Exacerbation of sleep-apnoea related nocturnal blood-pressure fluctuations in hypertensive subjects

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Exacerbation of sleep-apnoea related nocturnal blood-pressure fluctuations in hypertensive subjects. C. Planès, M. Leroy, G. Fayet, P. Aegerter, A. Foucher, B. Raffestin. ©ERS Journals Ltd 2002.
ABSTRACT: Obstructive sleep apnoea syndrome (OSAS) induces marked haemodynamic fluctuations during sleep that might be deleterious to the cardiovascular system. The influence of daytime blood pressure (BP) levels and aging on short-term BP variability during sleep in OSAS patients was investigated.

Twenty-nine subjects with newly-diagnosed untreated OSAS were categorised into three groups: normotensive subjects aged <50 yrs (n=10); subjects aged <50 yrs with untreated hypertension (n=8); and normotensive subjects aged >50 yrs (n=11). Beat-by-beat BP was recorded with a Finapres device during polysomnography. The average values±SD of apnoea-related BP elevations and the values of the frequency distribution of all BP variations during sleep were assessed to estimate short-term BP variability.

Apnoea-related systolic (or diastolic) BP elevations were significantly greater in hypertensives than in normotensives aged <50 yrs (50.3±4.88 *versus* 30.7±2.14 mmHg, p<0.001), as was the SD of systolic (or diastolic) BP variations during sleep (I9.6±2.22 *versus* 11.1±0.73, p<0.001). Short-term BP variability was not significantly increased in normotensive elderly patients.

To conclude, the results suggested that systemic hypertension is associated with a greater exacerbation of short-term variability during sleep in obstructive sleep apnoea syndrome patients.
Eur Respir J 2002; 20: 151–157.

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Systemic hypertension (HT) is highly prevalent in patients with obstructive sleep apnoea syndrome (OSAS) [1], and recent epidemiological studies [2–4] suggest that this association is not entirely explained by known confounding factors such as obesity, age and sex. It has been speculated that the cardiovascular morbidity of OSAS may, in part, be related to the oscillations in systemic blood pressure (BP) and increases in sympathetic discharges that occur repeatedly during the night [5, 6]. Indeed, BP falls in time with inspiratory efforts at the beginning of each obstructive episode and rises abruptly at apnoea termination, reaching a peak during the first postapnoeic breaths. Moreover, whereas in normal subjects sympathetic activity decreases during the night, measurements with microneurographical techniques have shown a progressive increase in sympathetic nerve activity during obstructive apnoea with a peak near the end of apnoea [5, 7]. Consequently, the significant decrease in the level and variability of BP normally observed during nonrapid eye movement (NREM) sleep is blunted in OSAS patients [7].

In subjects with untreated essential HT, arterial baroreceptor reflex operates at higher pressures and baroreceptor heart-rate reflex has been reported to be decreased [8]. The resulting increase in short-term variability of BP may play a role in the alteration of function and structure of the cardiovascular system, since in subjects with untreated systemic HT, target-organ damage has been shown to be related not only to the level of 24-h mean intraarterial BP, but also to BP variability [9, 10]. As nocturnal BP variability has been reported to be increased in patients with essential systemic HT, it led the authors to consider whether the association of systemic HT with OSAS could exacerbate the fluctuations of BP related to apnoeic episodes.

To address this question and examine the effect of age, which has been shown to be associated with an increase in sympathetic nerve activity [11], the BP variability during sleep of three groups of subjects with OSAS was compared using a prospective study. The three groups included: subjects aged <50 yrs with normal daytime BP; subjects aged <50 yrs with untreated daytime systemic HT; and subjects aged >50 yrs with normal daytime BP. Using a photoplethysmographic device (Finapres; Ohmeda Inc., Englewood, NJ, USA) to record beat-to-beat BP, the amplitude of apnoea-related BP elevations measured manually were first averaged, and then the short-term

variability of nocturnal BP was assessed by computing the sd of the distribution of BP variations according to their amplitude [12].

