

# Effects of continuous positive airway pressure on upper airway inspiratory dynamics in awake patients with sleep-disordered breathing

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Continuous positive airway pressure (CPAP) is the main treatment of the obstructive sleep apnoea syndrome (OSAS). We assessed its effects on the upper airway (UA) dynamics in response to bilateral anterior magnetic phrenic nerve stimulation (BAMPS) in 17 awake untreated OSAS patients (15 males;  $52 \pm 7$  years) whose effective CPAP ( $P_{\text{eff}}$ ) had been determined beforehand by a conventional titration sleep study. All twitch-related inspirations were flow-limited, flow first rising to a maximum ( $\dot{V}_{\text{Imax}}$ ), then decreasing to a minimum ( $\dot{V}_{\text{Imin}}$ ), and then increasing again (M-shaped pattern). Up to  $\dot{V}_{\text{Imin}}$ , the relationship between driving pressure ( $P_d$ ) and flow ( $\dot{V}$ ) could adequately be fitted to a polynomial regression model ( $\dot{V} = k_1 P_d + k_2 P_d^2$ ;  $r^2 = 0.71\text{--}0.98$ ,  $P < 0.0001$ ). At atmospheric pressure  $\dot{V}_{\text{Imax}}$  was  $700 \pm 377$  ml s<sup>-1</sup>,  $\dot{V}_{\text{Imin}}$  was  $458 \pm 306$  ml s<sup>-1</sup>,  $k_1$  was  $154.5 \pm 63.9$  ml s<sup>-1</sup> (cmH<sub>2</sub>O)<sup>-1</sup>, and  $k_2$  was  $10.7 \pm 7.3$  ml s<sup>-1</sup> (cmH<sub>2</sub>O)<sup>-1</sup>. CPAP significantly increased  $\dot{V}_{\text{Imax}}$  and  $\dot{V}_{\text{Imin}}$  (peak values  $1007 \pm 332$  ml and  $837 \pm 264$  ml s<sup>-1</sup>, respectively) as well as  $k_1$  and  $k_2$  (peak values  $300.9 \pm 178.2$  ml s<sup>-1</sup> (cmH<sub>2</sub>O)<sup>-1</sup> and  $55.2 \pm 65.3$  ml s<sup>-1</sup> (cmH<sub>2</sub>O)<sup>-1</sup>, respectively). With increasing CPAP,  $k_1/k_2$  increased up to a peak value before decreasing. We defined as  $P_{\text{eff,stim}}$  the CPAP value corresponding to the highest  $k_1/k_2$  value.  $P_{\text{eff,stim}}$  was correlated with  $P_{\text{eff}}$  ( $P_{\text{eff}} = 7.0 \pm 2.0$ ;  $P_{\text{eff,stim}} = 6.4 \pm 2.6$  cmH<sub>2</sub>O;  $r = 0.886$ ; 95% CI 0.696–0.960,  $P < 0.001$ ). We conclude that CPAP improves UA dynamics in OSAS and that the therapeutic CPAP to apply can be predicted during wakefulness using BAMPS.

(Resubmitted 23 July 2002; accepted after revision 21 October 2002; first published online 15 November 2002)

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The obstructive sleep apnoea syndrome is characterised by recurrent sleep-related episodes of complete or partial upper airway closure (Guilleminault *et al.* 1976; Remmers *et al.* 1978) that result from upper airway (UA) instability and lead to intermittent hypoxia and hypercarbia. Together with the perception of the increasing intensity of inspiratory effort that is conveyed by rib cage afferents (Hudgel & Harasick, 1990), the increase in pharyngeal pressure leads to arousal or awakening, which in turn increases UA muscle dilator activity and breaks the apnoea. This sequence of events recurs hundreds of times in a night. The disruption of sleep architecture leads to daytime sleepiness with its own consequences (Olson *et al.* 1995; Lloberes *et al.* 2000). The repeated hypoxic stimulations and their neurovegetative counterparts may account for the increased frequency of cardiovascular events (Peppard *et al.* 2000), in part through a hypercoagulable state (Eisenher & Noachtar, 2001; Arnulf *et al.* 2002). Diagnosing and treating the obstructive sleep apnoea syndrome is thus of the utmost importance.

Currently, the gold standard treatment consists of 'splinting' the UA by applying a positive pressure (continuous positive airway pressure, CPAP) (Sullivan *et al.* 1981) that preserves its patency throughout the night. This dramatically improves sleep architecture and the stability of gas exchanges (Sullivan *et al.* 1981; Lamphere *et al.* 1989) with positive effects on daytime vigilance and cognitive performance (Derderian *et al.* 1988), and a reversal of cardiovascular (Akashiba *et al.* 1999) and coagulation abnormalities (Chin *et al.* 1996; Chin & Ohi, 1998).

One of the main mechanisms of sleep-related UA closure is an asynchrony between UA dilator muscles and inspiratory muscles (Hudgel & Harasick, 1990). Indeed, UA dilator muscles normally contract before the inspiratory muscles, to open and stabilise the UA during inspiration. During sleep, the decrease in the neural drive to the UA dilator muscles delays their action and decreases their efficiency. The UA is therefore functionally passive or quasi so when the contraction of the diaphragm begins. The loss of the counterforce that normally opposes the negative inspiratory

**Table 1. Anthropomorphic and polysomnographic characteristics of the 17 patients included in the study**

Patient	Age (years)	Sex	BMI (kg m <sup>-2</sup> )	AHI (n h <sup>-1</sup> )	AI (n h <sup>-1</sup> )	P <sub>eff</sub> (cmH <sub>2</sub> O)
1	39	F	48.4	26.5	19.3	12
2	60	M	33.2	51.1	31.3	9
3	52	F	30.5	9.6	6.2	4
4	50	M	24	9.4	5.4	5
5	53	M	31.3	33.9	16.9	6
6	54	M	35.2	25	11.6	10
7	50	M	27.3	28.9	8.5	5
8	54	M	32.3	76.1	28.3	8
9	63	M	24.9	35.6	27.5	5
10	65	M	25.3	22.2	3.4	5
11	57	M	30.8	46.7	19.8	7
12	46	M	27.8	37.4	11.2	8
13	39	M	30.1	33.5	9.8	7
14	49	M	27.3	62.8	56.3	5
15	46	M	31.3	23	13.7	6
16	45	M	32.6	58.6	35	7
17	60	M	28.7	15.4	3.9	5
Mean	52		30.6	35.0	18.1	7
S.D.	7		5.4	18.2	13.5	2

