Sympathetic overactivity due to sleep fragmentation is associated with elevated diurnal systolic blood pressure in healthy elderly subjects: the PROOF-SYNAPSE study

F. Chouchou1*, V. Pichot1, J.L. Pépin2, R. Tamisier2, S. Celle1, D. Maudoux1, A. Garcin1, P. Lévy2, J.C. Barthélemy1, and F. Roche1, on behalf of the PROOF Study Group

1EA 4607 SNA-EPIS, Service de Physiologie Clinique et de l’Exercice, Pole NOL, CHU Nord, Faculté de Médecine Jacques Lisfranc, Université Jean Monnet, Saint-Etienne, PRES Université de Lyon, France; and 2Laboratoire HP2, Unité INSERM U1042, EA 3745, Université Joseph Fourier, Laboratoire du sommeil et EFCR, département de réhabilitation et de physiologie, Grenoble, France

Received 16 October 2012; revised 19 April 2013; accepted 23 May 2013; online publish-ahead-of-print 11 June 2013

Aims
Sleep fragmentation is a landmark of sleep disorders, because microarousals are systematically associated with sympathetic surges (i.e. sympathetic arousals). However, the impact of sympathetic sleep fragmentation on blood pressure (BP) remains understudied. We assessed the relationships between 24 h ambulatory BP monitoring, the autonomic arousal index (AAI) derived from pulse transit time, and heart rate variability indices. We hypothesized that repeated sympathetic arousals during sleep are associated with elevated BP in a large population of elderly volunteers.

Methods and results
Volunteer subjects (n = 780, 57.4% women) with a mean age of 68.7 years and free of known sleep-disordered breathing, coronary heart diseases, and neurological disorders underwent polygraphy, 24 h ECG Holter monitoring, and 24 h ambulatory BP monitoring. Multivariate regressions showed that sleep fragmentation, expressed by AAI, was associated with elevated diurnal (P = 0.008) and 24 h (P = 0.005) systolic BP and higher risk for 24 h [odds ratio (OR): 1.70 (1.04–2.80), P = 0.036] systolic hypertension, independently of confounders such as sleep-disordered breathing, body mass index, sex, diabetes, hypercholesterolaemia, and self-reported sleep duration and quality. Increased AAI was associated with higher nocturnal and diurnal low-frequency power (P < 0.001) and low-to-high-frequency ratio (P < 0.001), suggesting nocturnal and diurnal sympathetic overactivity.

Conclusion
In healthy elderly subjects, repetitive sympathetic arousals during sleep are associated with elevated systolic BP and higher risk of hypertension, after controlling for confounders. Sympathetic overactivity is the proposed underlying mechanism.

Clinical Trial registration
NCT00766584 and NCT00759304.

Keywords
Sympathetic activity • Sleep • Pulse transit time • Heart rate variability • Hypertension • Elderly

Introduction
The sympathetic overactivity that accompanies the majority of sleep disorders is a recognized factor for hypertension development.1 In sleep-disordered breathing (SDB),2 respiratory events end with a rise in vascular3 and cardiac4 sympathetic activity, but the respective roles of hypoxaemic load and arousal processes in sympathetic overactivity during sleep are difficult to separate. Nevertheless, several other causes of sleep fragmentation such as noise,5 pain,6 periodic leg movements or restless legs syndrome (PLM/RLS),7 and bruxism8 have also been shown to produce sympathetic overactivity during sleep. Sleep fragmentation is defined by the presence of arousals characterized by central nervous system reactivity that produces electroencephalographic activation and concomitant changes in

* Corresponding author. Tel: +33 4 77 82 83 00, Fax: +33 4 77 82 84 47, Email: florianchouchou@gmail.com
Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2013. For permissions please email: journals.permissions@oup.com
cardiovascular parameters under autonomic control, such as RR intervals (RR),\textsuperscript{5–8} blood pressure (BP),\textsuperscript{9} and systemic vascular resistance.\textsuperscript{9} Thus, both electroencephalographic and cardiovascular indices can be used to identify sleep fragmentation.