Material and methods

Study subjects

During a period of 18 months, 29 patients referred consecutively to the sleep laboratory for clinical suspicion of OSAS were recruited according to the following criteria: l) newly-diagnosed OSAS defined as an apnoea/hypopnoea index (AHI) of >15 h of sleep on nocturnal polysomnography; 2) no previous cardiovascular treatment or treatment stopped for $\geqslant 3$ weeks; 3) no symptoms of cardiac failure or arrhythmia; and 4) no previous treatment by hypnotic drugs or treatment stopped for $\geqslant 3$ weeks. The patients were divided into the following three groups according to their age and their daytime BP measured with a sphygmomanometer on three separate occasions. Group 1: patients aged <50 yrs without systemic HT (defined as systolic BP (SBP) $\geqslant 140$ mmHg, diastolic BP (DBP) $\geqslant 90$ mmHg) (n=10); group 2: patients aged <50 yrs with untreated systemic HT (n=8); group 3: patients aged >50 yrs without systemic HT (n=11). Among the eight subjects in group 2, two had stage 1 hypertension $(140 \leqslant SBP<159$ mmHg or $90 \leqslant DBP<99$ mmHg), three had stage 2 hypertension $(160 \leqslant SBP<179$ mmHg or $100 \leqslant DBP<109$ mmHg) and three had stage 3 hypertension (SBP $\geqslant 180$ mmHg or DBP $\geqslant 110$ mmHg) according to the classification of the World Health Organization. Clinical characteristics of the subjects are given in table 1.

Study design

All patients were studied using overnight polysomnography in the sleep laboratory and nocturnal BP was monitored simultaneously using a Finapres device (Ohmeda Inc.). Average values of BP elevations at the end of apnoea were determined, and BP variability during sleep was estimated for comparison between groups.

Polysomnography. The polysomnographic data were recorded with a 16-channel polygraph (Reega 2000, Alvar, Paris, France), as previously described [12]. Sleep staging was performed according to the criteria of RECHTSCHAFFEN and KALES [13]. Electroencephalographic (EEG) arousals were scored according to standard criteria of the American Sleep Disorder Association (ASDA) [14]. Apnoea was defined as cessation of oronasal airflow for >10 s and hypopnoea as a reduction of oronasal airflow to $\geqslant 50\%$ of the value prevailing during preceding normal breathing for $\geqslant 10$ s followed by transient EEG arousal.

Recording blood pressure during polysomnography. Beat-by-beat photoplethysmographic BP was monitored continuously with Finapres, with the exception of 10-min periods every 2 h where the system was turned off for patient comfort [12]. All systolic and diastolic BP values as well as pulse oximetry values (Criticare 504, Critcare Systems Inc., Waukeste, WI, USA; averaging time: 3 s) were synchronised with polysomnography and analysed on a personal computer using software developed by the authors.

Results

Measurement of blood pressure elevations associated with apnoeas. For every patient, 30 apnoeic/hypopnoeic events ending with a typical EEG arousal were randomly selected using random number tables during sleep stages 1 or 2, and the corresponding SBP and DBP elevations were measured manually. SBP (DBP) elevation was the difference between the highest value (peak) of SBP (DBP) recorded during the 10-s period immediately following the end of apnoea and the lowest value (nadir) of SBP (DBP) recorded during the 10-s period immediately preceding the end of apnoea. The minimal arterial oxygen saturation (Sa,O$_2$) and the degree of desaturation (ΔSa,O$_2$) at the termination of every selected event were noted, as well as the event duration.

Statistical analysis

Results are expressed as means±SEM. Between-group comparisons were performed using a Kruskal-Wallis test. When a significant difference was observed,

Table 1. – Subject characteristics

	Group 1	Group 2	Group 3
	Age <50 yrs normotensive	Age <50 yrs hypertensive	Age >50 yrs normotensive
Subjects n	10	8	11
Age yrs	39.9±2.31 (25–49)	42.0±2.88 (29–49)	61.2±1.82*** (54–71)
Body mass index kg·m^{-2}	32.2±2.40 (25–47)	33.4±2.01 (26–42)	28.9±1.72 (18–42)
Daytime SBP mmHg	126.5±2.24	162.5±3.78***	133.6±2.13
Daytime DBP mmHg	78.5±2.47	105.6±3.81***	82.3±1.04
Sex M:F	7:3	7:1	11:0
Smoking habits S:NS	3:7	3:5	1:10

Results are presented as mean±SEM (range). Daytime blood pressure was measured at least three times in the supine position using a sphygmomanometer. S: smoker; NS: nonsmoker; F: female; M: male; SBP: systolic blood pressure; DBP: diastolic blood pressure. ***: p<0.001, significantly different from group 1.

multiple pairwise comparisons were performed with the Bonferroni/Dunn procedure. Comparisons of percentages of total sleep time (TST) spent in stages 1–2 or with a Sa,O_2, of <90% were performed with a Chi-squared test. Relationships between variables were evaluated by a Spearman's rank correlation test. A p<0.05 was considered statistically significant.