BMI: body mass index; AHI: apnoea hypopnoea index (number of obstructive events per hour); AI: apnoea index (number of apnoea per sleep hour); P<sub>eff</sub>: effective continuous positive airway pressure.

pressure explains why the airways tend to close at their most collapsible locus, namely the pharynx (Series *et al.* 1999, 2000; Verin *et al.* 2002a). It is currently possible to reproduce this sequence of events in conscious patients by the use of phrenic nerve stimulation. Indeed, with this technique, the inspiratory driving pressure is generated by a diaphragm contraction that is not preceded by any pre-activation of the UA dilator muscles. Studying the relationship of inspiratory flow to driving pressure in response to phrenic nerve stimulation is thus an accurate method of characterising UA mechanics in a state very close to sleep (namely, not 'passive' because of the preserved tonic muscular activity, but not phasically active (Series *et al.* 1999, 2000; Verin *et al.* 2002a)). It has been previously shown that diaphragm twitches in response to phrenic nerve stimulation induce flow-limited inspirations in normal subjects and in patients with the obstructive sleep apnoea syndrome (Series *et al.* 1999, 2000; Verin *et al.* 2002a), and that they can be used to study the effects of external factors (Series *et al.* 2000; Verin *et al.* 2002a). The effects of varying CPAP levels on the behaviour of the UA confronted with the inspiratory-related drop in UA transpharyngeal pressure gradient remain unknown. This is in part due to the difficulties inherent in studies conducted during sleep, where numerous factors interfering with UA properties are impossible to control for (e.g. sleep stability and sleep stages, body position, nasal resistance, hypoxaemia/hypercarbia-induced ventilatory responses...). Phrenic nerve stimulation in conscious

patients, being free of such influences should eliminate these difficulties.

The aim of the present work was thus to further elucidate the effects of CPAP on upper airway inspiratory flow dynamics in patients with the obstructive sleep apnoea syndrome. In addition, a mathematical model of the pressure-flow relationship during diaphragm twitches was used to predict the effective level of external pressure needed to prevent flow limitation with reference to the conventionally determined value (CPAP titration over an all-night polysomnographic recording).

## METHODS

### Patients

Seventeen patients (Table 1) with a polysomnographically established diagnosis of obstructive sleep apnoea syndrome (American Academy of Sleep Medicine Task Force report, 1999) participated in this study. In all cases, nocturnal CPAP was retained as the treatment of choice. The protocol was designed and conducted in accordance with the Declaration of Helsinki, and had been approved by the ethical review board of the institution where the experiments were performed (Université Laval, Québec, Canada). Written consent was obtained from each participant after giving them full information on the aim of the study and the methods used.

### Sleep recordings

The polysomnographic recordings consisted of in-lab continuous acquisition of data from electroencephalograms, electro-

oculograms, submental electromyograms, transcutaneous pulsed oxymetry ( $\text{SpO}_2$ ), naso-oral airflow measured with thermistors, nasal pressure measured with nasal cannula (Series & Marc, 1999), chest and abdominal movements measured by impedance plethysmography (Respirace, Ambulatory Monitoring Inc., Ardsley, NY, USA), electrocardiograms, and breath sounds measured by means of two microphones connected to a calibrated sound analyser (Series *et al.* 1993). Sleep position was continuously assessed by the attending technician, on the monitor of an infrared camera. Two sleep studies were performed in each patient, the first to establish the diagnosis of OSA and the second to determine the optimal CPAP pressure level ( $P_{\text{eff}}$ ) (American Academy of Sleep Medicine Task Force report, 1999). During this last study, nasal flow was recorded using a pneumotachograph connected to the nasal CPAP mask, in place of the thermistors and nasal cannula.  $P_{\text{eff}}$  was defined as the pressure level that abolished snoring and obstructive events in all sleep stages and body positions (Bureau & Series, 2000). All variables were digitally recorded (Sandman Elite system, Mallinckrodt, Kenilworth, NJ, USA).

### Phrenic nerve stimulation

**Measurements.** Surface recordings of the right and left costal diaphragmatic electromyographic activity were obtained using silver cup electrodes placed in the lowest accessible intercostal space, close to the chondro-costal junction, in the mid-clavicular line (Verin *et al.* 2002b), and connected to an electromyograph (Biopac system, Biopac, Santa Barbara, CA, USA). Oesophageal pressure ( $P_{\text{oes}}$ ) was measured using a balloon-catheter system (Jaeger, Witzburg, Germany) passed through a nostril after topical anaesthesia (xylocaine 1%), positioned into the lower third of the oesophagus (Baydur *et al.* 1982), and connected using a 1.4 mm internal diameter polyethylene catheter to a differential pressure transducer linear over the  $\pm 100$  cmH<sub>2</sub>O range (Validyne, Northridge, CA, USA). A nasal stent was placed in the anterior nostrils (Nozovent; WPM international AB; Göteborg, Sweden) to prevent nasal collapse. An airtight nasal mask was then placed over the nose (Profile Light Nasal Mask, Respironics, Pittsburg, PA, USA). Mask pressure ( $P_{\text{mask}}$ ) was measured from a side port in the mask connected to a second pressure transducer of identical type.  $P_{\text{oes}}$  was referenced to  $P_{\text{mask}}$  to provide driving pressure ( $P_{\text{d}}$ ). A pneumotachograph (Hans Rudolph, model 112467-3850A, Kansas City, MO, USA) was connected to the mask, that was either open to the atmosphere or connected to a CPAP apparatus (Healthdyne Marietta, GA, USA), via a non-rebreathing valve (Respironics, Pittsburg, PA, USA). Pressures and flow were digitally recorded at a 300 Hz sampling rate (Digidata 1320, Axon Instrument, Union City, CA, USA) whereas EMG signals were digitised at a 10 000 kHz sample rate.