Non-respiratory sleep disorders are also thought to generate or aggravate hypertension. Several epidemiologic studies found elevated hypertension risk in patients suffering from PLM/RLS\textsuperscript{10–12} and in subjects living in noisy environments.\textsuperscript{13} More recently, pulse-wave amplitude attenuation (using digital plethysmography to identify sympathetic arousals) during sleep was associated with rises in office systolic and diastolic BP.\textsuperscript{14} However, these results need to be confirmed in large populations. Pulse transit time (PTT), or the time it takes the pulse wave to travel from the aortic valve to the pulse waveform, detected by a plethysmographic finger probe, is used to identify sleep arousals in normal subjects and during sleep disorders (Figure 1).\textsuperscript{15–17} Sympathetic activation increases BP and vascular tone, shortening the PTT. More commonly, heart rate variability (HRV) derived from RR is used to assess sympathetic [low-frequency power (LF), low-to-high-frequency power ratio (LF/HF ratio)], and parasympathetic [high-frequency power (HF)] activity. If the HF is well determined to be modulated by parasympathetic activity, LF is under the control of both the sympathetic and parasympathetic systems. Low-frequency power is thereafter suggested as a relative marker of sympathetic activity. Normalized indices such as the LF/HF ratio are proposed as markers of sympathovagal balance\textsuperscript{18} for assessing sympathetic activity.

First, the aims of the present study were to determine, in a large study in an elderly population, the impact of sympathetic sleep fragmentation on BP; secondly, we examined the association between sympathetic overactivity and elevated BP. The impact was assessed after adjusting for confounders, and HRV indices were used to objectively determine sympathetic activity during wake and sleep. Based on previous studies,\textsuperscript{10,11,13} we hypothesized that nocturnal sympathetic sleep fragmentation would induce elevated BP and predispose to hypertension, and that sympathetic overactivity contributes to elevated BP.

**Methods**

**Study population**

The population was recruited from the PROOF study, an observational prospective study that assessed the predictive value of autonomic nervous system (ANS) activity for severe cardiovascular and cerebrovascular events and mortality.\textsuperscript{19} An ancillary 7-year follow-up study addressing the association between SDB and cardiovascular and cerebrovascular morbidity was proposed to participants (SYNAPSE study). Volunteers were recruited in 2001 from the electoral list of the city of Saint-Etienne, France, according to age (65 years). Exclusion criteria were previous myocardial infarction or stroke, heart failure, insulin-dependent diabetes mellitus, atrial fibrillation or anti-arrhythmic treatment, and a severe disease limiting life expectancy to \(<5\) years. Inclusion criteria were absence of diseases preventing HRV assessment, no use of anti-arrhythmic drugs, and willingness to undergo polygraphy and 24 h BP monitoring (for details, see Barthélemy et al.\textsuperscript{19}). The data used in the present study were gathered from the second examination of the PROOF study (January 2003–December 2004). All volunteers enrolled in the PROOF study were eligible for participation in the SYNAPSE study, except those with diagnosed SDB (\(n=5\)). Of the original PROOF sample (1011 subjects), 780 volunteers (57.4\% women, mean age 68.7 years) were included when valid PTT measurements and ambulatory BP monitoring (ABPM) data were available (Table 1). Both the PROOF and SYNAPSE studies were approved by Ethics Committee (CCPRPB, Loire, France) and were conducted in

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/34/28/2122/457463)

