

Blood pressure responsiveness to obstructive events during sleep after chronic CPAP

O. Marrone, A. Salvaggio, M.R. Bonsignore, G. Insalaco, G. Bonsignore

Blood pressure responsiveness to obstructive events during sleep after chronic CPAP. O. Marrone, A. Salvaggio, M.R. Bonsignore, G. Insalaco, G. Bonsignore. ©ERS Journals Ltd 2003.

ABSTRACT: The aim of this study was to investigate whether chronic continuous positive airway pressure (CPAP) affects blood pressure (BP) responsiveness to obstructive events occurring on the first night of CPAP withdrawal in obstructive sleep apnoea (OSA) after chronic treatment.

Thirteen male subjects with severe OSA underwent nocturnal polysomnography with beat-by-beat BP monitoring before treatment and after 4.9±3.4 months of home CPAP (mean daily use 5.1±1.7 h). Variations in oxyhaemoglobin saturation ($\Delta S_{a,O_2}$), systolic (ΔP_s), and diastolic (ΔP_d) BP within nonrapid eye movement apnoeas and hypopnoeas were measured on a sample of pre- and post-treatment events. In addition, a pretreatment sample was selected for $\Delta S_{a,O_2}$ to match post-treatment events.

The higher the mean $\Delta S_{a,O_2}$ was in the full pretreatment sample, the more $\Delta S_{a,O_2}$, ΔP_s and ΔP_d were attenuated after treatment. Mean ΔP_s decreased from 47.3±8.5 in the full pretreatment sample to 42.2±6.9 in the selected pretreatment sample, to 31.5±5.9 mmHg in the post-treatment sample. The post-treatment value differed significantly from both the pretreatment values. The corresponding values for mean ΔP_d were 27.0±3.5, 24.0±3.1 and 19.6±3.7 mmHg, with all values differing significantly from each other.

Chronic continuous positive airway pressure is followed by a decrease in apnoea/hypopnoea-related blood pressure swings, possibly secondary to both reduced severity of event-related hypoxaemia and decreased responsiveness to obstructive events secondary to chronic prevention of nocturnal intermittent hypoxaemia.

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Continuous positive airway pressure (CPAP) is the most effective treatment for obstructive sleep apnoea (OSA). It abolishes upper airway obstruction during sleep for as long as it is applied, but its withdrawal is promptly followed by a reappearance of obstructive sleep-disordered breathing events, although with a lesser severity than before CPAP initiation [1–5]. Recent trials have demonstrated the efficacy of CPAP in improving daytime somnolence [6, 7]. However, other studies have shown that even a one-night withdrawal is followed by a sudden increase in sleepiness, as demonstrated by the multiple sleep latency test [3, 4].

The effects of CPAP on systemic blood pressure (BP) are less well understood. Despite contrasting results, most investigations demonstrate some decrease in BP after prolonged treatment [8–13]. In most studies, the effect of prolonged OSA treatment on BP was explored by comparing BP values recorded in the 24 h before CPAP initiation with those after treatment, by means of ambulatory intermittent BP monitoring [9–16]. CPAP was withdrawn in only one study [14] during BP monitoring performed after home treatment, while in most other studies CPAP was applied during the night [8, 9, 11, 12]. Importantly, this approach may affect nocturnal results: the extent of which a nocturnal decrease in BP is due to acute rather than chronic apnoea prevention is not clear, because CPAP, applied acutely, may decrease systolic nocturnal BP values in patients with sleep respiratory disorders [17, 18]. Besides, intermittent BP sampling during the night in untreated subjects with severe OSA may lead to an important over- or underestimation of average BP [19].

In this study, nocturnal BP swings, recorded beat-by-beat in patients with OSA, in nonrapid eye movement (NREM) apnoeas and hypopnoeas before and after chronic CPAP treatment at CPAP withdrawal were compared to verify whether chronic prevention of respiratory disturbances may be followed by a variation in the responsiveness of BP to the respiratory events. In addition, this study could help clarify whether the previously reported nocturnal BP decrease during chronic CPAP treatment may be attributed just to apnoea prevention or also to the effects of prolonged regularisation of nocturnal breathing.