**Stimulations.** Supramaximal bilateral anterior magnetic phrenic nerve stimulation (BAMPS) was performed with two Magstim 200 stimulators (Magstim Ltd, Whitland, Dyfed, UK) equipped with double 43 mm figure-of-eight coils of the 'branding iron' type, according to the technique described by Mills *et al.* (1996). The application of this technique to upper airway studies has been described in detail elsewhere (Series *et al.* 1999, 2000). In brief, each stimulating coil was positioned antero-laterally over the anatomical landmark of the phrenic nerve in the neck, at the posterior border of the sternomastoid muscle at the level of the cricoid cartilage, the handle of the coil making a 45° axis with both the mid-sagittal plane of the body and the horizontal plane. The intensity of stimulation was set at the maximum possible output of the stimulators. A simplified recruitment curve (motor

response to stimulation against stimulation intensity) was performed to verify the supramaximal nature of the stimulation. The patients were studied seated in a comfortable armchair with a 60° inclination and with their head maintained in a natural, 'neutral', position by a moulded pillow. Special attention was paid to avoiding any change in body, neck or head position during the experiments. All stimulations were delivered at the end of a relaxed expiration according to the monitoring of the flow and  $P_{\text{oes}}$  traces, to control as precisely as possible for the confounding effects of lung volume and abdominal configuration on the output of phrenic stimulation (Chen *et al.* 2000).

### Protocol

The phrenic nerve stimulation studies were performed within the week following the CPAP titration studies. BAMPS was applied with the patient breathing room air at the atmospheric pressure and under CPAP (3 cmH<sub>2</sub>O with 1 cmH<sub>2</sub>O stepwise increases in pressure up to  $P_{\text{eff}} + 3$  cmH<sub>2</sub>O). After 5 min of quiet breathing at each CPAP level, five stimuli were delivered at four to five breath intervals, and thereafter averaged.

### Data analysis

**Flow limitation.** The twitch-induced breaths were considered flow-limited when, beyond a maximal value ( $\dot{V}_{\text{Imax}}$ ), flow plateaued or decreased in spite of a persistent increase in driving pressure. The driving pressure value corresponding to  $\dot{V}_{\text{Imax}}$  is henceforth termed limiting pressure ( $P_{\text{d,lim}}$ ). Beyond  $\dot{V}_{\text{Imax}}$ , flow decreased to a minimal value ( $\dot{V}_{\text{Imin}}$ ) whereas  $P_{\text{d}}$  continued to increase, up to a peak value,  $P_{\text{d,peak}}$  (Fig. 1).

The resistance of the respiratory system was calculated at  $\dot{V}_{\text{Imax}}$  and  $\dot{V}_{\text{Imin}}$  ( $R\dot{V}_{\text{Imax}}$  or  $R\dot{V}_{\text{Imin}}$ ) as the ratio of the  $P_{\text{d,lim}}$  to  $\dot{V}_{\text{Imax}}$  and of  $P_{\text{d,peak}}$  to  $\dot{V}_{\text{Imin}}$ , respectively (Verin *et al.* 2002a). No correction was applied to take into account the portion of the measured pressure required to overcome the elastic properties of the lung, because the volume change during the analysed portion of the twitch has been considered as minimal in this regard (below 100 ml).

**Driving pressure-flow relationship.** Because of its hyperbolic shape, the twitch-related pressure-flow relationship from zero flow to  $\dot{V}_{\text{Imin}}$  was fitted to a polynomial equation of the form  $\dot{V}_I = k_1 P_{\text{d}} + k_2 P_{\text{d}}^2$  using the least squares method.

### Statistical Analysis

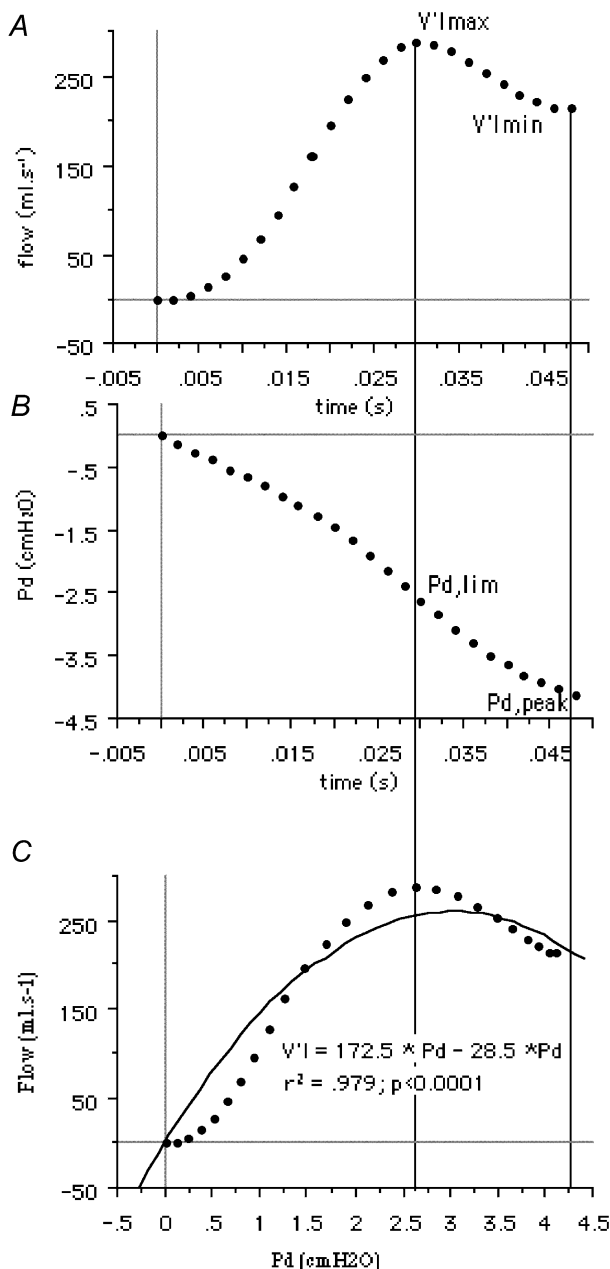
Statistical analysis was performed using the SuperAnova 4.5 software (Abacus Concept, Berkeley, CA, USA) running on an Apple Macintosh computer. Values are expressed as means  $\pm$  standard deviation (s.d.). Statistical associations between the characteristics of the twitch-related inspiratory flow and the severity of sleep-related respiratory disturbances were studied using the *z* test for correlation. The conventionally determined  $P_{\text{eff}}$  and the phrenic stimulation-derived estimate of  $P_{\text{eff}}$  ( $P_{\text{eff,stim}}$  see Results) were tested for agreement using the regression procedure described by Passing & Bablok (1983) and a graphical Bland and Altman representation (Bland & Altman, 1986). Statistical results were considered significant when the probability *P* of a type I error was 0.05 or less.

## RESULTS

Of the 491 twitches recorded, 95.4% could be analysed. In patient number 7, the CPAP-induced changes in inspiratory flow dynamics could not be studied, because of a leak around the nasal mask that produced major artefacts.

