Effectiveness of Controlled and Spontaneous Modes in Nasal Two-Level Positive Pressure Ventilation in Awake and Asleep Normal Subjects*

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Study objectives: The purpose of the present study was to compare in awake and asleep healthy subjects, under nasal intermittent positive pressure ventilation (nIPPV) with a two-level intermittent positive pressure device (two-level nIPPV), the efficacy of the controlled and spontaneous modes, and of different ventilator settings in increasing effective minute ventilation (Ve).

Participants: Eight healthy subjects were studied.

Setting: In the controlled mode, inspiratory positive airway pressure (IPAP) was kept at 15 cm H2O, expiratory positive airway pressure (EPAP) at 4 cm H2O, and the inspiratory/expiratory (I/E) time ratio at 1. The inspirator frequencies were 17 and 25/min. In the spontaneous mode experiment, IPAP was started at 10 cm H2O and progressively increased to 15 and 20 cm H2O; EPAP was kept at 4 cm H2O.

Measurements and results: We measured breath by breath the effective tidal volume (Vt with respiratory inductive plethysmography), actual respiratory frequency (f), and effective Ve. Using the controlled mode, effective Ve was significantly higher on nIPPV than during spontaneous unassisted breathing, except in stage 2 nonrapid eye movement sleep at 17/min of frequency; increases in f from 17 to 25/min led to a significant decrease in Ve reaching the lungs, during wakefulness; and sleep; effective Ve was higher at 25 than at 17/min of frequency only during sleep; periodic breathing was scarce and apneas were never observed. Using the spontaneous mode, with respect to awake spontaneous unassisted breathing, two-level nIPPV at 10 and 15 cm H2O of IPAP did not result in any significant increase in effective Ve either in wakefulness or in sleep; only IPAP levels of 20 cm H2O resulted in a significant increase in effective Ve during sleep; effective Ve was significantly lower than during wakefulness; respiratory rhythm instability (ie, periodic breathing and central apneas) were exceedingly common, and in some subjects extremely frequent, leading to surprisingly large falls in arterial oxygen saturation.

Conclusions: It appears that two-level nIPPV should be used in the controlled mode rather than in the spontaneous mode, since it seems easier to increase effective Ve with a lower IPAP at a high frequency than at a high pressure using the spontaneous mode. We suggest that the initial respirator settings in the controlled mode should be an f around 20/min, an I/E ratio of 1, 15 cm H2O of IPAP, and EPAP as low as possible.

Key words: controlled mode; noninvasive ventilation; spontaneous mode; two-level nasal intermittent positive pressure ventilation

Abbreviations: EMG=electromyogram; EMGdi=EMG of the diaphragm muscle; EMGm=submental chin EMG; EOG=electro-oculogram; EPAP=expiratory positive airway pressure; f= respiratory frequency; I/E=inspiratory/expiratory; IPAP=inspiratory positive airway pressure; MA=movement arousal; nIPPV=nasal intermittent positive pressure ventilation; NREM=nonrapid eye movement; PaCO2=end-tidal CO2 pressure; REM=rapid eye movement; SaO2=arterial oxygen saturation; Ti=inspiratory time; Ttot=total ventilatory cycle duration; Ve=minute ventilation; Vt=tidal volume

V entilatory failure may be defined as the inability to match minute ventilation (Ve) to the metabolic needs of the body. The main treatment of ventilatory failure, also called type II respiratory failure,1 is mechanical ventilation; its aim is to increase Ve to levels the patients are unable to attain, in order to match the metabolic requirements (ie, to decrease PaCO2). Mechanical ventilation can be performed noninvasively using either volumetric or barometric ventilators. The latter, under the form of two-level positive pressure devices (two-level nasal

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intermittent positive pressure ventilation [nIPPV]) has been used since 1990, initially in patients with obstructive sleep apnea, and later in the long-term treatment of ventilatory and respiratory failure secondary to neuromuscular diseases, chest wall deformities, or chronic airflow obstruction, as well as during acute respiratory failure. The efficacy of this therapy in patients with chronic airflow obstruction, stable or during acute exacerbations, is still under debate.

Using volumetric ventilators, we observed in healthy subjects, awake and asleep, glottic narrowing and closure in response to high-delivered VE, resulting in inefficient ventilation and even in apnea. The higher the delivered VE, the narrower the glottic width, leading to a progressive decrease in the percentage of delivered tidal volume (VT) effectively reaching the lungs. These data confirmed previous observations in patients with respiratory failure secondary to restrictive ventilatory defects under nIPPV.

To verify the glottic behavior and its consequences on effective VE (i.e., the VE calculated from the VT effectively reaching the lungs) during nIPPV performed using a two-level nIPPV device set in the controlled mode, we made a subsequent study in healthy subjects. Our results showed that increases in inspiratory positive airway pressure (IPAP) do not necessarily result in increases in effective VE reaching the lungs. Indeed, increases in IPAP can lead to glottic narrowing accompanied by significant decreases or absence of changes in effective VE.