Patients and methods

Among subjects routinely undergoing standard polysomnography for suspected OSA, 13 consecutive patients were selected on the basis of the following characteristics: male sex, apnoea/hypopnoea index (AHI) >30, oxyhaemoglobin saturation (S_{a,O_2}) while awake >90%, and no pharmacological treatment, diabetes or clinical evidence of cardiac disease. Diurnal BP was measured in the morning in the sitting position after a 15-min resting period. It was normal (≤ 140 over 90 mmHg) in 10 subjects and mildly elevated (≤ 150 over 95 mmHg) in the remaining three.

All subjects were prescribed CPAP for home treatment after manual nocturnal titration. After 4.9±3.4 months the patients were re-evaluated. Total hours of CPAP usage were checked by means of a ventilator in-built time counter, and mean daily

Institute of Biomedicine and Molecular Immunology, Section of Respiratory Pathophysiology, National Research Council, Palermo, Italy.

Correspondence: O. Marrone, Consiglio Nazionale delle Ricerche, IBIM, Fisiopatologia Respiratoria, Via Ugo La Malfa, 153, 90146 Palermo, Italy.
Fax: 39 916809122
E-mail: marrone@ifr.pa.cnr.it

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Table 1.—Characteristics of the patients before and after continuous positive airway pressure treatment

	Before treatment	After treatment	p-value
Age yrs	47.7±8.7		
Weight kg	95.8±13.5	92.7±14.7	*
BMI kg·m ⁻²	33.7±3.9	32.6±4.0	*
Morning P _s mmHg	128.5±13.9	130.4±13.9	NS
Morning P _d mmHg	83.5±7.7	82.7±8.3	NS

Data are presented as mean±SD. BMI: body mass index; P_s: systolic blood pressure; P_d: diastolic blood pressure; NS: nonsignificant. *: p<0.05.

CPAP use was calculated as total hours divided by number of days with CPAP at home. Body weight and diurnal BP were controlled. After ensuring that CPAP had been used the night before, a polysomnographic study was repeated without CPAP application, *i.e.* on the first night of CPAP withdrawal.

Polysomnographic studies included electroencephalography (EEG; unipolar leads C3A2 and O1A2), right and left electro-oculography, submental electromyography, thoracic and abdominal movements, oronasal airflow, Sa₂O₂ (Biox 3740 ear oximeter; Ohmeda, Louisville, CO, USA), body posture, and BP (Finapres 2300; Ohmeda). Finapres was automatically turned off for 5 min every 40 min to avoid finger discomfort. Apnoeas were scored when airflow was absent for ≥10 s, and were classified as central, mixed or obstructive according to standard criteria. Hypopnoeas were considered to be discernible reductions in airflow associated with either arousal or an Sa₂O₂ fall of ≥4%. AHI was calculated as (number of apnoeas+number of hypopnoeas)/hour of sleep time.

BP and Sa₂O₂ behaviour were evaluated on apnoeas and hypopnoeas in NREM sleep before and after treatment. In each patient, both before and after treatment, all apnoeic and hypopnoeic events with a BP signal free from artefacts over the whole respiratory event, and the following unoccluded ventilatory interval were considered for BP measurements. Events during which the Finapres device operated servo set-point adjustments that could affect the evaluation of BP swings were excluded; events had to be separated from a REM period by ≥10 min, as sleep stage may influence BP behaviour during sleep in OSA [20]. The following variables were measured: difference between highest BP after and lowest BP during the event (systolic (ΔP_s) and diastolic (ΔP_d) BP values, respectively), highest Sa₂O₂ preceding the event, lowest Sa₂O₂ following the event, and difference between these two values (ΔSa₂O₂). The lowest P_s and P_d values were taken during expiratory time, in order to exclude acutely decreasing BP values caused by negative intrathoracic pressure. Absolute BP values were not considered in the analysis since the Finapres device is more accurate in detecting BP changes than its absolute levels [21]. Finally, out of the pretreatment apnoeas and hypopnoeas, a subsample of events was selected to match events with similar degrees of oxygen desaturation before and after treatment. The selection was operated by progressively eliminating the most desaturating events, until the remaining ones showed a mean ΔSa₂O₂ that differed from the ΔSa₂O₂ of the post-treatment events <±1%.