## Flow limitation

Flow-limitation was consistently absent during tidal breathing. Conversely, twitch-induced breaths were flow-limited in all subjects and at all CPAP levels.



**Figure 1.** Example of the changes in inspiratory flow (A) and driving pressure (B) in response to a phrenic nerve stimulation-induced diaphragm twitch, in a representative subject

$\dot{V}'_{\text{Imax}}$  and  $\dot{V}'_{\text{Imin}}$  stand respectively for the maximal and minimal flow values reached during the twitch.  $P_{\text{d,lim}}$  indicates the driving pressure corresponding to  $\dot{V}'_{\text{Imax}}$ .  $P_{\text{d,peak}}$  indicates the driving pressure corresponding to  $\dot{V}'_{\text{Imin}}$ . C, flow–pressure relationship up to  $\dot{V}'_{\text{Imin}}$ . The dotted line corresponds to the actual data points. The solid line corresponds to the pressure–flow fit by a polynomial of order 2.

## Driving pressure–flow relationship

A typical example is shown in Fig. 1. The  $\dot{V}'_I = k_1 P_d + k_2 P_d^2$  model adequately described the relationship between driving pressure and the flow in all twitches ( $r^2 = 0.71$  to  $0.98$ ,  $P < 0.0001$ ) in all cases. The mean values at atmospheric pressure were as follows:  $\dot{V}'_{\text{Imax}} = 700 \pm 377$  ml s<sup>-1</sup>;  $\dot{V}'_{\text{Imin}} = 458 \pm 306$  ml s<sup>-1</sup>;  $P_{\text{d,lim}} = -7.7 \pm 4.7$  cmH<sub>2</sub>O;  $P_{\text{d,peak}} = -12.6 \pm 5.1$  cmH<sub>2</sub>O;  $k_1 = 154.5 \pm 63.9$  ml s<sup>-1</sup> (cmH<sub>2</sub>O)<sup>-1</sup>,  $k_2 = 10.7 \pm 7.3$  ml s<sup>-1</sup> (cmH<sub>2</sub>O)<sup>-1</sup>. CPAP significantly increased  $\dot{V}'_{\text{Imax}}$  and  $\dot{V}'_{\text{Imin}}$  ( $1007 \pm 332$  ml s<sup>-1</sup> and  $837 \pm 264$  ml s<sup>-1</sup>, respectively), at the highest CPAP value tested in each patient, corresponding to mean increases of 43 and 85% as compared to baseline ( $P < 0.0001$  and  $P < 0.05$ ). The  $k_1$  and  $k_2$  coefficients also increased ( $300.9 \pm 178.2$  ml s<sup>-1</sup> (cmH<sub>2</sub>O)<sup>-1</sup> and  $55.2 \pm 65.3$  ml s<sup>-1</sup> (cmH<sub>2</sub>O)<sup>-1</sup>, respectively), corresponding to 94 and 414% increases compared to baseline ( $P < 0.0001$ ). Conversely,  $P_{\text{d,lim}}$  and  $P_{\text{d,peak}}$  did not significantly change with CPAP. As a result,  $R\dot{V}'_{\text{Imax}}$  or  $R\dot{V}'_{\text{Imin}}$  both decreased with increasing CPAP ( $P < 0.001$ ; Fig. 2).

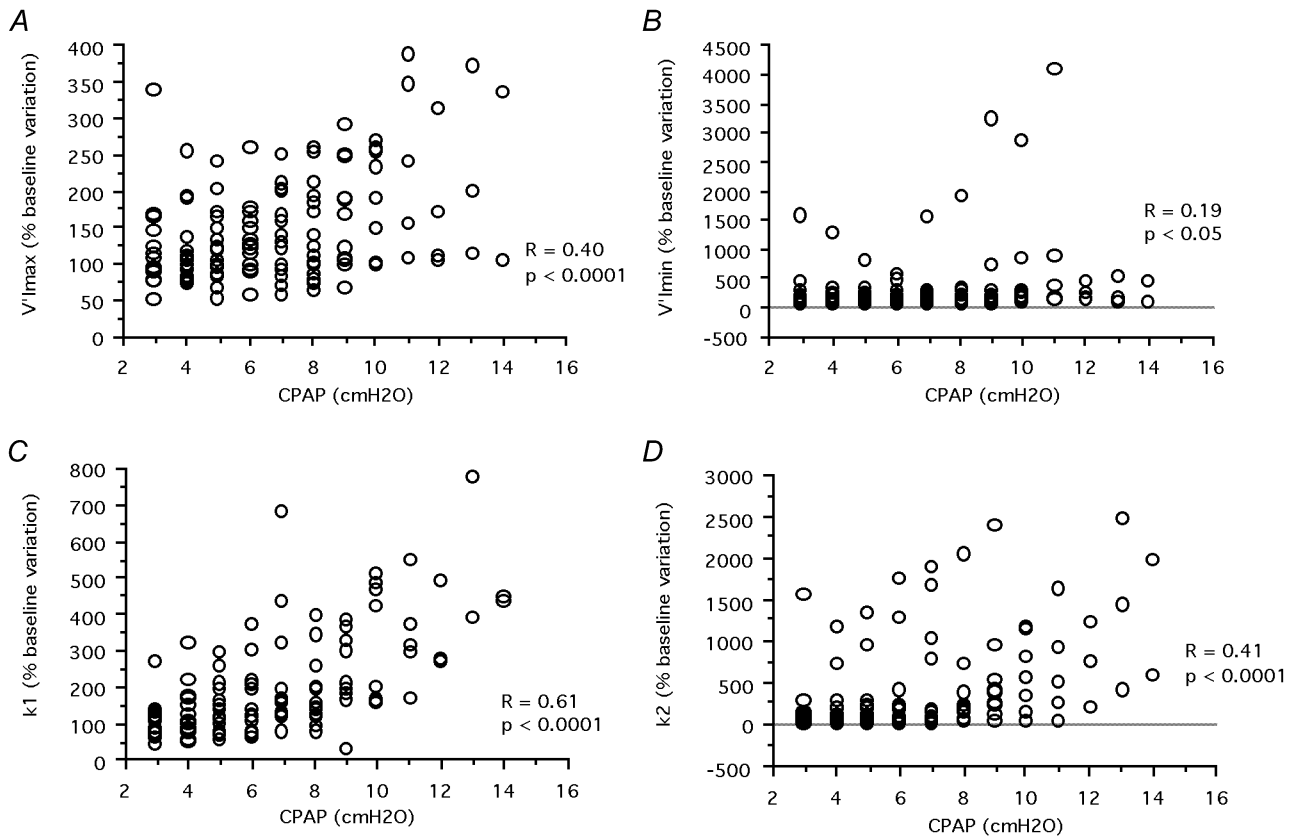
Solving  $\dot{V}'_I = k_1 P_d + k_2 P_d^2$  for  $\dot{V}' = 0$  with  $P_d$  different from zero gives  $P_d = -k_1/k_2$ , which is the  $P_d$  value that should correspond to full airway collapse. The  $k_1/k_2$  ratio is thus a descriptor of UA stability (the higher the value of  $k_1/k_2$ , the better the upper airway opposes the inspiration-related collapsing force). In all but two cases, increasing CPAP resulted in a progressive increase of  $k_1/k_2$  up to a maximum that was followed by a subsequent decrease. (Fig. 3).  $k_1/k_2$  as function of CPAP level was accurately described by a polynomial regression of order 2 ( $r^2$  from 0.69 to 0.99,  $P < 0.05$  except in patient number 3 where  $P = 0.06$ ). The  $k_1/k_2$  peak was assumed to correspond to the CPAP level ensuring maximal UA stability and thus termed  $P_{\text{eff,stim}}$  (Fig. 4).