Moreover, periodic breathing (cyclic oscillations of glottic width accompanied by corresponding variations in VT, with or without periods of apnea) was fairly common at different levels of inspiratory pressure, amounting to 10.5±11.0% of ventilation time during sleep. Although we did not explore the effects of an increase in the imposed respirator frequency (f) on effective VE, we suggested that with two-level nIPPV devices, the spontaneous ventilatory mode might perhaps be the ideal one, since in this mode inspiration is initiated by the subject’s activation of the inspiratory muscles and of the inspiratory glottic abductors, with the consequent glottic widening. Moreover, inspiratory and expiratory pressures are generated for a time determined by the subject. Hence, the respiratory drive is not inhibited, and respiratory pump and laryngeal muscle function are preserved.

We recently tested this hypothesis by studying normal subjects using a two-level IPPV device, in the spontaneous mode. We found that with this ventilatory mode, the glottis did not play any significant role in determining the final effective ventilation reaching the lungs. However, during wakefulness, we observed that inspiratory pressures of 10 and 15 cm H2O did not result in increases in effective VE, with respect to spontaneous unassisted breathing. Only at 20 cm H2O of inspiratory pressure did effective VE increase. This was due to a change in breathing pattern, with progressive increase in VT being offset by progressive decreases in frequency at 10 and 15 (but not at 20) cm H2O of IPAP. Moreover, the few data available suggested instability of respiratory rhythm to be induced during sleep, with the presence of central apneas leading to falls in arterial oxygen saturation (SaO2).

Therefore, it appears that it is difficult to increase the effective VE using two-level nIPPV either in the controlled mode (glottic narrowing) or in the spontaneous mode (changes in the pattern of breathing). The purpose of the present study was to compare the efficacy of these two modes (and of different ventilator settings), in increasing effective VE in a separate group of normal subjects. Indeed, in our previous studies, subjects had been ventilated with only one of the two modes. Moreover, we wished to investigate the effects of sleep on the efficiency of two-level nIPPV (only few data during sleep were available in our previous studies). In summary, our aim was to define the ventilator mode and settings allowing the greater increase in effective VE.

Materials and Methods

In both wakefulness and sleep, we studied eight healthy medical students (four women, four men) without evidence of respiratory diseases, snoring, or daytime somnolence, during nIPPV using a two-level positive pressure ventilator. Their age range was 19 to 24 years, and their body mass index was 22±2 (SD) (range, 18 to 24 kg/m2). In the week preceding the day of the experiment, subjects were habituated to noninvasive ventilation during two training sessions (2 h each) under both spontaneous and controlled modes. All the subjects gave written informed consent and received financial remuneration for their participation in the study. The protocol was approved by the ethical committee of the hospital.

Signals and Recording Equipments

The EEG, electro-oculogram (EOG), and submental chin electromyogram (EMG) were obtained from surface electrodes using standard techniques. The EMG of the diaphragm muscle (EMGdi) was obtained from surface electrodes placed around the fifth intercostal space. The EMGdi signal was filtered between 30 and 3000 Hz, but not rectified or integrated. The ECG was obtained from two surface electrodes placed on the chest. VT was obtained by respiratory inductive plethysmography (Respitrace; Ambulatory Monitoring, Ardsley, NY) calibrated with the isovolume technique in the same position that the subjects maintained throughout the whole recording period (see Procedure). The accuracy of measurement of VT by inductive plethysmography is satisfactory as long as the body position remains constant after the isovolume maneuver. The sum of the thorax and abdominal signals was calibrated against a water-
sealed spirometer. Mask pressure was measured from a port in the nasal mask with a transducer (Honeywell type 162 FC 01 D; Micro Switch Division, Honeywell; Freeport, Ill) calibrated with an alcohol-filled manometer. End-tidal CO₂ pressure (PETCO₂) was measured from CO₂ recordings made with a catheter passing through a plastic hollow conical piece (Nasal Adapter Set; Datex; Helsinki, Finland) introduced in the right nare, so that the nare was kept open and the extremity of the catheter remained in the center of the airstream. The catheter was passed through a sealed orifice pierced on the nasal mask and connected to a CO₂ analyzer apparatus (Normocap 200; Datex). Mouth airflow was assessed by one thermocouple in front of the mouth. Transcutaneous SaO₂ and pulse rate were recorded by pulse oximetry (Nellcor N-100; Pleasanton, Calif; or Criticare Poni; Wankesha, Wis) using a finger probe. All these signals were recorded with a digital acquisition system (OSG Brainlab; Antwerp, Belgium), as previously described.13

Procedure

The subjects arrived at the sleep laboratory at 1 PM, and had been asked to sleep a maximum of 3 h during the night preceding the study. Subjects lay comfortably in bed, in the supine position, with pillows on both sides, and with the head of the bed raised 15°, securing a fixed posture and avoiding any shift of the body during recording. Electrodes, Respiration oxygen recorder, and the finger sensor of the pulse oximeter were then applied. The CO₂ sampling catheter and nasal mask (nasal continuous positive airway pressure [CPAP] mask; Respironics; Monroeville, Pa) were then placed and two-level nIPPPV was started. The first 10 to 15 min of recordings were not retained for analysis. The ventilator was used initially in the controlled mode and afterwards in the spontaneous mode. In some subjects, a second recording with the controlled mode was performed. In all subjects, signals were acquired at the end of the study, after discontinuation of nIPPPV, during awake spontaneous unassisted breathing.