Anthropometric and polysomnographic data before and after treatment were compared by means of two-tailed Student's t-test for paired data. The events chosen for analysis in each subject were identified as full pretreatment, selected pretreatment and post-treatment samples, respectively. Differences in BP and Sa₂O₂ behaviour among respiratory events of the three samples were evaluated by one-way analysis of variance for repeated measures, followed by Scheffé's test for paired comparisons. Correlations between variables were

Table 2.—Polysomnographic data before and after continuous positive airway pressure treatment

	Before treatment	After treatment	p-value
TST min	268.7±56.0	248.7±70.4	NS
Subjects with REM	12	7	
REM %TST	9.8±4.8	6.2±3.9	NS
Arousal index	74.3±18.8	61.7±20.6	NS
AHI	80.1±13.4	64.6±24.6	*
AHI NREM	81.3±15.8	64.7±24.5	*
AHI REM	66.2±13.5	65.3±30.3	NS
AI NREM	74.0±18.8	53.3±28.0	#
HI NREM	7.3±8.3	11.4±28.6	NS
AH in NREM	27.4±6.8	25.2±9.2	NS

Data are presented as mean±SD. TST: total sleep time; REM: rapid eye movement; AHI: apnoea/hypopnoea index; NREM: nonrapid eye movement; AI: apnoea index; HI: hypopnoea index; AH: apnoea and hypopnoea duration; NS: nonsignificant. *: p<0.05; #: p<0.005.

assessed by linear regression analysis. A p-value of <0.05 was considered significant.

Results

Characteristics of the patients are shown in table 1. No significant changes in diurnal BP were observed after treatment. On average, patients showed a good compliance to CPAP treatment (mean daily use 5.1±1.7 h).

Data obtained from polysomnographic studies are shown in table 2. After treatment, patients showed a lower AHI, either if calculated on total sleep time or on NREM sleep alone. The decrease in AHI was accounted for by a decrease in apnoeas, since the rate of hypopnoeas remained unmodified. Mean NREM apnoea/hypopnoea duration did not change significantly.

Data measured in the samples of events analysed in both studies are shown in table 3. The number of respiratory events analysed in each patient in the full pretreatment sample and in the post-treatment sample represented 30.9±4.3% and 29.1±7.1% of the total number of respiratory events in NREM sleep,

Table 3.—Blood pressure and oxyhaemoglobin saturation in the analysed events

	Before treatment		After treatment
	Full sample	Selected sample	
Events analysed n	104±29	45±29	73±38
ΔP _s mmHg	47.3±8.5	42.2±6.9	31.5±5.9 ^{#,†}
ΔP _d mmHg	27.0±3.5	24.0±3.1*	19.6±3.7 ^{#,†}
ΔSa ₂ O ₂ %	10.5±3.4	6.9±2.7*	6.7±2.7 [†]
Mean Sa ₂ O ₂ before events %	95.1±2.0	95.0±2.1	96.0±1.3
Mean lowest Sa ₂ O ₂ after events %	84.6±4.2	88.2±3.4 [#]	89.3±2.5 [†]

Data are presented as mean±SD. ΔP_s: difference between highest systolic blood pressure value after, and lowest value during, apnoeic/hypopnoeic events; ΔP_d: difference between highest diastolic blood pressure value after, and lowest value during, apnoeic/hypopnoeic events; ΔSa₂O₂: difference between highest oxyhaemoglobin saturation value preceding and lowest oxyhaemoglobin saturation value following apnoeic/hypopnoeic events. *: p<0.05 versus full pretreatment sample; #: p<0.005 versus full pretreatment sample; †: p<0.05 versus selected pretreatment sample.

respectively. From the full pretreatment to the post-treatment sample, ΔP_s , ΔP_d and $\Delta Sa,O_2$ changed by a variable extent among subjects. On average, ΔP_s and ΔP_d decreased by 15.8 mmHg (range -0.1–41.4) and 7.5 mmHg (range -0.4–16.9), respectively. Neither the decrease in ΔP_s nor in ΔP_d were correlated to age, body mass index (BMI) or AHI values either before or after treatment, to a decrease in BMI or AHI, or to CPAP use. Both the decrease in ΔP_s and ΔP_d were correlated to the $\Delta Sa,O_2$ value before treatment ($r=0.77$ and 0.73 , respectively, $p<0.005$; fig. 1). On average, $\Delta Sa,O_2$ decreased by 3.4% (range 0.9–9.5%). The change in $\Delta Sa,O_2$ was due to a significant increase in mean lowest Sa,O_2 following respiratory events (from $84.6\pm 4.2\%$ to $89.3\pm 2.5\%$, $p<0.001$) associated with a nonsignificant change in mean Sa,O_2 preceding them (from $95.1\pm 2.0\%$ to $96.0\pm 1.3\%$). In the group of patients, the larger the $\Delta Sa,O_2$ before treatment, the larger the decrease after treatment ($r=0.63$, $p<0.025$).