Polysomnography data and blood pressure values during sleep

There were no significant differences between the degree of sleep disturbance in the three groups as assessed by AHI, arousal index, sleep structure and percentage of nocturnal time spent with a Sa,O_2 of <90%, or mean Sa,O_2, during TST (table 2). Only four subjects (two from group 2 and two from group 3) displayed severe oxygen desaturations at the end of apnoea, with an average minimal Sa,O_2 of <75%, and a mean Sa,O_2 during TST of <90%, while Sa,O_2 did not decrease <85% in the remaining 25 subjects.

BP values obtained with Finapres at the beginning and end of the night were close (within 10 mmHg) to the values simultaneously measured with a sphygmomanometer. Nocturnal Finapres BP recordings were satisfactory in all patients (mean duration of analysis: 294±12.2 min, representing 77±2.0% of TST), but the average values of SBP and DBP and the SD of the distribution of BP variations during sleep could not be calculated in two of the 11 subjects from group 3 because of a computer problem. As shown in figure 1, all the subjects with untreated daytime hypertension had either probable (127<SBP<137 mmHg or 79< DBP <87 mmHg) or definite (SBP >137 mmHg or DBP >87 mmHg) nocturnal hypertension according to the meta-analysis of STAESSEN *et al.* [15]. SBP and DBP values during sleep were significantly higher in group 2 than in group 1 or 3, but did not differ between groups 1 and 3 (table 3).

Apnoea-related blood pressure elevations

The mean amplitudes of SBP (DBP) elevations at the termination of obstructive events in stages 1 or 2
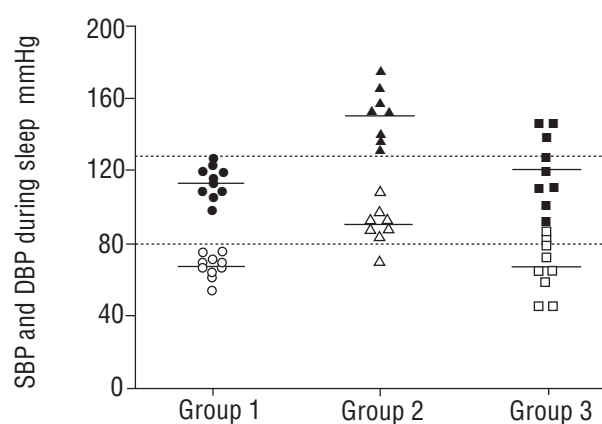

Fig. 1.–Individual values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) during sleep. Data are shown for individual patients and as average values for the group as a whole. ●, ▲, ■: average SBP values; ○, △, □: average DBP values. The higher dotted line indicates the upper limit of normal for nocturnal SBP (127 mmHg), the lower dotted line indicates the upper limit of normal for nocturnal DBP 79 mmHg, according to the meta-analysis of STAESSENS *et al.* [15].