## Comparison of nocturnal and diurnal effective pressure values

$P_{\text{eff,stim}}$  was strongly correlated with the conventional  $P_{\text{eff}}$  ( $P_{\text{eff}} = 7.0 \pm 2.0$ ;  $P_{\text{eff,stim}} = 6.4 \pm 2.6$  cmH<sub>2</sub>O;  $r = 0.886$ ; 95% confidence interval 0.696–0.960,  $P < 0.001$ ). A regression analysis according to the method of Passing & Bablok (1983) showed that there was no significant systematic difference between the two methods. The Bland and Altman graphic representation (Bland & Altman, 1986; Fig. 4A) set the lower limit of agreement between the two methods at  $-1.9$  cmH<sub>2</sub>O and the upper limit at  $2.8$  cmH<sub>2</sub>O and showed that only one data point fell outside this interval.

## DISCUSSION

This study confirms that the dynamics of inspiratory flow in sleep apnoea patients is dramatically influenced by a positive pressure applied to the upper airway and provides,

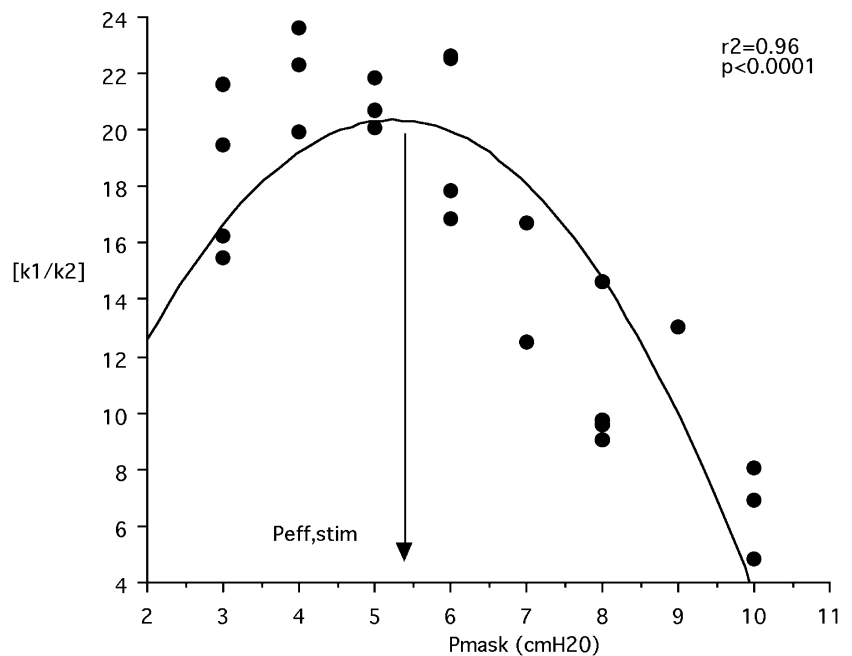


**Figure 2. Effects of an increasing level of continuous positive airway pressure (CPAP) on the measured variables**

A, effect on the maximal inspiratory flow observed in response to the diaphragm twitch ( $\dot{V}'_{I_{max}}$ ), B, effect on the minimal inspiratory flow ( $\dot{V}'_{I_{min}}$ ), and C and D, the effects on coefficients  $k_1$  (C) and  $k_2$  (D) of the  $\dot{V}'_I = k_1 P_d + k_2 P_d^2$  equation describing the flow–pressure relationship up to maximal flow, see text for details. Each data point represents the averaged results of all stimulations performed at a given CPAP level in a given subject.

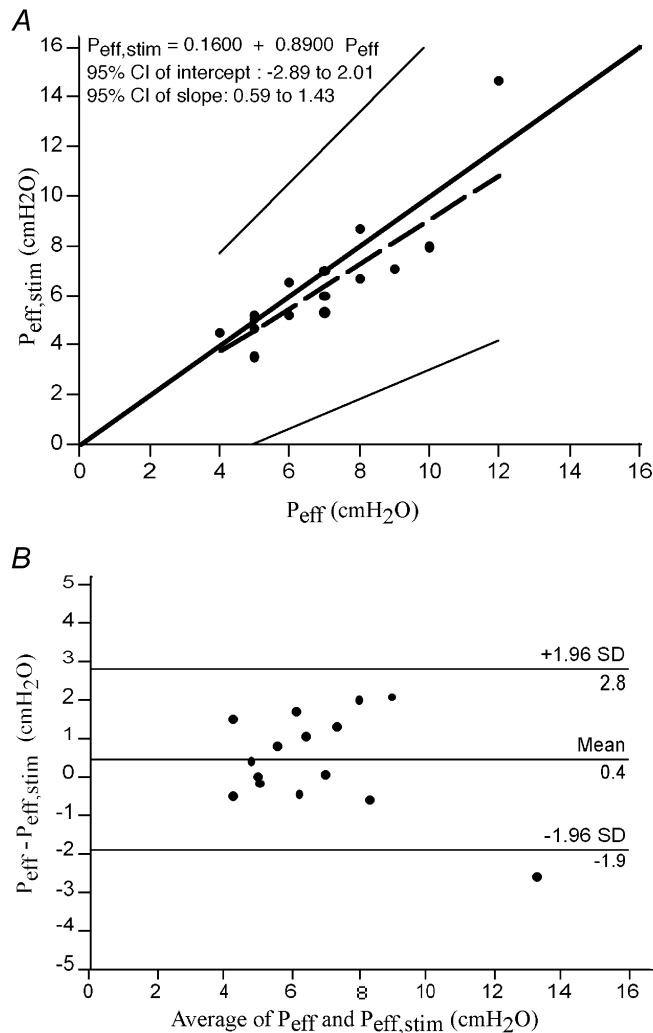
**Figure 3. Illustration, in one patient, of the effects of increasing the level of positive pressure applied at the airway ( $P_{mask}$ )**