Among the pretreatment events, 45 ± 29 events per patient were further selected to match Sa,O_2 features of the post-treatment sample. Mean ΔP_s , ΔP_d and $\Delta Sa,O_2$ values measured in all subjects in the respiratory events of the full pretreatment, selected pretreatment, and post-treatment sample are shown in table 3, while mean individual data are shown in figure 2. Mean ΔP_s did not differ significantly between full *versus* selected

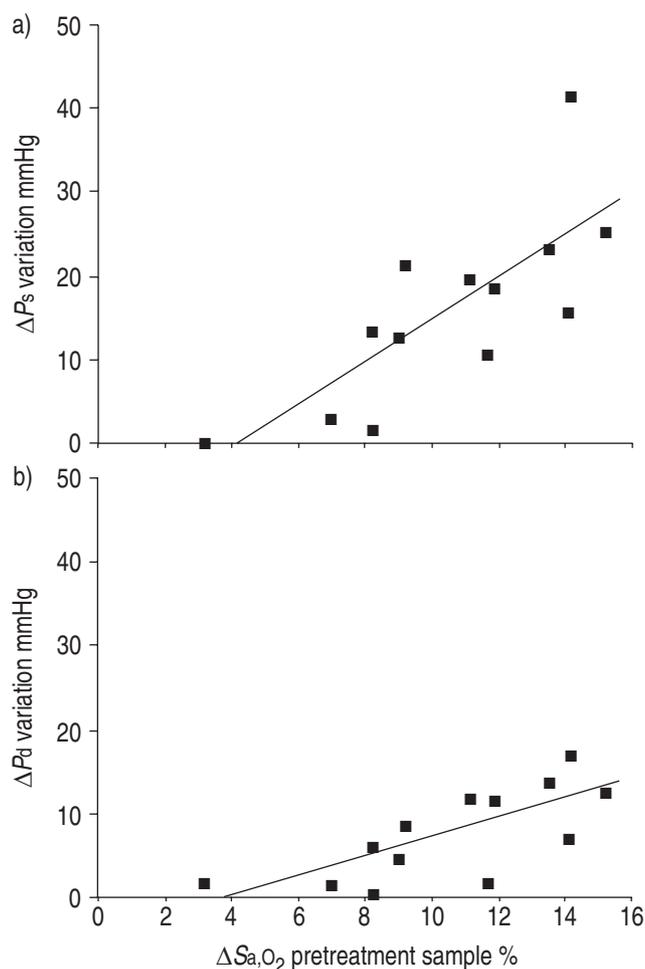


Fig. 1. – Correlation between mean oxyhaemoglobin saturation swings ($\Delta Sa,O_2$) recorded in each patient in apnoeic and hypopnoeic events included in the full pretreatment sample, and the difference in a) mean systolic (ΔP_s) or b) diastolic (ΔP_d) blood pressure swings between respiratory events included in the full pretreatment sample and those included in the post-treatment sample.