Table 2. – Polysomnography data

	Group 1	Group 2	Group 3
	Age <50 yrs normotensive	Age <50 yrs hypertensive	Age >50 yrs normotensive
Subjects n	10	8	11
TST min	380±11.2 (304–408)	415±10.5 (383–464)	351±28.8 (180–448)
Time spent in stages 1–2 %TST	76.0±3.82 (55–94)	73.6±3.75 (56–87)	78.6±4.15 (60–99)
Apnoea/hypopnoea index events·h^{-1}	45.5±4.14 (19–92)	55.4±7.46 (35–89)	54.5±4.53 (26–88)
Arousal index events·h^{-1}	30.4±3.19 (14–41)	28.8±4.81 (7–46)	32.8±4.96 (16–65)
Time with Sa,O_2 <90% %TST	6.5±2.23 (0–20)	23.4±9.36 (1–77)	16.0±6.14 (0–67)
Mean Sa,o_2 during sleep %	94.5±0.41 (92.2–96.1)	90.6±2.12 (77.6–94.9)	92.0±1.11 (82.1–94.9)
Sa,O_2 nadir during apnoeas (stages 1–2) %	91.2±1.01 (86.5–95.3)	85.7±3.18 (71.5–94.7)	87.1±2.26 (71–94.6)
ΔSa,O_2 during apnoeas (stages 1–2) %	3.5±0.58 (1.6–7.8)	5.7±1.39 (1.3–13.3)	5.6±1.34 (1.5–16.9)
Duration of apnoeas (stages 1–2) s	19.8±1.31 (15–26)	22.2±1.85 (17–32)	27.4±2.71 (15–43)

Results are presented as mean±SEM (range). Sa,O_2: arterial oxygen saturation; TST: total sleep time. Sa,O_2 nadir during apnoeas and ΔSa,o_2 during apnoeas represent the mean minimal Sa,O_2 and the mean degree of desaturation during the 30 selected apnoeas, respectively.

Table 3. – Blood pressure values during sleep

	Group 1	Group 2	Group 3
	Age <50 yrs normotensive	Age <50 yrs hypertensive	Age >50 yrs normotensive
Subjects n	10	8	11
SBP mmHg	114±2.7	150±5.6***	121±5.7
Within-individual SD mmHg	13.5	21.5*	15.2
Individual coefficient of variation %	11.6	15.1	12.3
DBP mmHg	67±2.0	90±3.7***	67±4.8
Within-individual SD mmHg	9.1	14.9**	9.8
Individual coefficient of variation %	13.1	17.7	14.2

SBP: systolic blood pressure; DBP: diastolic blood pressure. SBP and DBP values are given as mean±SEM of individual values obtained during total sleep time. Within-individual SD represents the square root of pooled within-individual variances for SBP and DBP. Individual coefficients of variations are given as means for the group. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$, significantly different from group 1.

were significantly larger in subjects with untreated hypertension than in normotensive subjects (fig. 2), and correlated positively with daytime SBP (DBP) values obtained using a standard sphygmomanometer when all the subjects aged <50 yrs (groups 1 and 2) were pooled together ($p<0.01$, $r=0.59$). In these subjects (groups 1 and 2), the mean amplitude of apnoea-related SBP elevations did not correlate with either the average value of minimal Sa,O_2 or $\Delta Sa,O_2$ during apnoeas ($p=0.19$ and 0.24, respectively), or the mean duration of apnoeas ($p=0.31$). However, the two hypertensive subjects with the most profound desaturations (minimal Sa,O_2 <75%) also had the highest values of apnoea-related BP elevations, suggesting that the latter could be influenced by the severity of hypoxaemia. Nevertheless, when these two subjects were excluded, the average value of apnoea-related SBP (DBP) elevations remained significantly higher in the group of hypertensive subjects without severe desaturation (mean minimal Sa,O_2 at apnoea termination: 90.3±1.44 versus 91.2±1.00% in normotensives, NS) than in the normotensives (44.7±4.06 versus 30.7±2.14 mmHg, respectively, $p<0.01$). Neither systolic nor diastolic apnoea-related BP elevations were significantly correlated with age.

Blood pressure variability during sleep

Within-individual SD of beat-by-beat SBP and DBP values during sleep was also significantly increased in group 2 when compared to group 1 (table 3). It is worth noting that, during stages 1–2, the SD of the distribution of SBP (DBP) variations according to their amplitude was strongly correlated with the value of apnoea-related SBP (DBP) elevations (fig. 3). When assessed over the TST, this index of short-term variability of BP was also significantly higher in subjects with untreated hypertension than in normotensive subjects of similar age (fig. 4), but did not differ between the two normotensive groups of different age.

