} (kPa)	p	$PaCO_{2SB}$ (kPa)	$PaCO_{2NIV}$ (kPa)	p
Group A	7.4 ± 1.28	9.5 ± 2.31	0.058	6.68 ± 0.45	6.1 ± 1.08	0.01
Group B	8.7 ± 1.2	10.4 ± 1.83	< 0.001	6.46 ± 1.4	5.6 ± 1.21	< 0.01

Group A: patients with an ineffective efforts index > 100 ev/h.
Group B: patients with an ineffective efforts index < 100 ev/h.

"epidemiology" of mismatching in the general population, assuming that "usual" ventilator settings may be associated with poor synchrony, despite achieving an improvement in gas-exchange, compared to unsupported breathing.[9] Further studies are needed to assess the presence of I/E in patients poorly tolerant to NIV.

Factors that could contribute to the onset of IE may differ from patient to patient: reduction in respiratory drive, reduction in respiratory muscle strength, increased inspiratory load due to augmented upper airway resistance and mouth leaks may all contribute to the inability to trigger the ventilator adequately.[8,12] We found that the patients with recurrent wasted breathing during sleep were those with the highest level of inspiratory assistance. High levels of inspiratory assistance, that produce larger tidal volume, may induce dynamic hyperinflation, also implicated in the genesis of ineffective IE.[10,15–17] Furthermore, in PSV and assisted volume-cycled ventilation, the end of the ventilator's inflation cycle is not always synchronized with the end of the patient's inspiratory effort. As a result, inflation may continue into the phase of neural expiration.[18,19] When the ventilator cycle extends into neural expiration, the time available for expiratory flow, before the next inspiratory effort, is reduced. If passive functional residual capacity is not reached during the shortened expiratory phase, dynamic hyperinflation occurs or is worsened. Dynamic hyperinflation increases the work of breathing and makes it difficult for the patient to trigger the ventilator[20] so that the occurrence of IE is likely.[21–24] In this study we have found that patients with the highest level of IE are those with the greater IPAP and an high respiratory rate, two conditions that may contribute in increasing auto-PEEP.

Another factor affecting the patient/ventilator interaction and the efficacy of ventilation is the presence of air leaks.[25] In a mathematical model and laboratory analysis it was shown that for a given inspiratory effort, the presence of leaks can be accompanied by a marked variation in duration of the inspiratory phase and in auto-PEEP, more evident when the respiratory rate is high.[26] In our study we were unable to monitor the amount of air leaks during NIV; however, patients with the highest number of IE were those who required the higher level of inspiratory assistance and had a faster respiratory rate during mechanical ventilation, suggesting a higher probability of air leaks. Our patients used at home different type of ventilators: some of them did not measure continuously air leaks and in others it is not possible to transfer data in the polygraph to analyse breath by breath the amount of leaks and to correlate them with presence of IE.

Overall, the main aims of long-term NIV are to reduce $PaCO_2$, to reduce sleep hypoventilation and to improve sleep quality.[27,28] In our study, we observed that patients with the highest number of IE were those with the poorest gas exchange during the night. In a previous study, conducted on patients with neuromuscular diseases,[9] we found that the onset of patient/ventilator mismatching during sleep resulted in poor sleep quality, a high number of arousals and less effective NIV. Changing the ventilator settings improved both sleep quality and the effectiveness of the mechanical ventilation.

Our data suggest that patients requiring a high level of inspiratory assistance and patients with faster respiratory rates during mechanical ventilation, even during periods of synchronized NIV, are at risk of developing ventilator mismatch during the night. Since the effectiveness of mechanical ventilation is reduced in the presence of IE, and since this asynchrony is not predicted by data obtained during wakefulness, we suggest to monitor patient-ventilator synchrony during the night in all patients who enter a long-term NIV programme in order to identify those for whom a change in ventilator settings or ventilator make would be beneficial.

Conflict of interest statement

The authors for this article have no conflicts of interest to declare.

References

1. Mehta S, Nill N. Non invasive ventilation. *Am J Respir Crit Care Med* 2001;**163**:540–77.
2. Jones SE, Packham S, Hebden M, Smith AP. Domiciliary nocturnal intermittent positive pressure ventilation in patients with respiratory failure due to severe COPD: long-term follow up and effect on survival. *Thorax* 1998;**53**:495–8.
3. Gay PC, Hubmayr RD, Stroetz RW. Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. *Mayo Clin Proc* 1996;**71**:533–42.
4. Strumpf DA, Millman RP, Carlisle CC, Grattan LM, Ryan SM, Erickson AD, et al. Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. *Am Rev RespirDis* 1991;**144**:1234–9.
5. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *Am J Respir Crit Care Med* 1995;**152**:538–44.

6. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, et al. Rehabilitation and Chronic Care Study Group, Italian Association of Hospital Pulmonologists (AIPO). The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002;**20**:529–38.

7. Annane D, Chevrolet JC, Chevret S, Raphael JC. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. *Cochrane Database of Systematic Reviews*. Issue 1, 2001.

8. Nava S, Bruschi C, Rubini F, Palo A, Iotti G, Braschi A. Respiratory response and inspiratory effort during pressure support ventilation in COPD patients. *Intensive Care Med* 1995;**21**:871–9.

9. 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**:619–24.

10. Jubran A, Van de Graaff WB, Tobin MJ. Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;**152**:129–36.

11. Vitacca M, Bianchi L, Zanotti E, Vianello A, Barbano L, Porta R, et al. Assessment of physiologic variables and subjective comfort under different levels of pressure support ventilation. *Chest* 2004;**126**:851–9.

12. Nava S, Ceriana P. Patient-ventilator interaction during noninvasive positive pressure ventilation. *Respir Care Clin* 2005;**11**:281–93.

13. Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Med* 2006;**32**:34–47.

14. Younes M, Kun J, Webster K, Roberts D. Response of ventilator-dependent patients to delayed opening of exhalation valve. *Am J Respir Crit Care Med* 2002;**166**:21–30.

15. Nava S, Bruschi C, Fracchia C, Braschi A, Rubini F. Patient-ventilator interaction and inspiratory effort during pressure support ventilation in patients with different pathologies. *Eur Respir J* 1997;**10**:177–83.

16. Rossi A, Appendini L. Wasted efforts and dyssynchrony: is the patient-ventilator battle back? *Intensive Care Med* 1995;**21**:867–70.

17. Parreira VF, Delguste P, Jounieaux V, Aubert G, Dury M. Effectiveness of controlled and spontaneous modes in nasal two-level positive pressure ventilation in awake and asleep normal subjects. *Chest* 1997;**112**:1267–77.

18. Younes M. Proportional assist ventilation and pressure support ventilation: similarities and differences. *Update Intensive Care Emerg Med* 1991;**15**:361–80.

19. Aslanian P, Brochard LJ. Partial ventilatory support. Marini JJ, Slutsky AS, editors. *Physiological basis of ventilatory support. Lung biology in health and disease*, Vol. 118. New York: Marcel Dekker; 1998. p. 817–46.

20. Marini JJ. Dynamic hyperinflation. Marini JJ, Slutsky AS, editors. *Physiological basis of ventilatory support. Lung biology in health and disease*, Vol. 118. New York: Marcel Dekker; 1998. p. 453–90.

21. Younes M. Patient–ventilator interaction with pressure-assisted modalities of ventilatory support. *Semin Respir Med* 1993;**14**:229–322.

22. Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator mode on triggering, patient's effort, and dyspnea. *Am J Respir Crit Care Med* 1997;**155**:1940–8.

23. Giannouli E, Webster K, Roberts D, Younes M. Response of ventilator-dependent patients to different levels of pressure support and proportional assist. *Am J Respir Crit Care Med* 1999;**159**:1716–25.

24. Tobin MJ, Jubran A, Laghi F. Patient-ventilator interaction. *Am J Respir Crit Care Med* 2001;**163**:1059–63.

25. Richards GN, Cistulli PA, Ungar RG, et al. Mouth leaks with nasal continuous positive airway pressure increases nasal airway resistance. *Am J Respir Crit Care Med* 1996;**154**:182–6.

26. Hotchkiss JR, Adams AB, Dries DJ, Marini JJ, Crooke PS. Dynamic behavior during noninvasive ventilation. *Am J Respir Crit Care Med* 2001;**163**:374–8.

27. Becker HF, Piper AJ, Flynn WE, McNamara SG, Grunstein RR, Peter JH, et al. Breathing during sleep in patients with nocturnal desaturation. *Am J Respir Crit Care Med* 1999;**159**:112–8.

28. Schönhofer B, Köhler D. Effect of non-invasive mechanical ventilation on sleep and nocturnal ventilation in patients with chronic respiratory failure. *Thorax* 2000;**55**:308–13.