The ventilator used (Ventil+; SEFAM; Nancy, France) is a flow-triggered two-level positive pressure ventilator allowing the possibility of the separate control of inspiratory and expiratory pressures, f, and inspiratory/expiratory (I/E) time ratio.

In the controlled mode experiment, the ventilator was set in the following way: the IPAP was kept at 15 cm H₂O, the expiratory positive airway pressure (EPAP) was kept at 4 cm H₂O, which is the minimum EPAP possible with this type of device. The I/E ratio was kept at 1. The f was fixed at 17 breaths/min, slightly above the spontaneous f of the subjects, and afterwards it was increased to 25 breaths/min. The change in f was generally performed after at least 1 min of stable-state recordings without any artifact problems, during both wakefulness and sleep.

In the spontaneous mode experiment, the ventilator was set in the following way: IPAP was started at 10 cm H₂O and progressively increased to 15 and 20 cm H₂O (pressures refer to actual mask levels, not to the values on the ventilator control panel). EPAP was kept at 4 cm H₂O. The device sensitivity was adjusted as necessary so that each inspiratory effort was able to generate the switch from EPAP to IPAP. The changes in IPAP levels were performed after at least 1 min of stable-state recordings without any artifact problems at a given pressure level.

Measurements

Sleep/wake status was scored according to standard criteria in 30-s epochs.15 Movement arousals (MAs) were defined as the reappearance of an alpha rhythm in the EEG during a sleep epoch, accompanied by an increase in EMG activity.16 Sleep efficiency was defined as the percentage of sleep time with respect to total recording time. Periods preceded by at least 1 min of stable sleep/wake state, and absence of swallowing and of diaphragmatic (see Discussion for problems with EMGdi signal) and phasic chin EMG activity were considered for analysis of steady-state levels. Stages 3 and 4 of nonrapid eye movement (NREM) sleep were analyzed together. For the group of subjects, 104±31 (SD) min were recorded during the controlled mode experiment and 92±18 (SD) min during the spontaneous mode experiment (see details in Tables 1 and 2).

For each analyzed period, all individual values for effective inspiratory Vt, inspiratory time (Ti), total ventilatory cycle duration (Ttot), mask pressure, PETCO₂, SaO₂, and pulse rate were obtained directly via the digital acquisition system. We calculated breath by breath, the actual f from Ttot (f=60/Ttot), and the effective Vt from Vt and f.

Periodic breathing was defined as the presence of cyclic oscillations in the Vt with lowest Vt<50% of the highest one of the period. Apnea was defined as the absence of recorded subject’s Vt longer than 10 s in duration. Periods with periodic breathing and/or apneas were not retained for analysis of steady-state periods.

Data are presented as the mean±SD. Group comparisons were performed by Wilcoxon test; a value of p≤0.05 was considered to be significant. When group comparisons were not possible (not enough subjects with available data), intraindividual

<table>
<thead>
<tr>
<th>Table 1—Sleep Architecture for Eight Subjects During nIPPPV Using a Two-Level Positive Pressure Ventilator in the Controlled Mode*</th>
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<tbody>
<tr>
<td>Subject No.</td>
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<tr>
<td>-------------</td>
</tr>
<tr>
<td>TRT, min</td>
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<tr>
<td>TST, min</td>
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<tr>
<td>% 1</td>
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<tr>
<td>% 2</td>
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<tr>
<td>% 3</td>
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<tr>
<td>% 4</td>
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<tr>
<td>%REM</td>
</tr>
<tr>
<td>MA/hs</td>
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<tr>
<td>S Eff, %</td>
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</tbody>
</table>

*TRT=total recording time; TST=total sleep time; %1, %2, %3, and %4 refer to NREM sleep and REM to REM sleep, all in percentage of TST; MA/hs=MA expressed per hour of sleep; S Eff, %=sleep efficiency during this part of the study. Subjects 1, 2, 6, and 8 are female.
comparisons were performed with the unpaired Student’s t test. Using the Bonferroni correction, a value of $p \leq 0.001$ was considered as significant. Pearson product correlation coefficient was used to investigate association between variables; a $p < 0.0005$ was considered as significant using the Bonferroni correction.