Effects on the absolute value of the  $k_1/k_2$  ratio ( $k_1$  and  $k_2$ , coefficients of the  $\dot{V}'_I = k_1 P_d + k_2 P_d^2$  equation describing the flow–pressure relationship up to maximal flow, see text for details) are shown. The peak of the  $k_1/k_2$  curve corresponds to optimal upper airway stability. From the pressure–flow response to phrenic nerve stimulation established at various CPAP levels, it is thus possible to calculate what would theoretically be the efficient pressure  $P_{eff}$  ( $P_{eff,stim}$ ) in a given individual. In this patient,  $P_{eff,stim}$  was 5.3 cmH<sub>2</sub>O, whereas the  $P_{eff}$  conventionally determined during a titration sleep recording was 7 cmH<sub>2</sub>O.



Subject 12

seemingly for the first time, a quantitative description of this phenomenon. It also suggests that the adequate positive pressure level to treat a given patient could be predicted from phrenic nerve stimulation performed during consciousness.



**Figure 4. Comparison of the values of efficient pressure determined conventionally during a titration sleep recording ( $P_{\text{eff}}$ ) with the value of efficient pressure derived from phrenic nerve stimulation performed at various levels of positive pressure applied to the airway ( $P_{\text{eff,stim}}$ )**

A, results of the Passing & Bablok regression (1983) of  $P_{\text{eff,stim}}$  against  $P_{\text{eff}}$ . The thick solid line is the line of identity; the dashed line is the regression line; the thin solid lines mark the 95% confidence interval of the regression. There was no significant deviation from linearity ( $P > 0.10$ ). The 95% confidence interval for the intercept contained zero and the 95% confidence interval for the slope contained 1, indicating the absence of systematic difference between the two methods. B, scatter diagram of the differences plotted against the averages of the two measurements, according to the method devised by Bland & Altman (1986).

### Study population

Three patients (patients 3, 4, 17) had an upper airway high resistance syndrome, defined as repetitive episodes of partial upper airway closure with flow limitation, leading to arousal but not causing hypopnoea. (Guilleminault *et al.* 1993). They were included in the study because its primary aim was to evaluate the influence of CPAP on UA dynamics in patients requiring this therapeutic intervention. As expected,  $P_{\text{eff}}$  values were low in these three cases (4.0, 5.0 and 5.0 cmH<sub>2</sub>O, respectively), but they were well matched with the  $P_{\text{eff,stim}}$  values (4.5, 4.6 and 5.1 cmH<sub>2</sub>O). The inclusion of these patients, could be viewed as a problem because it made the study population heterogeneous, but was, in fact, an advantage because it broadened the range of the comparison of  $P_{\text{eff}}$  with  $P_{\text{eff,stim}}$  (Fig. 4).

Of note, the severity of the obstructive sleep apnoea syndrome, assessed in terms of the number of obstructive events per unit of time (apnoea–hypopnoea index, AHI), varied greatly in our patients (Table 1). The relationship of the AHI with  $P_{\text{eff}}$  in the OSAS is not a simple one, as illustrated by the lack of statistical association between the two parameters in this study and in others (Sforza *et al.* 1995).  $P_{\text{eff,stim}}$  was not correlated with the AHI, and, more importantly, nor was the  $P_{\text{eff}} - P_{\text{eff,stim}}$  difference ( $R = 0.08$ ,  $P = 0.31$ ). Figure 4 shows that there was no systematic deviation of  $P_{\text{eff,stim}}$  from  $P_{\text{eff}}$  as a function of the  $P_{\text{eff}}$  level, suggesting that phrenic nerve stimulation could be useful regardless of the severity of upper airway abnormalities.

### Driving pressure–flow relationship

Because we used oesophageal pressure instead of supra-laryngeal pressure to measure driving pressure, the calculated resistance was that of the respiratory system as a whole and not solely that of the upper airway. However, UA resistance accounts for most of the total respiratory resistance during nasal breathing (Skatrud & Dempsey, 1985; Hudgel, 1986), and it is likely that the differences in flow dynamics that we observed during continuous positive pressure trials were mainly due to changes induced at the UA level and not below.

Different models have been used to describe the pressure–flow relationship in the upper airway, in conscious subjects (Rohrer, 1915) or during sleep (Hudgel *et al.* 1988). They could not be applied to our data, because of the particular shape of the pressure–flow relationship during diaphragm twitches. Indeed, in this setting, inspiratory flow rises in response to driving pressure up to a maximal value ( $\dot{V}_{\text{imax}}$ ) (Series *et al.* 1999), then decreases to a minimal value ( $\dot{V}_{\text{imin}}$ ) corresponding to the peak driving pressure, and later increases again. This M-shape is markedly different from the plateau appearance typically observed in OSAS patients during spontaneous breathing. It is consistent with a ‘passive’, or more precisely ‘not phasically active’,