In this sleep apnoea patient, obstructive events end with a microarousal detected by an abrupt dip in PTT (dashed circle). Note also the concurrent increase in blood pressure (Finapress), reflecting a surge in sympathetic activity.
Table 1  Clinical and polygraphic data for all subjects according to autonomic arousal index tertiles: (A) nominal data, (B) parametric continuous data, and (C) non-parametric continuous data

|                      | Total (n = 780) | Low AAI group (n = 260) | Moderate AAI group (n = 260) | High AAI group (n = 260) | P     |
|----------------------|-----------------|-------------------------|-----------------------------|-------------------------|-------|
|                      | n (%)           | n (%)                   | n (%)                       | n (%)                   |       |
| **A**                |                 |                         |                             |                         |       |
| Women                | 448 (57.4)      | 155 (59.6)              | 147 (56.5)                  | 146 (56.2)              | 0.783 |
| Diabetes             | 43 (5.5)        | 10 (3.8)                | 15 (5.8)                    | 18 (6.9)                | 0.284 |
| Current/past smoking | 201 (25.7)      | 65 (25.0)               | 70 (26.9)                   | 66 (25.4)               | 0.827 |
| Use of antihypertensive treatment | 196 (25.1) | 72 (27.7) | 65 (25.0) | 59 (22.7) | 0.465 |
| **Type of antihypertensive treatment** |          |                         |                             |                         |       |
| Renin–Angiotensin    | 77 (9.9)        | 28 (10.7)               | 24 (9.2)                    | 25 (9.6)                | 0.854 |
| Beta-blocker         | 74 (9.5)        | 26 (10.0)               | 28 (10.7)                   | 20 (7.7)                | 0.466 |
| Calcium channel blocker | 58 (7.4)    | 21 (8.1)                | 19 (7.3)                    | 18 (6.9)                | 0.896 |
| Diuretic             | 88 (11.3)       | 27 (10.4)               | 26 (10.0)                   | 35 (13.5)               | 0.379 |
| Peripheral vasodilator | 11 (1.4)    | 3 (1.2)                 | 4 (1.5)                     | 4 (1.5)                 | 0.905 |
| Others               | 11 (1.4)        | 1 (0.4)                 | 8 (3.1)                     | 2 (0.8)                 | 0.018 |
| Dyslipidaemia        | 267 (34.2)      | 86 (33.1)               | 93 (35.8)                   | 88 (33.8)               | 0.736 |
| **24 h systolic hypertension ($\geq 130$ mmHg) | 154 (19.7) | 40 (15.4) | 50 (19.2) | 64 (24.6) | 0.029 |
| **Daytime systolic hypertension ($\geq 135$ mmHg) | 152 (19.5) | 42 (16.2) | 49 (18.8) | 61 (23.5) | 0.108 |
| **Nighttime systolic hypertension ($\geq 120$ mmHg) | 144 (18.5) | 46 (17.7) | 36 (13.8) | 62 (23.8) | 0.015 |
| **24 h diastolic hypertension ($\geq 80$ mmHg) | 166 (21.3) | 57 (21.9) | 54 (20.8) | 55 (21.2) | 0.941 |
| **Daytime diastolic hypertension ($\geq 85$ mmHg) | 127 (16.3) | 37 (14.2) | 43 (16.5) | 47 (18.1) | 0.500 |
| **Nighttime diastolic hypertension ($\geq 70$ mmHg) | 238 (30.5) | 78 (30.0) | 67 (25.8) | 93 (35.8) | 0.053 |
| **B**                |                 |                         |                             |                         |       |
| Age (years)          | 68.7 ± 1.0      | 68.7 ± 0.9              | 68.7 ± 1.1                  | 68.7 ± 0.9              | 0.964 |