### Results

**Controlled Mode Experiment**

Table 1 shows the sleep architecture of all subjects for the part of the recording concerning the controlled mode experiment. Seven of the eight subjects presented stable periods, periods preceded by at least 1 min of stable sleep/wake state, and absence of swallowing and of diaphragmatic—where EMGdi signal was available—and phasic chin EMG activity as described in the Materials and Methods section, during both wakefulness and sleep. Subject 2 presented only one period of stable state (2 min during stage 2 NREM sleep), and was therefore excluded from analysis. The seven retained subjects had stages 1 and 2 NREM sleep, five of the seven had stages 3 and 4 of NREM sleep, and none had rapid eye movement (REM) sleep. Their number of movement arousals (MAs) was normal, but sleep efficiency was poor: $52 \pm 18\%$ (range, 29 to 84%). The average length of records was $104 \pm 31$ min (range, 76 to 175 min).

For the group of subjects, 46 periods of steady state were analyzed: 18 during wakefulness, 20 during stage 2 NREM sleep, and 8 during stages 3 and 4 of NREM sleep. The average length of steady-state periods was $2.7 \pm 1.7$ min. The number of periods analyzed per subject was $7 \pm 2$, with a total of 2,588 breaths ($370 \pm 121$ per subject).

**Wakefulness Data: Tidal Volume:** Figure 1 shows the individual and group mean data of Vt for the two levels of f. For the group as a whole, increases in f from 17 to 25 breaths/min resulted in significant decreases in Vt. With respect to spontaneous unassisted breathing, there was a significant increase in Vt at 17 breaths/min, but not at 25 breaths/min of f.

**Minute Ventilation:** Figure 2 shows the individual and group mean data of VE for the two levels of f. For the group of subjects, increases in f did not result in any significant change in effective VE. With respect to spontaneous unassisted breathing, effective VE was significantly higher at both 17 and 25 breaths/min of f.

**Sleep Data**

**Stage 2 NREM Sleep: Tidal Volume:** Figure 3 shows the individual and group mean data of Vt for the two levels of f during stage 2 NREM sleep. For the group of subjects, increases in f led to a significant decrease in Vt. With respect to awake spontaneous unassisted breathing, Vt did not significantly change at 17 or 25 breaths/min of f.

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### Table 2—Sleep Architecture for Eight Subjects During nPPV Using a Two-Level Positive Pressure Ventilator in the Spontaneous Mode*

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>TRT, min</th>
<th>TST, min</th>
<th>% 1</th>
<th>% 2</th>
<th>% 3</th>
<th>% 4</th>
<th>REM</th>
<th>MAhs</th>
<th>S Eff, %</th>
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</table>

*See Table 1 footnotes.
Minute Ventilation: Figure 4 shows the individual and group mean data of Ve for the two levels of f. The Ve was significantly higher at the higher frequency. With respect to awake spontaneous unassisted breathing, Ve was marginally higher at an f of 17 breaths/min (p=0.06), and significantly higher at 25 breaths/min of f.

Stages 3 and 4 of NREM Sleep: In the four subjects in whom data were available, results during stages 3 and 4 of NREM sleep were similar to those observed in stage 2 NREM sleep.

Wakefulness vs Sleep: For the frequency of 17 breaths/min, comparisons of Vt and effective ventilation between wakefulness and stage 2 NREM sleep (the only stage in which data were available for comparisons) showed that during sleep, there was a trend to decrease in both Vt and effective Ve (p<0.06). In fact, six of the seven subjects had a lower Vt and effective Ve during sleep and one subject showed the opposite result. For the frequency of 25 breaths/min, there was no significant difference in Vt and effective Ve between wakefulness and stage 2 NREM sleep (see mean results in Figs 1-4).

Periodic Breathing: Periodic breathing was observed during wakefulness and stage 2 NREM sleep, at 17 and 25 breaths/min of frequency, respectively. Subject 5 showed one period of periodic breathing (2.5 min) with five cycles during stage 2 NREM sleep at 25 breaths/min of f. The length of these cycles was 31±18 s. The SaO2 following each cycle fell slightly and the lowest level was 92%. Subject 8 presented one period of periodic breathing, with two cycles, during wakefulness at the frequency of 17 breaths/min. These cycles had 56 and 52 s of duration, respectively. The SaO2 fell to 96% and 94%. Apneas were never observed.

Spontaneous Mode Experiment

Table 2 shows the sleep architecture for the part of the recording concerning the spontaneous mode experiment. Subject 2 had excessive sleep fragmentation (36 MA/h) and was excluded from analysis. Seven subjects presented data available during wakefulness and sleep. All subjects had stages 1 and 2
NREM sleep. Five subjects had stages 3 and 4 of NREM sleep and only one entered REM sleep. All subjects except one had a normal number of MAs, but a poor sleep efficiency was observed: 46±19% (range, 20 to 70%). The average length of records during spontaneous mode experiment was 92±18 min (range, 58 to 119 min).