behaviour of the UA when the diaphragm contraction occurs, the late second increase in flow probably being accounted for by a negative pressure-triggered reflex activation of UA dilator muscle (Series *et al.* 1999). The first part of the flow–pressure relationship was adequately described by a polynomial regression model  $\dot{V}_1 = k_1 P_d + k_2 P_d^2$  with a negative  $k_2$  value. The  $k_1$  and  $k_2$  coefficients bore a strong relationship to the level of positive pressure applied to the UA, and are thus probably relevant descriptors of their mechanical characteristics. As a matter of fact, these terms relate to airway conductance,  $k_1$  being the counterpart of  $R_{ua} \dot{V}_{lmax}$  and  $k_2$  that of  $R_{ua} \dot{V}_{lmin}$ . Strong statistical associations were found between  $k_1$  and  $1/R_{ua} \dot{V}_{lmax}$  ( $R = 0.81$ , 95% CI 0.78–0.84) and between  $k_2$  and  $1/R_{ua} \dot{V}_{lmin}$  ( $R = 0.71$ , 95% CI 0.66–0.75). The  $k_1/k_2$  ratio seems particularly interesting to examine. Indeed, it determines the driving pressure value that should lead to the complete collapse of the UA (see Results), and should therefore represent an index of UA stability. The fact that  $k_1/k_2$  increased to a maximum with increasing levels of CPAP and then decreased is an important result. It indicates that positive pressure stabilises the UA up to a certain point beyond which it becomes less efficient. Together with the augmentation of critical pressure associated with excessive CPAP levels during sleep that has previously been reported by Schwartz *et al.* (1989), this gives a physiological basis to the therapeutic choice of the lowest efficient positive pressure in a given patient. This novel observation derives directly from the fact that phrenic stimulation, in response to which the inspiratory driving pressure builds up fully in the absence of UA dilator muscle activity (as opposed to what happens during spontaneous breathing even in OSAS patients), makes it possible to observe flow limitation in situations where it would not normally occur. This is the case in normal subjects (Series *et al.* 1999) and in OSAS patients receiving CPAP at values exceeding  $P_{eff}$  (this study).

### Comparison with previous data

The treatment of the obstructive sleep apnoea syndrome by continuous positive pressure was first described by Sullivan *et al.* (1981) who demonstrated that nasal CPAP dramatically reduced the frequency of apnoeas both during non-rapid eye movement sleep and rapid eye movement sleep. Several mechanisms are involved in the effectiveness of CPAP. They include relatively complex phenomena, such as an increased UA dilator muscle activity due to the stimulation of mechanoreceptors (Rapoport *et al.* 1983) or of superficial receptors in the nasal mucosa sensitive to airflow (Basner *et al.* 1989). The simplest mechanism at play is purely mechanical in nature and relates to the pneumatic splitting effect of the applied pressure (Series *et al.* 1992). In this respect, Schwartz *et al.* (1989) have shown that CPAP markedly decreased inspiratory resistance and increased UA collapsibility

during sleep in six OSAS patients. Isono *et al.* (1993), by direct endoscopic examination performed in nine sleeping OSAS patients, have correlated this finding with a positive pressure-related increase in the cross-sectional area of the velopharynx. The observations that we made in our patients (effects of CPAP on UA dynamics, agreement between  $P_{eff}$  and  $P_{eff,stim}$ ) are in line with these conclusions. This suggests that the effects of CPAP on UA dynamics are not radically different during sleep and wakefulness. It also suggests that the difference in upper airway dilator muscle tone that exists between sleep and wakefulness is not a major confounding factor relating to the behaviour of the upper airway during a diaphragm twitch when phrenic nerve stimulation is applied at end-expiration.

### Prediction of $P_{eff}$

Predicting  $P_{eff}$  without resorting to all-night polysomnography with CPAP titration is a major clinical issue. It would save money, increase the availability of the sleep medicine resources, and shorten the time during which OSAS patients must wait for their treatment to begin. Several prediction models based on anthropomorphic data and the AHI have been devised (Miljeteig & Hoffstein, 1993; Hoffstein & Mateika, 1994). They are useful to shorten titration sleep studies (Hoffstein & Mateika, 1994) or to optimise the settings of automatic CPAP devices (Series, 2000). However, the information that they provide is thus only of a ‘statistical’ nature and they do not take pathophysiological data into account. The prediction method that we used in this study relies on the observation of actual pressure–flow relationships established from phrenic stimulation at various CPAP levels. Its ‘pathophysiological nature’ probably constitutes an important advantage in terms of clinical usefulness. For example, it can be anticipated that it would be useful in non-obese patients suffering from the OSAS. It must also be noted that phrenic stimulation allows an investigator to predict a  $P_{eff}$  value corresponding not only to the suppression of apnoeas, hypopnoeas and snoring, but also to the suppression of flow-limited breaths inducing arousals (Meurice *et al.* 1998). The comparison of  $P_{eff}$  and  $P_{eff,stim}$  shows an average difference between the two methods of 0.4 cmH<sub>2</sub>O with limits of agreement that appear to be clinically acceptable (Fig. 4). The clinical validity of our  $P_{eff}$  prediction method must nevertheless be tested by prospective studies comparing the results of CPAP therapy adjusted from phrenic nerve stimulation data with in-laboratory conventional titration methods.

Meanwhile, we feel that the present study provides a potentially useful contribution to the understanding of the effects of CPAP on the behaviour of the UA in the sleep apnoea syndrome. The same approach could be used to characterise other therapeutic techniques such as mandibular advancement.