| Cholesterol (L/g)    | 2.2 ± 0.3       | 2.2 ± 0.2               | 2.2 ± 0.4                   | 2.2 ± 0.3               | 0.663 |
| Glucose (L/g)        | 1.0 ± 0.2       | 1.0 ± 0.2               | 1.0 ± 0.2                   | 1.0 ± 0.2               | 0.298 |
| Body mass index (kg/m²) | 25.5 ± 3.8  | 25.2 ± 3.8              | 25.3 ± 3.9                  | 25.9 ± 3.6              | 0.121 |
| Autonomic arousal index (events/h) | 37.1 ± 16.3 | 36.0 ± 3.9 | 42.7 ± 6.6 | 55.4 ± 10.5 | < 0.001 |
| Respiratory (events/h) | 15.5 ± 10.6  | 14.3 ± 4.7              | 14.3 ± 4.7                  | 14.3 ± 4.7              | < 0.001 |
| Non-respiratory (events/h) | 21.7 ± 11.5  | 21.6 ± 5.4              | 21.6 ± 5.4                  | 21.6 ± 5.4              | < 0.001 |
| Recording time (min) | 463.8 ± 71.6   | 467.7 ± 74              | 468.2 ± 70.9                | 455.5 ± 69.3            | 0.073 |
| **24 h systolic blood pressure (mmHg) | 119.2 ± 13.8  | 117.6 ± 12.8            | 117.6 ± 12.9                | 121.7 ± 14.7            | < 0.001 |
| **Daytime systolic blood pressure (mmHg) | 123.3 ± 14.6  | 121.6 ± 13.4            | 122 ± 14.2                  | 125.9 ± 15.3            | 0.001 |
| **Nighttime systolic blood pressure (mmHg) | 107.2 ± 15.2  | 106.7 ± 15.8            | 105.2 ± 12.9                | 109.5 ± 15.8            | 0.005 |
| **24 h diastolic blood pressure (mmHg) | 74.5 ± 7.8    | 74.6 ± 7.5              | 73.8 ± 7.5                  | 74.9 ± 8.2              | 0.285 |
| **Daytime diastolic blood pressure (mmHg) | 77.2 ± 8.2    | 77.3 ± 8                | 76.7 ± 8.1                  | 77.5 ± 8.4              | 0.569 |
| **Nighttime diastolic blood pressure (mmHg) | 66.6 ± 8.6    | 66.9 ± 8.5              | 65.5 ± 7.7                  | 67.3 ± 9.4              | 0.044 |
| **Office systolic blood pressure** | 139.2 ± 16.2  | 139.4 ± 16.3            | 138.2 ± 15.3                | 139.9 ± 16.9            | 0.488 |
| **Office diastolic blood pressure** | 86.1 ± 8.5   | 86.6 ± 8.8              | 85.8 ± 8.4                  | 85.7 ± 8.3              | 0.41  |
| **Self-reported sleep duration (h) | 6.8 ± 1.6     | 6.9 ± 1.5               | 6.6 ± 1.7                   | 6.9 ± 1.6               | 0.073 |
| **Sleep quality (/6) | 4.1 ± 1.1       | 4.1 ± 1.2               | 4.2 ± 1.1                   | 4.1 ± 1.1               | 0.554 |
| **Recording time (min) | 463.8 ± 71.6  | 467.7 ± 74              | 468.2 ± 70.9                | 455.5 ± 69.3            | 0.073 |
| **Mean oxygen saturation (%) | 95.3 ± 1.8   | 95.1 ± 2.1              | 95.4 ± 1.5                  | 95.4 ± 1.6              | 0.093 |
| **Minimum oxygen saturation (%) | 89.6 ± 4.2    | 89.9 ± 3.8              | 89.8 ± 4.2                  | 89.1 ± 4.5              | 0.029 |
| **C**                |                 |                         |                             |                         |       |
| Triglyceride (L/g)   | 1.0 (0.5)       | 0.9 (0.5)               | 0.9 (0.5)                   | 1 (0.5)                 | 0.679 |
| Epworth Sleepiness Scale score (/24) | 5.0 (5.0)     | 5.0 (5.0)               | 5.0 (5.0)                   | 5.0 (5.0)               | 0.013 |
| Apnoea/hypopnoea index (events/h) | 17.3 (19.4)  | 13.4 (14.8)             | 17.9 (17.9)                 | 24.2 (24.6)             | < 0.001 |
| Obstructive (events/h) | 16 (17.2)     | 12.3 (12.9)             | 16 (16.2)                   | 22 (19.6)               | < 0.001 |
Table I  Continued