For the group of subjects, 53 periods of stable state were analyzed: 25 during wakefulness, 19 during stage 2 NREM sleep, 7 during stages 3 and 4 of NREM sleep, and 2 during REM sleep. The average length of these periods was 1.8±0.7 min. The number of periods analyzed per subject was 7.5±2.6, with a total of 1,436 breaths (205±125 per subject).

**Wakefulness Data: Effects of Increases in IPAP**

Table 3 shows the group results, for VT, f, and effective VE for the three levels of inspiratory pressure and for spontaneous unassisted breathing. Increases in IPAP from 10 to 15 as well as from 10 to 20 cm H₂O resulted in significant increases in VT. When IPAP was raised from 15 to 20 cm H₂O, the difference in VT was not significant. With respect to spontaneous unassisted breathing, VT was significantly increased at 15 and 20 cm H₂O of IPAP. For the group of subjects, increases in IPAP from 10 to 15 and to 20 cm H₂O led to a significant decrease in f. With respect to spontaneous unassisted breathing, the only significant difference was a higher f at 10 cm H₂O of IPAP. Increases in IPAP from 10 to 15 and to 20 cm H₂O resulted in significant increases in VE. With respect to spontaneous unassisted breathing only at 20 cm H₂O of IPAP, there was a significant increase in effective VE.

**Sleep Data: Effects of Increases in IPAP: Stage 2 NREM Sleep**

During stage 2 NREM sleep, data were available for group comparisons at 10 and 15 cm H₂O of IPAP. Figures 5 to 7 show the individual and group mean data of, respectively, VT, f, and VE. VT and effective VE were significantly higher, whereas f was significantly lower, at 15 cm H₂O of IPAP than at 10 cm H₂O of IPAP.

**Figure 5.** Mean individual values of VT at two levels of IPAP, during stage 2 NREM sleep. IPAP-10 and IPAP-15 refer to, respectively, 10 and 15 cm H₂O of IPAP. Asterisk refers to the mean VT during awake spontaneous unassisted breathing in these five subjects. Figures represent mean values for the group. For significance of changes, see text.

For comparisons between awake spontaneous unassisted breathing and IPAP levels of 10 and 15 cm H₂O during stage 2 NREM sleep, there was a significant change only for VT at 10 cm H₂O of IPAP (VT was lower during assisted ventilation, see Fig 5). The effective VE was not significantly different with or without two-level nIPPV.

During stage 2 NREM sleep, subjects 1 and 5 showed at 20 cm H₂O of IPAP, with respect to 10 and 15 cm H₂O, a higher VT (respectively, 434±45 and 802±41 mL), a lower f (respectively, 12±1 and 13±1 breaths/min) and a higher effective VE (respectively, 5.1±0.7 and 10.8±0.8 L/min). With respect to awake spontaneous unassisted breathing, 20 cm H₂O of IPAP resulted in a significant increase in

**Figure 6.** Mean individual values of f at two levels of IPAP, during stage 2 NREM sleep. IPAP-10 and IPAP-15 refer to, respectively, 10 and 15 cm H₂O of IPAP. Asterisk refers to the mean f during awake spontaneous unassisted breathing in these five subjects. Figures represent mean values for the group. For significance of changes, see text.

<table>
<thead>
<tr>
<th>IPAP</th>
<th>VT, mL</th>
<th>f, Breaths/min</th>
<th>Effective VE, L/min</th>
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<tr>
<td>10</td>
<td>365±120</td>
<td>19±3</td>
<td>7.0±2.2</td>
</tr>
<tr>
<td>15</td>
<td>749±198</td>
<td>14±2</td>
<td>9.8±4.3</td>
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<td>951±347</td>
<td>12±1</td>
<td>11.7±4.6</td>
</tr>
<tr>
<td>SP</td>
<td>407±156</td>
<td>15±4</td>
<td>5.6±1.1</td>
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</table>

*10, 15, and 20=IPAP levels in cm H₂O; SP=spontaneous unassisted breathing. Data are presented as mean±SD. For statistical significance of differences, see text.
VT and effective V̇E, despite a significant decrease in f (for comparisons, see Figs 5 to 7).

Stages 3 and 4 of NREM Sleep and REM Sleep: Data were available in four subjects during stages 3 and 4 of NREM sleep, and in one subject during REM sleep. Results were similar to those observed during stage 2 NREM sleep.

Wakefulness vs Sleep: Group comparisons (for five subjects) between stable-state periods of wakefulness and stage 2 NREM sleep were possible at 10 cm H2O. Sleep induced a significant decrease in V̇E (from 7.0±2.2 to 4.3±1.1 L/min; p=0.04). VT and f remained statistically unchanged (from 365±120 to 252±58 mL and from 19±3 to 18±3 breaths/min, respectively).