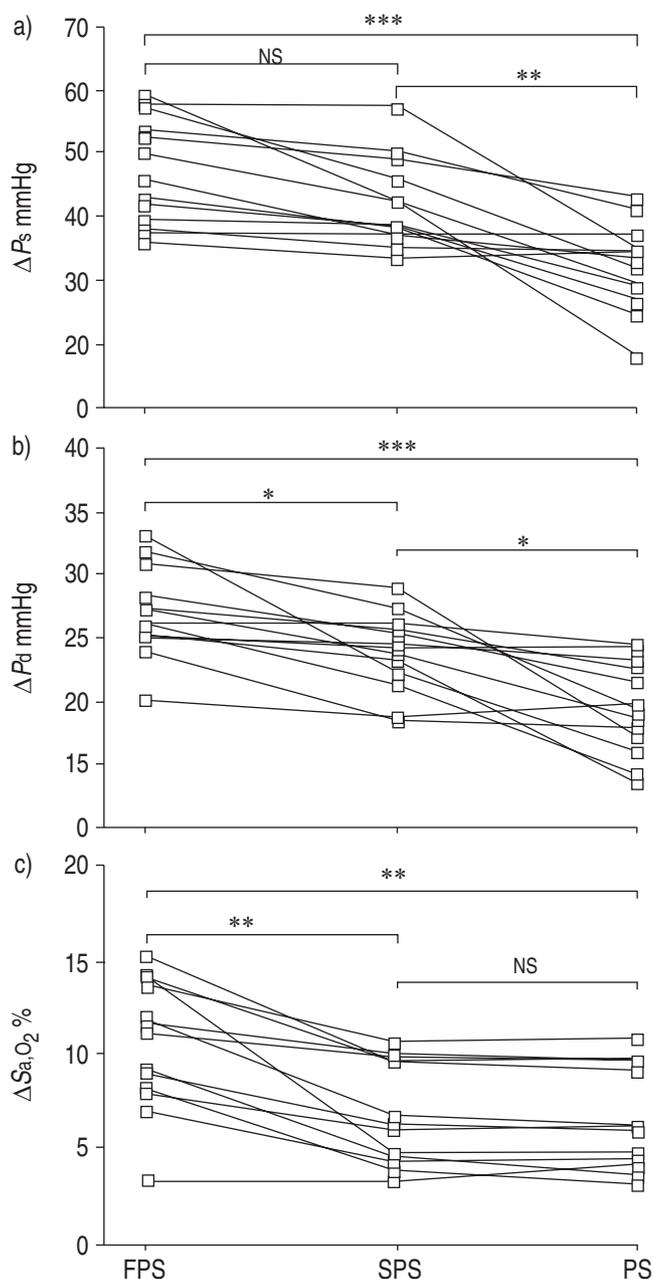


Fig. 2. – Mean values of a) systolic blood pressure swing (ΔP_s), b) diastolic blood pressure swing (ΔP_d), and c) oxyhaemoglobin saturation swing ($\Delta Sa,O_2$), recorded in each patient in the full pretreatment (FPS), selected pretreatment (SPS) and post-treatment (PS) apnoea and hypopnoea samples. NS: nonsignificant. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

pretreatment samples, while both values were significantly higher than the value in the post-treatment sample. Mean ΔP_d showed a progressive significant decrease from the full pretreatment sample to the selected pretreatment sample to the post-treatment sample. Mean $\Delta Sa,O_2$ was significantly higher in the full pretreatment sample than in both the selected pretreatment and post-treatment samples.

Discussion

Acute CPAP withdrawal after chronic treatment was followed by reductions in the amplitude of apnoea/hypopnoea-related BP swings. These reductions were strongly related to the amplitude

of Sa,O_2 falls occurring with obstructive events before CPAP treatment.

In addition to the reduction in BP swings, the severity of sleep respiratory disorders decreased after CPAP. This finding is in agreement with several previous reports of changes in characteristics of breathing during sleep at CPAP withdrawal, consisting of a decrease in AHI [2–4], in Sa,O_2 falls [2, 4, 5], or decrease in apnoeas unaccompanied by a decrease in hypopnoeas [22]. In this study, the combination of a small increase in the percentage of hypopnoeas over the total number of respiratory disorders, a minor decrease in event duration and a minor increase in Sa,O_2 preceding the events may have led to the attenuation in Sa,O_2 falls induced by the sleep respiratory disorders. As demonstrated previously [1], the reduction in Sa,O_2 falls was more evident in the subjects with the most severe desaturations before treatment. The causes of the improvement in breathing after CPAP have not been clarified; a decrease in upper airway oedema, an improvement in genioglossal function or an increase in responsiveness to chemical stimuli have been suggested as possible explanations.

BP behaviour in obstructive events during sleep is influenced by several different tightly intercorrelated factors, including event duration, oesophageal pressure, arousals, chemical stimuli, and autonomic nervous system activity. The duration of events, which has been reported as one of the most important correlates of postapnoeic BP rise [23], remained almost unmodified and probably did not significantly affect the changes in BP behaviour.