|                              | Total (n = 780) | Low AAI group (n = 260) | Moderate AAI group (n = 260) | High AAI group (n = 260) | P  |
|------------------------------|----------------|------------------------|-----------------------------|-------------------------|----|
| Central (events/h)           |                |                        |                             |                         |    |
| Oxygen desaturation index     | 0.9            | 2                      | 0.6                         | 1.4                     |    |
| Number of antihypertensive    | 6.6            | 10.7                    | 5.3                         | 8.6                     |    |
| treatment                   | 1.0            | 1.0                     | 1.0                         | 1.0                     |    |

SD, standard deviation; IRQ, interquartile range.
*P < 0.05 with low AAI group.
*P < 0.05 with moderate AAI group.

accordance with the Declaration of Helsinki. All subjects gave their written informed consent to participate.

Clinical examination

All subjects underwent standard clinical examination, including assessment of clinical and anthropometric characteristics. The Epworth Sleepiness Scale (ESS) assessed daytime sleepiness20 and the Saint Mary’s Hospital questionnaire31 assessed self-reported sleep duration and sleep quality. Use, type, and number of antihypertensive drugs and hypertension history were also assessed during the medical examination. Subjects were considered previously hypertensive if they have been prescribed antihypertensive drugs. Office BP was systematically measured with a mercury sphygmomanometer at each visit, twice in lying position after a 15 min rest and once immediately after in orthostatic position.

Polygraphic study

After clinical examination, all subjects underwent one full night of cardiorespiratory polygraphy at home using a portable multi-channel recording system (HypnoPTT, Tyco Healthcare, Puritan Bennett, USA). The portable system recorded ECG signals (one lead), pulse oximetry, respiratory effort (thoracic and abdominal belts), body position, nasal pressure, PTT, and RR intervals.22 Subjects underwent a second monitoring night if reported sleep latency exceeded 2 h on the first night (n = 10) or if one respiratory channel was missing (n = 45). At least five consecutive hours of recording were required to validate the polygraphic recording. All recordings were manually scored for apnoea–hypopnoea events by a blinded investigator. Hypopnoea was defined as a 50% or greater reduction in airflow from baseline lasting at least 10 s and associated with at least 3% oxygen desaturation. Apnoea was defined as the absence of airflow on the nasal cannula lasting at least 10 s.22 The apnoea–hypopnoea index (AHI) was established as the ratio of the number of apnoeas and hypopnoeas per recording hour. The following nocturnal hypoxaemia indices were used: mean oxygen desaturation (SaO2), minimum SaO2, and the oxygen desaturation index (ODI: the number of oxygen desaturation episodes per recording hour during which SaO2 fell by 3% or more).

Data acquisition

Pulse transit time measurement

According to manufacturer’s instructions, PTT was calculated as the time interval between the ECG R wave and a point on the pulse waveform (detected by a plethysmography finger probe) which is 50% of the pulse-wave height.15–17 The electrocardiogram and pulse were sampled at 500 Hz. Pulse transit time is typically ~250 ms with 2-ms accuracy and were therefore oversampled at 5 Hz. From continuously monitored PTT signals, an autonomic arousal index (AAI) based on a shorter PTT was obtained using the manufacturer’s analysis software (Figure 1). The AAI was subsequently differentiated into respiratory-related and non-respiratory-related autonomic arousals according to the presence of respiratory events before autonomic events, which were visually validated by investigators.

Heart rate variability

The same day as polygraphic recording, standard three-channel ECG Holter tape recorders were used for 24 h monitoring (Novacor System, Rueil-Malmaison, France). ECG signals were sampled at 200 Hz and subjected to peak-to-peak analysis to detect QRS complex (R waves) using Matlab (MathWorks, Naticks, MA, USA). Each QRS complex was validated, and cubic-spline interpolation was used to correct for artefacts and ectopic beats.18 Heart rate variability was calculated on RR intervals extracted from recordings. Fast Fourier transform (FFT) was applied to RR intervals over series of 256 consecutive RR for all recordings. The following HRV indices were calculated from the mean of consecutive FFT analyses, according to published criteria18: total (Ptot: 0.00–0.40 Hz), very low (VLF: 0.00–0.04 Hz), low-frequency (LF: 0.04–0.15 Hz), and high-frequency (HF: 0.15–0.40 Hz) powers. Normalized low-frequency (LF%) and high-frequency (HF%) powers were calculated as 100 × LF and 100 × HF, respectively, divided by Ptot-VLF. The LF/HF ratio was also calculated. Overall, LF is controlled by both the sympathetic and parasympathetic systems, while HF is controlled by the parasympathetic system. Normalized indices (LF/HF ratio and LF%) are used to approach relative sympathetic activity. Ptot was related to overall autonomic activity. Very low-frequency power was related to parasympathetic activity as well as hormonal control,23 a finding that remains to be fully explained. All variables were calculated for daytime and night, synchronized using ‘lights on’ and ‘lights off’ as markers.