Periodic Breathing and Apneas: Periodic breathing was observed only once in subject 3 (a period of 35 s of duration, in stage 2 NREM sleep at 15 cm H2O of IPAP). Apneas were observed during wakefulness and/or sleep at different levels of IPAP. All subjects had apneas, except subject 3. All apneas were of central type. Table 4 shows, for each subject, the number of apneas, their duration, the corresponding IPAP levels, and the lowest SaO2 following the apneas. Figure 8 presents typical records of central apneas during both wakefulness and sleep.

**DISCUSSION**

The main results of this study are that during nIPPV, using a two-level positive pressure ventilator in healthy subjects, (1) in the controlled mode, effective V̇E was always significantly higher than during awake spontaneous unassisted breathing (except in stage 2 NREM sleep at 17 breaths/min of f, where the differences fell just short of statistical significance). During sleep, but not during wakefulness, effective V̇E was higher at 25 than at 17 breaths/min of f. Periodic breathing was scarce during both wakefulness and sleep, without apneas. (2) With respect to awake spontaneous unassisted breathing, two-level nIPPV in the spontaneous mode at 10 and 15 cm H2O of IPAP did not result in any significant increase in effective V̇E either in wakefulness or in sleep; only IPAP levels of 20 cm H2O resulted in a significant increase in effective V̇E. For a given IPAP level, sleep decreased the efficiency of nIPPV (ie, effective V̇E was lower during sleep). Respiratory rhythm instability (ie, periodic breathing and central apneas) was exceedingly common, and in some subjects extremely frequent, leading to surprisingly large falls in SaO2. It seems therefore that

![Graph](image)

**Figure 7.** Mean individual values of effective V̇E at two levels of IPAP, during stage 2 NREM sleep. IPAP-10 and IPAP-15 refer, respectively, to 10 and 15 cm H2O of IPAP. Asterisk refers to the mean V̇E during awake spontaneous unassisted breathing in these five subjects. Figures represent mean values for the group. For significance of changes, see text.

**Table 4—Description of Central Apneas for Seven Subjects Using a Two-Level nIPPV Set in Spontaneous Mode, During Both Wakefulness and Sleep**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Wakefulness</th>
<th>Sleep</th>
</tr>
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<tbody>
<tr>
<td>No.</td>
<td>Duration</td>
<td>SaO2</td>
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<tr>
<td>1</td>
<td>—</td>
<td>—</td>
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<td>3</td>
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*No.=number of apneas; duration=mean±SD duration in seconds; SaO2=mean±SD of lowest SaO2 levels following the apneas, range in parentheses; TWT=total wakefulness time; TST=total sleep time; IPAP=levels of IPAP, in cm H2O, corresponding to the apnea periods.*
two-level nIPPV should be used in the controlled rather than in the spontaneous mode. Indeed, it seems easier to increase effective VE with a lower IPAP using the controlled mode at a high frequency than using the spontaneous mode at a high pressure. Moreover, apneas were never observed in the controlled mode contrary to the spontaneous mode, where sometimes large drops in SaO$_2$ following apneas were recorded.

In the controlled mode, we observed a significant decrease in VT when f was increased from 17 to 25 breaths/min. During two-level nIPPV, in the controlled mode, VT results from a complex interaction among airflow resistance, applied inspiratory pressure and flow, ventilatory system compliance, the presence and amount of leaks, and Ti. The IPAP and EPAP levels used (15 and 4 cm H$_2$O, respectively) were the same at both frequencies and probably do not explain the difference in VT between the two frequencies. We believe that the observed decrease in effective VT was glottic related. Indeed, glottic narrowing accompanied by a decrease in VT was previously observed under direct vision with a fiberoptic bronchoscope during assisted ventilation in the controlled mode using either volumetric or barometric ventilators. An additional factor could also explain the decrease in VT at the higher f: the decrease in Ti. Indeed, Ti decreased from 1.8 to 1.2 s when f increased from 17 to 25 breaths/min. Moreover, the correlations observed between Ti and VT were significant during wakefulness (r=0.246) and during stage 2 NREM sleep (r=0.123). However, these correlation values are so weak that the influence of the decrease of Ti on the decrease in VT is probably small, if any.

Effective VE was similar during wakefulness for the two f's in the controlled mode. Increases in f were just sufficient to compensate for the decrease in VT. By contrast, during stage 2 NREM sleep, a significant increase in effective VE was found when f was raised. The different results observed during wakefulness and sleep were probably due to a different degree of glottic narrowing and its effects on VT as previously demonstrated in subjects under nIPPV. During sleep, glottic narrowing is exaggerated, so that there is less room for a further decrease in glottic width when f is increased. By contrast, the nIPPV-related glottic narrowing is probably less important during wakefulness at 17 breaths/min of f, and the glottis can further narrow at an f of 25 breaths/min, therefore significantly reducing VT. Figures 1 and 3 show indeed that VT was much lower during sleep than during wakefulness at an f of 17 breaths/min, whereas the difference between wakefulness and sleep is much less at an f of 25 breaths/min.