When all the subjects aged <50 yrs (groups 1 and 2) were considered, the SD value of the distribution of SBP (DBP) variations during TST were positively correlated with the daytime SBP (DBP) value

($p<0.007$, $r=0.60$) and the average SBP (DBP) value during TST, and negatively correlated with the mean value of Sa,O_2 during sleep ($p<0.01$, $r=-0.72$). However, when only the subjects with a mean Sa,O_2 during sleep of >90% were considered (excluding two hypertensive subjects), the SD values of the distribution of SBP or DBP variations were still significantly higher in hypertensive than in normotensive subjects (SD of systolic variations: 17.9±2.28 versus 11.1±0.73 mmHg,
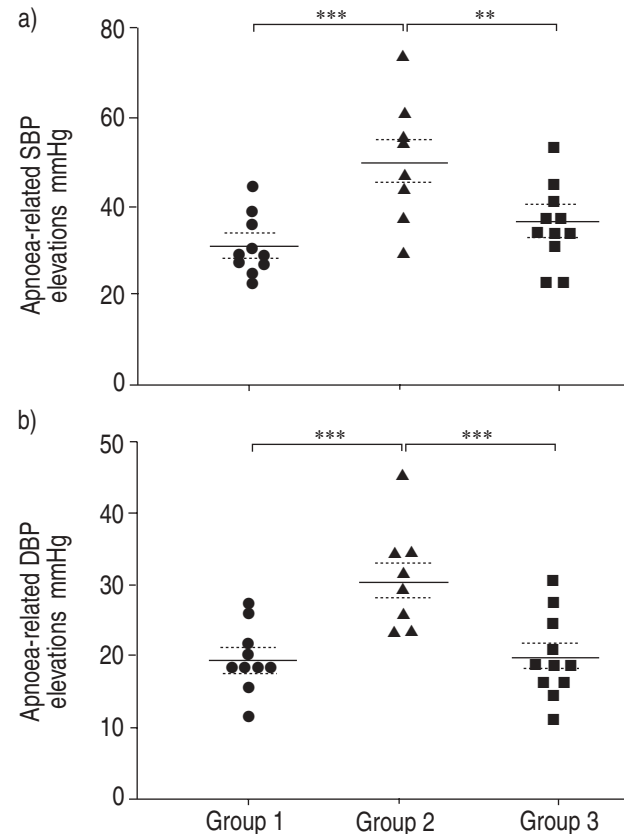

Fig. 2. – Individual values of apnoea-related systolic blood pressure (SBP) and diastolic blood pressure (DBP) elevations during sleep stages 1–2. Data are shown for individual patients and as average values for the group as a whole (solid horizontal lines)± SEM (dotted horizontal lines). **: $p<0.01$; ***: $p<0.001$.
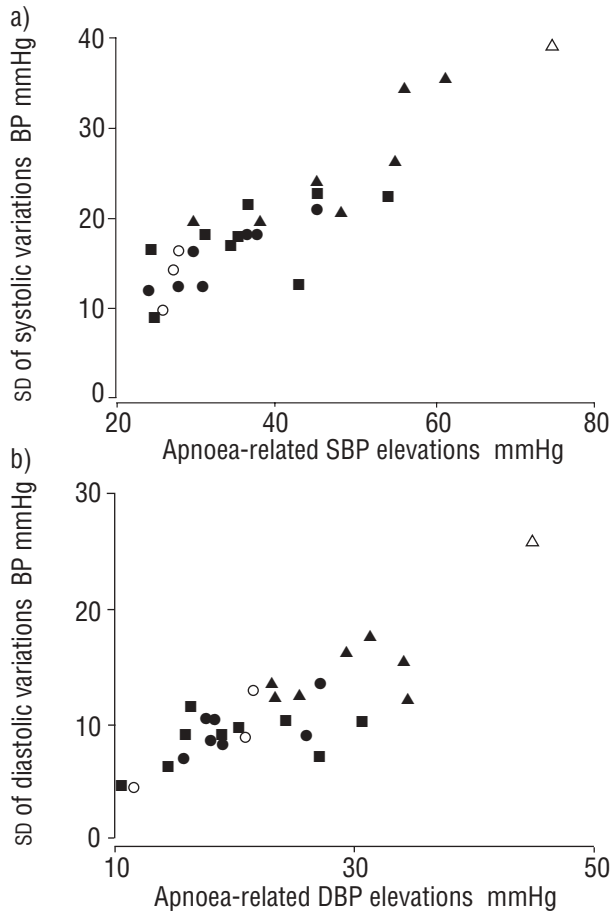
Fig. 3. – Correlation between individual values of a) apnoea-related systolic blood pressure (SBP) (r=0.89, p<0.001) or b) diastolic blood pressure (DBP) (r=0.83, p<0.001) elevations and the SD of the distribution of systolic or diastolic variations during sleep stages 1 and 2 in the three groups of obstructive sleep apnoea syndrome (OSAS) patients. ●: normotensive patients, aged <50 yrs; ▲: hypertensive patients, aged <50 yrs; ■: normotensive patients, aged >50 yrs. Open symbols: females; closed symbols: males.