Blood pressure monitoring

Twenty-four hour ABPM was performed using a portable recording system (Diaysis Integra, Novacor, Rueil-Malmaison, France). Blood pressure on the non-dominant arm was automatically measured at 15 min intervals in the daytime and 30 min intervals at night. Average systolic and diastolic BP were calculated across recording periods: daytime, nighttime, and over 24 h, according to self-reported sleep, and awake time. Hypertension was defined according to the 24 h ABPM (130/80 mmHg for the 24 h period, 135/85 mmHg for the daytime period, and 120/70 mmHg for the nighttime period, according to recommended limits).24 Ambulatory BP monitoring recordings were performed the
day after the home polygraphic study to avoid interference between polygraphic results and automated BP measurements.

**Statistical analysis**

Data were analysed using Statview® software (SAS Institute, Inc., Cary, NC, USA) and presented as mean ± standard deviation (SD).

To determine the relationship between AAI and BP, separate univariate and multivariate regression analyses were performed between AAI, systolic BP, and diastolic BP in the 24 h, nighttime, and daytime period. Adjustments were made for AHI, ODI, BMI, sex, previous hypertensive status, glucose, cholesterol, polygraphic monitoring duration, and self-reported sleep duration and quality (items 7 and 9 of the Saint Mary’s Hospital questionnaire).

Multivariate regressions were adjusted for body mass index, polygraphic monitoring duration, self-reported sleep duration and quality (Saint Mary’s Hospital questionnaire), sex, presence of hypertensive treatment, number of hypertensive treatments, oxygen desaturation, apnoea–hypopnoea indices, glucose, and cholesterol.

The same process was applied for the relationship between AAI and HRV indices.

To assess the clinical relevance of the association between AAI and BP hypertension, adjusted multivariate logistic regression analyses were performed according to pre-specified AAI tertiles and the presence of hypertension, expressed as odds ratio (OR) and using a 95% confidence interval (95% CI). Adjustments were made for the following confounding factors: AHI, ODI, BMI, sex, previous hypertensive status, diabetes, hypercholesterolaemia, polygraphic monitoring duration, and self-reported sleep duration and quality (items 7 and 9 of the Saint Mary’s Hospital questionnaire).

### Table 2 Univariate and multivariate regressions for continuous variables between blood pressure and (A) the total autonomic arousal index (AAI), (B) the respiratory AAI, and (C) the non-respiratory AAI (n = 780)