In the present study, the use of 15 cm H$_2$O of IPAP in the controlled mode resulted in a significant increase in effective VE with respect to spontaneous unassisted breathing, at the two f's we used, except at 17 breaths/min during stage 2 NREM sleep in which there was a tendency for effective VE increase on nIPPV. During our previous study, at 10 cm H$_2$O
of IPAP and 17 breaths/ min of f, effective Ve was 7.1±2.9 L/min during wakefulness and 6.2±2.9 L/min during sleep. These figures are close to the
5.6±1.1 L/min observed in the present study during awake spontaneous unassisted breathing, suggesting that an IPAP level of 10 cm
H2O at an f of 17 breaths/ min may not be high enough to grant an increase in effective Ve. Hence, it seems wise to
recommend the use of 15 cm H2O and an f higher than 17 breaths/ min in the controlled mode. A
pressure of 15 cm H2O, however, may be more disturbing for sleep than a lower pressure of 10 cm
H2O. Whereas a poor sleep quality may not be deleterious for a single night, this issue may be more
important in the long-term use of nocturnal nIPPV.

We recently reported that in awake normal sub¬
djects during two-level nIPPV in the spontaneous
mode, significant increases in effective Ve (with
respect to spontaneous unassisted breathing) were
obtained only at 20 cm H2O of IPAP. This was due
to a decrease in f that offset the increase in VT attained when IPAP was raised from 10 to 15 cm
H2O. In other words, surprisingly, effective Ve remains unchanged whether the subject is receiving
mechanical ventilation or not. Being connected to a
ventilator is not, using noninvasive ventilation, syn-
onymous to being ventilated. Our present data con-
firm this trend during wakefulness and extend these
observations to sleep. During stage 2 NREM sleep,
our data in stable state were available for group
comparisons at 10 and 15 cm H2O of IPAP. We
observed that a rise in IPAP led to a significant
increase in VT accompanied by a significant decrease
in f. The net result, in the present study, was a
significant increase in effective Ve. However, with
respect to awake spontaneous unassisted breathing,
no significant changes were observed, except for VT
at 10 cm H2O of IPAP: surprisingly, VT was lower
during assisted ventilation with a positive pressure
than during spontaneous unassisted breathing (Fig
5). How can this paradox be explained? The glottis
probably does not play any role. Indeed, we have
shown previously that during two-level nIPPV in the
spontaneous mode, the glottis did not play any
significant role in determining the final ventilation
reaching the lungs. Another explanation stems from
the observation of the inductive plethysmographic
traces. As shown in Figure 9, inspiration was “inter-
rupted” by an end-inspiratory plateau despite persis-
tency of positive inspiratory mask pressure. We have
already observed such a behavior in one subject in
our previous study, when fiberoptic endoscopic im-

![Figure 9](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21754/)

**Figure 9.** Polygraph recording of EOG, EMGm, EEG, EMGdi, ECG, thorax, abdomen, and sum
signals from the Respitrace oxygen recorder, mask pressure, PetCO2, mouth airflow, SaO2, and pulse
rate (heart rate) recorded in subject 5 ventilated with an inspiratory pressure of 10 cm H2O in the
spontaneous mode. For records duration, see scale of 3 s. Note the inductive plethysmographic traces
with an end-inspiratory plateau despite correct inspiratory pressure mask.
ages showed that this was not due to glottic closure (unpublished observations during the study reported in reference 14). Therefore, we can only postulate that this phenomenon must correspond to an active isometric muscular contraction of abdominal muscles and perhaps of the diaphragm and intercostals, opposing any further change in thoracic and abdominal dimensions. We have absolutely no proof of this hypothesis, but we do not see any other explanation that fits the data. The above behavior was seen at 10 cm H₂O of IPAP in stage 2 NREM sleep in all but one subject having stable-state periods as well as in two of the three subjects who had data in stages 3 and 4 NREM sleep, and also during REM sleep in subject 5. During wakefulness, only one subject had this type of inspiratory “interruption.” To account for the decrease in VT in the other subjects and sleep/wake states, we can only advocate that under a low level of IPAP (10 cm H₂O), subjects adopted, for unknown reasons, a “rapid shallow breathing” type pattern, explaining the increase in f and the decrease in VT. Alternatively, this inspiratory plateau may be due to an insensitivity of the ventilator switching from inspiration to expiration. However, for the same device sensibility and pressure levels, this phenomenon was not constant, suggesting that this was not the case.