Oesophageal pressure was not measured. One study showed that oesophageal pressure swings at CPAP withdrawal after chronic CPAP decreases [5]. If a similar decrease occurred in the subjects in this study, it could have affected BP during apnoeas. However, negative intrathoracic pressure during apnoeas transiently reduces BP during each respiratory effort, but exerts no major effect on BP after the effort release [24]. BP measurements during apnoeas were always taken during the expiratory portion of the occluded breath so that the most prominent possible effect of strong respiratory efforts could not influence the calculated BP swing.

Arousals occurred at the end of most events both before and after treatment. Almost all arousals occurred at the end of respiratory events. BP rise after sleep-disordered breathing events is influenced by arousal duration [25] and it could also be affected by its EEG expression [26]. More studies are warranted to investigate whether CPAP treatment is followed by changes in the characteristics of arousals that could affect BP behaviour.

Some effects of chronic CPAP could also result from relief of sleepiness. Recovery from sleep deprivation could reduce BP reactivity, as demonstrated in dogs in which sleep deprivation increases BP response to airway obstruction. However, as apnoea-induced hypoxaemia worsened after sleep deprivation, it is possible that the effect on BP was mediated by the increase in hypoxaemia [27].

Hypoxaemia and BP in OSA are strongly related. In each apnoea, BP rise and Sa,O_2 falls are significantly correlated [28–30]. Although BP after apnoeas may rise even when hypoxaemia is heavily blunted by oxygen administration [23, 31, 32], hypoxaemia is recognised as one of the most important factors contributing to the BP rise [33]. As discussed below, the results of this study lend further support to an influence of hypoxaemia on BP behaviour.

The authors observed that larger Sa,O_2 swings before treatment gave rise to more attenuated BP swings by CPAP treatment, suggesting that chronic prevention of large Sa,O_2 swings led to a decrease in BP responsiveness to obstructive events and, as a consequence, to an attenuation of BP oscillations. However, $\Delta Sa,O_2$ after treatment was attenuated proportionally to the amplitude of Sa,O_2 swings before

treatment, as a result of an increase in postapnoeic Sa,O_2 . Contrary to the previous hypothesis, this could suggest that BP swings decreased because characteristics of the events that reappeared after treatment resembled those of the least severe events recorded before treatment. In other words, treatment might have not modified the BP responsiveness to obstructive events, but BP showed smaller oscillations, as hypertensive stimuli, including hypoxaemia, were weaker. The detection of smaller BP swings in the events selected for mild desaturations before treatment (selected pretreatment samples) compared with the events recorded during the same night that showed larger mean Sa,O_2 falls (full pretreatment samples), supports the fact that the lesser severity of hypoxaemia, such as that found after treatment, could contribute to the decrease in BP swings.

However, the prevention of chronic intermittent hypoxaemia with CPAP may also attenuate BP reactivity to apnoeas and hypopnoeas. Indeed, this study found lower BP swings in the post-treatment events (post-treatment samples) compared with the pretreatment events with similar oxygen desaturations (selected pretreatment samples), in agreement with a chronic effect of hypoxaemia on increasing BP reactivity to apnoeas. In animals, chronic intermittent hypoxaemia enhances the acute BP response to hypoxia through increased sympathetic activity [34], which, in turn, influences postapnoeic BP rise [35–37]. Similarly, in normal male humans, exposure to hypoxia for 1 month, in a high-altitude environment increased BP responsiveness to hypoxia. This increase was associated with a parallel increase in BP oscillations during periodic breathing in NREM sleep [38]. Sympathetic tone has been observed to decrease after prolonged OSA treatment [14, 39–41], whereas baroreflex control of heart rate improves [42, 43]. The authors hypothesise that the improvement in autonomic control is more prominent in subjects with large oxygen desaturations, and that this may contribute to the observed reduction in BP responsiveness to apnoeas. In fact, no decrease in BP swings occurred in the patients with mild degrees of hypoxaemia during sleep before treatment.

It could be suggested that some of the responsiveness to BP of the events of the pretreatment selected samples was due to a carry-over effect of hypoxaemia produced by the surrounding apnoeas. However, although exposure to hypoxia causes an increase in sympathetic discharge that outlasts its duration by some minutes, reversal of hypoxia is followed readily by a return to baseline of both heart rate and BP [44, 45].