|                  | Univariate regression | Multivariate regression |
|------------------|-----------------------|-------------------------|
|                  | t         | r         | P          | t         | P          |
| **A** Systolic blood pressure |
| 24 h             | 3.96     | 0.14     | <0.001    | 2.78     | 0.005     |
| Diurnal          | 3.76     | 0.13     | 0.002     | 2.68     | 0.008     |
| Nocturnal        | 2.71     | 0.10     | 0.007     | 1.20     | 0.233     |
| Diastolic blood pressure |
| 24 h             | 0.96     | 0.04     | 0.340     | −0.19    | 0.853     |
| Diurnal          | 0.67     | 0.02     | 0.505     | −0.24    | 0.812     |
| Nocturnal        | 1.02     | 0.04     | 0.306     | −0.70    | 0.483     |
| **B** Systolic blood pressure |
| 24 h             | 5.27     | 0.19     | <0.001    | 2.48     | 0.014     |
| Diurnal          | 4.75     | 0.17     | <0.001    | 2.42     | 0.016     |
| Nocturnal        | 4.64     | 0.17     | <0.001    | 0.53     | 0.594     |
| Diastolic blood pressure |
| 24 h             | 3.53     | 0.13     | <0.001    | 0.26     | 0.796     |
| Diurnal          | 2.82     | 0.10     | 0.005     | 0.23     | 0.817     |
| Nocturnal        | 4.20     | 0.15     | <0.001    | −0.83    | 0.405     |
| **C** Systolic blood pressure |
| 24 h             | 0.78     | 0.03     | 0.434     | 2.26     | 0.024     |
| Diurnal          | 0.96     | 0.04     | 0.339     | 2.15     | 0.032     |
| Nocturnal        | −0.37    | 0.01     | 0.714     | 1.27     | 0.204     |
| Diastolic blood pressure |
| 24 h             | −1.86    | 0.07     | 0.063     | −0.39    | 0.698     |
| Diurnal          | −1.63    | 0.06     | 0.104     | −0.44    | 0.658     |
| Nocturnal        | −2.34    | 0.09     | 0.019     | −0.46    | 0.647     |

[Table 2](#) Univariate and multivariate regressions for continuous variables between blood pressure and (A) the total autonomic arousal index (AAI), (B) the respiratory AAI, and (C) the non-respiratory AAI (n = 780)

Multivariate regressions were adjusted for body mass index, polygraphic monitoring duration, self-reported sleep duration and quality (Saint Mary’s Hospital questionnaire), sex, presence of hypertensive treatment, number of hypertensive treatments, oxygen desaturation, apnoea–hypopnoea indices, glucose, and cholesterol.

### Table 3 Univariate and multivariate regressions for continuous variables between blood pressure and the total autonomic arousal index in (A) a subgroup (n = 64) of subjects free of sleep-disordered breathing (apnoea–hypopnoea index < 5 events/h), (B) a subgroup of normotensive subjects (n = 584), and (C) a subgroup of hypertensive subjects (n = 196)

|                  | Univariate regression | Multivariate regression |
|------------------|-----------------------|-------------------------|
|                  | t         | r         | P          | t         | P          |
| **A** Systolic blood pressure |
| 24 h             | 2.20     | 0.27     | 0.032     | 2.02     | 0.048     |
| Diurnal          | 2.21     | 0.27     | 0.031     | 2.02     | 0.049     |
| Nocturnal        | 1.98     | 0.25     | 0.052     | 1.49     | 0.143     |
| Diastolic blood pressure |
| 24 h             | 0.78     | 0.10     | 0.436     | 0.65     | 0.517     |
| Diurnal          | 0.78     | 0.10     | 0.436     | 0.81     | 0.424     |
| Nocturnal        | −0.37    | 0.05     | 0.712     | −0.48    | 0.636     |
| **B** Systolic blood pressure |
| 24 h             | 3.60     | 0.15     | <0.001    | 2.32     | 0.021     |
| Diurnal          | 3.20     | 0.14     | 0.015     | 2.00     | 0.047     |
| Nocturnal        | 2.58     | 0.11     | 0.010     | 1.00     | 0.319     |
| Diastolic blood pressure |
| 24 h             | 1.35     | 0.06     | 0.179     | −0.16    | 0.987     |
| Diurnal          | 0.90     | 0.04     | 0.368     | −0.29    | 0.774     |
| Nocturnal        | 1.35     | 0.06     | 0.178     | −0.27    | 0.790     |
| **C** Systolic blood pressure |
| 24 h             | 1.99     | 0.14     | 0.048     | 1.86     | 0.064     |
| Diurnal          | 2.26     | 0.16     | 0.025     | 2.12     | 0.036     |
| Nocturnal        | 1.36     | 0.10     | 0.176     | 1.03     | 0.304     |
| Diastolic blood pressure |
| 24 h             | 0.12     | <0.01    | 0.908     | −0.17    | 0.866     |
| Diurnal          | 0.27     | 0.19     | 0.791     | −0.07    | 0.946     |
| Nocturnal        | 0.14     | 0.10     | 0.889     | −0.66    | 0.511     |