Using the controlled mode, periodic breathing was observed during wakefulness at 17 breaths/min of f and during sleep at 25 breaths/min of f. These cycles of periodic breathing had small durations, and the final SaO₂ values following these periods were never lower than 92%. Apneas were never observed. Using the spontaneous mode, periodic breathing was observed only once in subject 3, and was less common than in our previous study. By contrast, central apneas were observed in six of the seven subjects (Table 4). In our previous study during two-level nIPPV in spontaneous mode, central apneas were unrelated to glottic aperture (the glottis could be open or closed). The apneas of the present study occurred during wakefulness in subject 6 but especially during sleep in all subjects. Subjects 4 and 6 had 53 and 30 apneas representing, respectively, 41% and 28% of their total sleep time. In most of these apneas, there was a drop in SaO₂ at the end of apneas and sometimes the minimum levels attained were as low as 88%, 77%, 69%, and even 54% in one case (Table 4). Falls in SaO₂ were previously observed in patients receiving two-level nIPPV using the timed mode, but especially when the spontaneous mode was used. If we compare the presence of periodic breathing and apneas with the one observed in our first study using two-level nIPPV set in the spontaneous mode, periodic breathing was much less common, but apneas were much more frequent in the present study. One may wonder if the presence of the fiberoptic bronchoscope is not related to these modifications of respiratory rhythm between the two studies. Indeed, mechanical stimuli of the pharyngolaryngeal region are known to affect breathing pattern in quite a variable way.²² In the present study, the experimental conditions are more close (ie, less invasive) to those verified in patients submitted to nIPPV therapy with a two-level positive pressure ventilator. These data underline the differences in VE, VT, and f, between wakefulness and sleep during two-level nIPPV in the spontaneous mode. Not only were apneas common during sleep but not during wakefulness, but also, during steady-state periods, effective VE was lower during stage 2 NREM sleep than during wakefulness.

Two-level assisted ventilation is almost universally used in the spontaneous or timed mode. This latter implies a back-up controlled f of 10 to 12 breaths/min²¹,²³,²⁴ or unknown.⁶ Our data call for extreme vigilance, especially during sleep, since the presence of apneas could also be a problem in real-life patients submitted to two-level nIPPV. Extrapolating from our data (which we admit has to be confirmed in patients), a back-up f of 17 breaths/min seems reasonable.

Comparing the spontaneous mode to the controlled mode, it can be seen during wakefulness that, to obtain a similar effective VE, IPAP has to be higher in the spontaneous than in the controlled mode: 11.7±4.6 L/min at 20 cm H₂O of IPAP in the spontaneous mode (Table 3) vs 11.8±4.9 L/min at 15 cm H₂O, f of 25 breaths/min in the controlled mode (Fig 2). During stage 2 NREM sleep, the group data suggest a higher effective Ve (for the same IPAP of 15 cm H₂O) using the controlled mode (Figs 4 and 7).

All analyzed stable-state periods were periods with silent EMGdi and preceded by at least 1 min of stable wake/sleep state and absence of swallowing. The EMGdi was assessed by surface electrodes. This method is questionable. Despite the fact that we made every effort to have a good-quality signal at the start of the experiment, sometimes the signal was lost during the night’s study. If this happened, we did not consider the EMGdi signal in our definition of steady state.

A last caveat seems worthwhile. Our experimental studies were performed in normal subjects, based on the (albeit unproven) assumption that the key to a high effective VE lies on the glottis width, and not in thoracopulmonary mechanics. The extrapolation to patients with alveolar hypoventilation and hypercapnia is not necessarily straightforward. However, the use of nIPPV in patients aims at increasing alveolar ventilation and inducing a relative and/or absolute
hypocapnia, at least with respect to their own CO₂ arterial level during spontaneous unassisted breathing. Therefore we believe, although we do not have direct proof, that our findings probably apply also to patients with hypoventilation and hypocapnia.

In summary, our data show that in healthy subjects awake or asleep, submitted to a two-level nIPPV, the following occur: (1) with respect to awake spontaneous unassisted breathing, effective VE was higher when the ventilator was set in the controlled mode with a frequency of 17 or 25 breaths/min and an IPAP of 15 cm H₂O; (2) using the spontaneous mode, only an IPAP of 20 cm H₂O resulted in a significant increase in effective VE; (3) for a given level of inspiratory pressure, effective VE was higher in the controlled than in the spontaneous mode, in both wakefulness and sleep; (4) instability of the respiratory rhythm was frequently present during two-level nIPPV only in the spontaneous mode and especially during sleep, with apneas leading to large falls in SaO₂; and (5) our data of the present and previous studies suggest that during nIPPV therapy performed with two-level positive pressure devices, the ventilatory mode should be the controlled mode, where significant increases in effective VE were obtained with an IPAP level lower than in the spontaneous mode, and respiratory rhythm was stable without apneas or periodic breathing. We can suggest that the initial ventilator settings in the controlled mode should be an f around 20 breaths/min, with an I/E ratio of 1, 15 cm H₂O of IPAP, and EPAP as low as possible. If the controlled mode is not used, then the spontaneous-paced mode is to be preferred to the spontaneous mode. A back-up frequency of around 17 breaths/min seems adequate.

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REFERENCES