Fig. 4. – SD of the distribution of all a) systolic blood pressure (SBP) and b) diastolic blood pressure (DBP) variations during total sleep time (▨) and sleep stages 1 and 2 (□) in the three groups of obstructive sleep apnoea syndrome patients. Group 1: normotensive patients, aged <50 yrs; group 2: hypertensive patients, aged <50 yrs; group 3: normotensive patients, aged >50 yrs. Results are presented as mean±SEM. **: p<0.01; ***: p<0.001.

respectively, p<0.001; SD of diastolic variations: 13.2± 1.05 versus 9.3±0.85 mmHg, respectively, p<0.05).

Discussion

The major finding of the present study was that systemic HT was associated with greater sleep-apnoea related variability of BP. The amplitude of apnoea-related BP elevations and the SD of the distribution of all BP variations according to their amplitude, which was used as a computerised index of short-term variability of BP during sleep, were both markedly increased in hypertensive subjects with OSAS when compared to normotensives. In contrast, aging only minimally, and not significantly, affected BP variability during sleep in apnoeic patients. From a methodological point of view, this study also demonstrated that the SD of the distribution of all BP variations according to their amplitude, a parameter which can
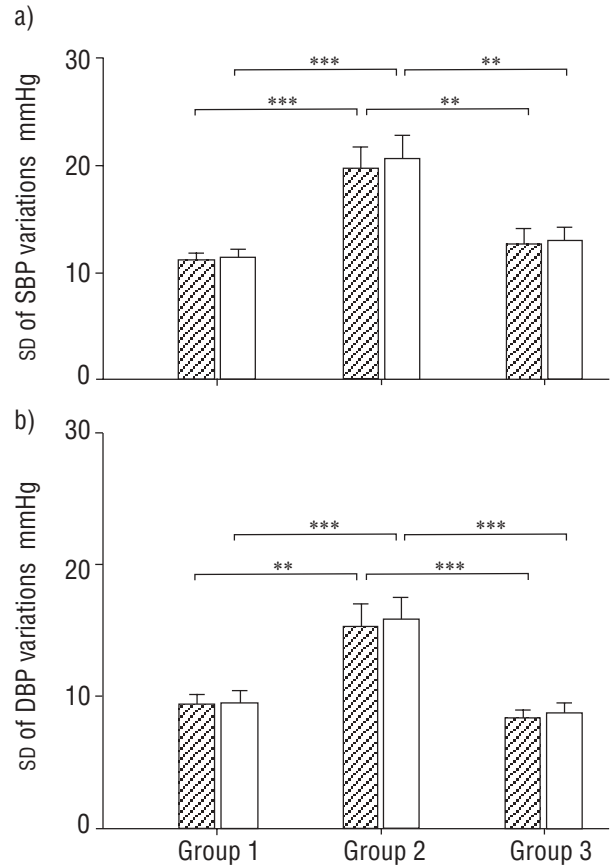
be easily computed during sleep studies, is a valuable index of apnoea-related BP elevations.

The present study population comprised exclusively of patients with moderate-to-severe OSAS, who were free of cardiovascular medication. Normotensive and hypertensive OSAS patients aged <50 yrs were comparable in age, body masss index (BMI), AHI and arousal index and sleep structure. This ruled out several confounding factors that could influence BP variability such as obesity, aging and sleep fragmentation, all of which have been shown to be associated with an increase in sympathetic drive [11, 16]. Nocturnal beat-by-beat BP was recorded with a Finapres system synchronised with polysomnography, a non-invasive technique that has been shown to be an accurate method for monitoring fast BP changes [17] and induces only minimal sleep disturbance [5, 7]. When compared with measurements from a brachial-artery catheter, the Finapres may slightly overestimate SBP and its variability [18]. However, as this overestimation is not related to BP level, the Finapres may be satisfactory for comparing BP variability between subjects.