In summary, the data of this study, although not excluding possible roles of many different pathogenetic factors, suggest that blunting of apnoea/hypopnoea-related hypoxaemia and prevention of chronic intermittent hypoxaemia are among the most important factors responsible for the attenuation of BP swings during obstructive events after chronic CPAP treatment.

No other study has examined changes in nocturnal BP behaviour at CPAP withdrawal. As in previous investigations that evaluated breathing during sleep at CPAP withdrawal, the first night after CPAP was taken into account in this study. Since prolonged interruption of CPAP may be followed by a progressive worsening, towards the pretreatment condition, of sleep respiratory disorders and of their consequences, it was necessary to analyse data collected during the first night of CPAP withdrawal. Such analysis may provide the best possible data to demonstrate a possible carry-over effect of CPAP on BP responsiveness to obstructive apnoeas and hypopnoeas.

Recent controlled studies were able to demonstrate a role for chronic CPAP treatment in decreasing daytime BP with relatively large samples of patients. The absolute decrease in BP, although statistically significant, was quite small [12, 13]. Although no significant change in morning BP was found in this study after CPAP, the patient sample may have been insufficient to show significant changes in values measured only during one morning visit. Most studies on BP before and after

CPAP in OSA were performed by ambulatory BP monitoring [9–16]. Although such instruments are accurate for diurnal measurements of absolute BP values in isolated heart beats, they have limitations in that they cannot detect the very rapid BP changes occurring in apnoea-ventilation cycles in OSA. Furthermore, the high short-term variability of nocturnal BP in OSA lessens the accuracy of the assessment of mean nocturnal BP values at usual rates of BP sampling [19]. For the nocturnal measurements, a device (Finapres) that is able to monitor beat-by-beat BP noninvasively was used, which is invaluable for the detection of the fast BP changes occurring in apnoea-ventilation cycles. Measurements performed by Finapres proved accurate with regard to BP variations, but may be rather inaccurate for absolute BP values [21]. BP measurements by Finapres are critically dependent on the position of the hand where the probe is applied, as any change in hand position causes a shift in BP readings. While artefactual changes in BP readings related to hand movements are easy to detect in single apnoea-ventilation cycles, they are difficult to identify when comparing different parts of one nocturnal recording. Therefore, the analysis was limited to BP swings and did not take into consideration absolute BP values. The search for events in which all BP signal requirements were fulfilled and separated from REM sleep by >10 min led to the selection of approximately one-third of the respiratory events for BP analysis. Nevertheless, the number of events analysed was a substantial percentage (30%) of the total respiratory events. It has been demonstrated that analysing $\leq 25\%$ of a polysomnographic study in patients with OSA provides a fully reliable assessment of most sleep and respiratory parameters [46].

The data obtained may have interesting implications for the interpretation of the data from previous studies in which the effects of chronic CPAP on BP were explored. Although a similar decrease in diurnal and nocturnal BP after CPAP, as found in some studies [9, 13], can be attributed to effects of chronic treatment, it is not clear if a reduction in BP limited to [15] or prevalent in [8, 12] the nocturnal hours during CPAP application, may be the acute consequence of apnoea prevention or a chronic effect of regularisation of breathing. These results suggest that in subjects who had mild desaturations before treatment, a purely nocturnal decrease in BP could be mainly an acute effect of apnoea prevention by CPAP administration, while in subjects with severe desaturations, it could also be a consequence of the chronic treatment. In future studies, it would be interesting to separately analyse the effects of long-term CPAP on absolute 24-h BP values in subjects with different degrees of apnoea-induced hypoxaemia.

In conclusion, continuous positive airway pressure withdrawal after chronic treatment is associated with a decrease in apnoea/hypopnoea-related blood pressure swings that are proportional to the degree of hypoxaemia induced by the obstructive events before treatment initiation. This decrease could be secondary to both the acute effect of a reduction in apnoea-induced hypoxaemia at continuous positive airway pressure withdrawal and to a decrease in blood pressure responsiveness to obstructive events due to chronic prevention of nocturnal intermittent hypoxaemia. These results suggest that the detection of a decrease in nocturnal blood pressure during continuous positive airway pressure administration after chronic continuous positive airway pressure treatment may be secondary to the simple effect of apnoea prevention when apnoeas provoke mild nocturnal hypoxaemia, and also to an effect of chronic treatment when they induce severe hypoxaemia.

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