## REFERENCES

- Akashiba T, Minemura H, Yamamoto H, Itoh D, Kosaka N, Saitoh O & Horie T (1999). Effects of nasal continuous positive airway pressure on pulmonary haemodynamics and tissue oxygenation in patients with obstructive sleep apnoea. *Respirology* **4**, 83–87.
- American Academy of Sleep Medicine Task Force report (1999). Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* **22**, 667–689.
- Arnulf I, Merino-Andreu M, Perrier A, Birolleau S, Similowski T & Derenne JP (2002). Obstructive sleep apnea and venous thromboembolism. *JAMA* **287**, 2655–2656.
- Basner RC, Simon PM, Schwartzstein RM, Weinberger SE & Weiss JW (1989). Breathing route influences upper airway muscle activity in awake normal adults. *J Appl Physiol* **66**, 1766–1771.
- Baydur A, Behrakis PK, Zin WA, Jaeger M & Milic-Emili J (1982). A simple method for assessing the validity of the esophageal balloon technique. *Am Rev Respir Dis* **126**, 788–791.
- Bland JM & Altman DG (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* **1**, 307–310.
- Bureau MP & Series F (2000). Comparison of two in-laboratory titration methods to determine effective pressure levels in patients with obstructive sleep apnoea. *Thorax* **55**, 741–745.
- Chen R, Kayser B, Yan S & Macklem PT (2000). Twitch transdiaphragmatic pressure depends critically on thoracoabdominal configuration. *J Appl Physiol* **88**, 54–60.
- Chin K & Ohi M (1998). New insights into the therapy and pathophysiology of patients with obstructive sleep apnoea syndrome. *Respirology* **3**, 139–143.
- Chin K, Ohi M, Kita H, Noguchi T, Otsuka N, Tsuboi T, Mishima M & Kuno K (1996). Effects of NCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* **153**, 1972–1976.
- Derderian SS, Bridenbaugh RH & Rajagopal KR (1988). Neuropsychologic symptoms in obstructive sleep apnea improve after treatment with nasal continuous positive airway pressure. *Chest* **94**, 1023–1027.
- Eisenher I & Noachtar S (2001). Haematological aspects of obstructive sleep apnoea. *Sleep Med Rev* **5**, 207–221.
- Guilleminault C, Stoohs R, Clerk A, Cetel M & Maistros P (1993). A cause of excessive daytime sleepiness: the upper airway resistance syndrome. *Chest* **104**, 781–787.
- Guilleminault C, Tikiak A & Dement W (1976). The sleep apnea syndrome. *Annu Rev Med* **27**, 465–464.
- Hoffstein V & Mateika S (1994). Predicting nasal continuous positive airway pressure. *Am J Respir Crit Care Med* **150**, 486–488.
- Hudgel D (1986). Variable site of airway narrowing among obstructive sleep apnea patients. *J Appl Physiol* **61**, 1403–1409.
- Hudgel DW & Harasick T (1990). Fluctuation in timing of upper airway and chest wall inspiratory muscle activity in obstructive sleep apnea. *J Appl Physiol* **69**, 443–450.
- Hudgel DW, Hendricks C & Hamilton HB (1988). Characteristics of the upper airway pressure-flow relationship during sleep. *J Appl Physiol* **64**, 1930–1935.
- Isono S, Morrison DL, Launois SH, Feroah TR, Whitelaw WA & Remmers JE (1993). Static mechanics of the velopharynx of patients with obstructive sleep apnea. *J Appl Physiol* **75**, 148–154.
- Lamphere J, Roehrs T, Wittig R, Zorick F, Conway W A & Roth T (1989). Recovery of alertness after CPAP in apnea. *Chest* **96**, 1364–1367.
- Lloberes P, Levy G, Descals C, Sampol G, Roca A, Sagales T & de la Calzada MD (2000). Self-reported sleepiness while driving as a risk factor for traffic accidents in patients with obstructive sleep apnoea syndrome and in non-apnoeic snorers. *Respir Med* **94**, 971–976.
- Meurice JC, Paquereau J, Denjean A, Patte F & Series F (1998). Influence of correction of flow limitation on continuous positive airway pressure efficiency in sleep apnoea/hypopnoea syndrome. *Eur Respir J* **11**, 1121–1127.
- Miljeteig H & Hoffstein V (1993). Determinants of continuous positive airway pressure level for treatment of obstructive sleep apnea. *Am Rev Respir Dis* **147**, 1526–1530.
- Mills GH, Kyrroussis D, Hamnegard CH, Polkey MI, Green M & Moxham J (1996). Bilateral magnetic stimulation of the phrenic nerves from an anterolateral approach. *Am J Respir Crit Care Med* **154**, 1099–1105.
- Olson LG, King MT, Hensley MJ & Saunders NA (1995). A community study of snoring and sleep-disordered breathing symptoms. *Am J Respir Crit Care Med* **152**, 707–710.
- Passing H & Bablok W (1983). A new biometrical procedure for testing the equality of measurements from two different analytical methods. Application of linear regression procedures for method comparison studies in clinical chemistry, Part I. *J Clin Chem Clin Biochem* **21**, 709–720.
- Peppard PE, Young T, Palta M & Skatrud J (2000). Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* **342**, 1378–1384.
- Rapoport DM, Garay SM & Goldring RM (1983). Nasal CPAP in obstructive sleep apnea: mechanisms of action. *Bull Eur Physiopathol Respir* **19**, 616–620.
- Remmers JE, Degroot WJ, Sauerland EK & Anch AM (1978). Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* **44**, 931–938.
- Rohrer F (1915). The resistance in the human airway and the influence of branching of bronchial systems on frequency of breathing at different lung volumes. *Pflügers Arch* **162**, 255–299.
- Schwartz AR, Smith PL, Wise RA, Bankman I & Permutt S (1989). Effect of positive nasal pressure on upper airway pressure-flow relationships. *J Appl Physiol* **66**, 1626–1634.
- Series F (2000). Accuracy of an unattended home CPAP titration in the treatment of obstructive sleep apnea. *Am J Respir Crit Care Med* **162**, 94–97.
- Series F, Cormier Y, La Forge J & Desmeules M (1992). Mechanisms of the effectiveness of continuous positive airway pressure in obstructive sleep apnea. *Sleep* **15**, S47–49.
- Series F, Demoule A, Marc I, Sanfacon C, Derenne JP & Similowski T (1999). Inspiratory flow dynamics during phrenic nerve stimulation in awake normals during nasal breathing. *Am J Respir Crit Care Med* **160**, 614–620.
- Series F & Marc I (1999). Nasal pressure recording in the diagnosis of sleep apnoea hypopnoea syndrome. *Thorax* **54**, 506–510.
- Series F, Marc I & Atton L (1993). Comparison of snoring measured at home and during polysomnographic studies. *Chest* **103**, 1769–1773.
- Series F, Straus C, Demoule A, Attali V, Arnulf I, Derenne JP & Similowski T (2000). Assessment of upper airway dynamics in awake patients with sleep apnea using phrenic nerve stimulation. *Am J Respir Crit Care Med* **162**, 795–800.



- Sforza E, Krieger J, Bacon W, Petiau C, Zamagni M & Boudewijns A (1995). Determinants of effective continuous positive airway pressure in obstructive sleep apnea. Role of respiratory effort. *Am J Respir Crit Care Med* **151**, 1852–1856.
- Skatrud JB & Dempsey JA (1985). Airway resistance and respiratory muscle function in snorers during NREM sleep. *J Appl Physiol* **59**, 328–335.
- Sullivan CE, Issa FG, Berthon-Jones M & Eves L (1981). Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* **1**, 862–865.
- Verin E, Series F, Locher C, Straus C, Zelter M, Derenne JP & Similowski T (2002a). Effects of neck flexion and mouth opening on inspiratory flow dynamics in awake humans. *J Appl Physiol* **92**, 84–92.
- Verin E, Straus C, Demoule A, Mialon P, Derenne JP & Similowski T (2002b). Validation of improved recording site to measure phrenic conduction from surface electrodes in humans. *J Appl Physiol* **92**, 967–974.

#### Acknowledgements

This study was supported by Medical Research Council of Canada, grant MT 13 768 and ADOREP (Association pour le Développement et l'Organisation de la Recherche en Pneumologie) Paris, France. The authors are indebted to Dr Alan Matthews for his help with the English language.