The amplitude of BP elevations at the termination of obstructive respiratory events was markedly

increased in the hypertensive group and was correlated with daytime as well as night-time BP levels. The apnoeas or hypopnoeas used for measurements were selected randomly during stages 1 or 2 of NREM sleep and ended with a typical cortical EEG arousal, thus ruling out differences in sleep stage [7, 12, 19] or in the type and duration of EEG arousal [20] that might influence the amplitude of apnoea-related BP surges. The degree of arterial hypoxaemia is another factor that might influence systemic BP during apnoea [21]. Studying intra-individual correlations between BP and Sa,O_2, SHEPARD [22] previously showed that the degree of desaturation modulated the surge in pressure at apnoea termination, accounting for ~30% of its amplitude. In contrast, the present study examined interindividual correlations and found that the amplitude of apnoea-related SBP (DBP) elevation was not significantly correlated with Sa,O_2 nadir at the end of apnoea. This may be explained by the fact that all of the study subjects, with the exception of two (belonging to the hypertensive group), had only mild-to-moderate nocturnal oxygen desaturations (Sa,O_2, nadir >85%). Moreover, the average value of apnoea-related SBP (DBP) elevation was still significantly higher in the subgroup of hypertensive subjects without severe desaturation than in the normotensive subjects. These observations argue against the possibility that the greater BP fluctuations observed in the hypertensive population could simply be a reflection of the more profound hypoxaemia. However, it is likely that the severity of hypoxemia might in some way influence the amplitude of apnoea-related BP elevation.

In the present study, the SD of beat-by-beat SBP and DBP values during TST, an estimate of short- and long-term variability of BP, was significantly increased in the hypertensive compared with the normotensive apnoeics. MANCIA et al. [23] previously reported that the absolute variability of BP was increased during sleep in subjects with mild and severe essential HT. Since ~30% of patients with essential HT may be expected to have OSAS [24, 25], it is likely that their study population included both apnoeic and non-apnoeic subjects. The present results showed that the SD of the distribution of all-night SBP (DBP) variations according to their amplitude was also markedly increased in hypertensive subjects, and was significantly correlated with both the daytime SBP (or DBP) value and mean SBP (or DBP) during sleep. This computerised index was specifically designed to assess BP variability during sleep in patients with sleep-disordered breathing, as it can be computed even during nonstationary periods of varying durations. It reflected short-term variability of BP since all the BP changes computed lasted <20 s and were influenced by sleep fragmentation [12, 26]. However, a difference in OSAS severity could not account for the difference between the normotensive and hypertensive groups as both populations had comparable AHI, arousal index and sleep structure. It was found that the SD of the distribution of SBP (DBP) variations was significantly correlated with mean Sa,O_2 during sleep, suggesting that hypoxaemia could influence short-term variability of BP during sleep in OSAS. However, this index

was also significantly higher in the subgroup of hypertensive subjects without severe nocturnal hypoxemia (mean Sa,O_2 >90%) than in normotensive subjects with comparable nocturnal Sa,O_2. Therefore, hypoxaemia alone was probably not sufficient to explain the greater short-term variability of BP in the hypertensive group.

As systemic hypertension is very common in obstructive sleep apnoea syndrome the present results, highlighting as they do the greater short-term variability of blood pressure during sleep in apnoeic patients with untreated systemic hypertension, may have important clinical relevance. Since excessive blood-pressure variability has been linked to target-organ damage, sleep apnoea patients with systemic hypertension might be at particular risk. The computation of the SD of the distribution of blood-pressure variations during sleep, a computerised index of short-term blood-pressure variability with a good correlation with the amplitude of apnoea-related blood-pressure elevations, might be helpful in appreciating the effect of obstructive sleep apnoea syndrome treatment or antihypertensive medication on nocturnal blood-pressure variability in hypertensive patients with sleep apnoea.

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