Subjects were classified according to antihypertensive drug use (see Clinical examination in Methods section for classification details). Multivariate regressions were adjusted for body mass index, polygraphic monitoring duration, self-reported sleep duration and quality (Saint Mary’s Hospital questionnaire), sex, presence of hypertensive treatment, number of hypertensive treatments, glucose, and cholesterol.
reported sleep duration and quality. Clinical, anthropometric, and polygraphic characteristics of the three tertiles were compared using two-sided Kruskal–Wallis and Tukey post hoc tests, or using two-sided ANOVA with one between factor and Newman–Keuls post hoc tests. Percentages were compared using Pearson’s two-sided \( \chi^2 \) test. Significance was set at \( P < 0.05 \).

**Results**

Table 1 presents the anthropometrics, history, and polygraphic data for all subjects according to AAI tertiles.

**Autonomic arousal index and blood pressure**

Univariate regressions showed that the AAI was significantly related to systolic BP in 24 h and daytime periods (\( P < 0.001 \) and \( P = 0.002 \), respectively). In multivariate regressions adjusted for usual confounders for BP (Table 2A), these relationships were preserved (\( P = 0.005 \) and \( P = 0.008 \), respectively). Autonomic arousal index was also significantly related to nighttime systolic BP in univariate (\( P = 0.007 \)) but not multivariate regressions.

We therefore tested the relationship between BP and AAI in a subgroup (\( n = 64 \)) of subjects free of SDB (Table 3A). Autonomic arousal index remained significantly related to systolic BP in 24 h (\( P = 0.048 \)) and diurnal (\( P = 0.049 \)) periods independently of usual confounders, and tended towards significance in univariate regression with nighttime systolic BP (\( P = 0.052 \)) but not multivariate regressions.

We tested the relationship between BP and respiratory and non-respiratory AAI (Table 2B and C). Respiratory and non-respiratory AAI remained significantly related to systolic BP in the 24 h (\( P = 0.014 \) and 0.024, respectively) and daytime period (\( P = 0.016 \) and 0.032, respectively), independently of usual confounders. The absence of correlation between non-respiratory AAI and BP (\( P = 0.434 \)) in the univariate analysis is attributable to the high frequency of respiratory events in the entire group, which weakens the relationship between non-respiratory AAI and BP.

In a subgroup of normotensive (\( n = 584 \)) and previous hypertensive subjects (\( n = 196 \)), AAI remained significantly related to systolic BP in the daytime period in both subgroups (\( P = 0.047 \) and 0.036, respectively), independently of the usual confounders, but only for normotensive subjects in the 24 h period (\( P = 0.021 \) and 0.064, respectively).

**Polygraphic, ECG Holter, and ambulatory blood pressure monitoring according to autonomic arousal index tertiles**

To determine the clinical relevance of sleep fragmentation assessed by PTT monitoring, data were analysed according to AAI tertiles. The low tertile corresponded to 0.0–29.5 autonomic arousals per hour, the intermediate tertile 29.6–43.1 autonomic arousals per hour, and the high tertile 43.1–98.7 (Table 1). In the high tertile, high ESS scores indicated greater daytime sleepiness, whereas polygraphic monitoring duration and self-reported sleep duration indicated equal sleep duration for all tertiles. Only systolic BP in the high AAI tertile was significantly higher than in other tertiles (Figure 2) in the 24 h (\( P < 0.05 \)), nighttime (\( P < 0.05 \)), and daytime (\( P < 0.05 \)) period. This AAI effect on BP measured by ABPM was undetected by office measurements (Table 1). Adjusted multivariate analyses revealed that the high AAI tertile was associated with 24 h
Heart rate variability and sleep fragmentation expressed as the autonomic arousal index

Concerning HRV, adjusted multivariate regressions showed that the AAI was significantly related to diurnal and nocturnal Ptot (P = 0.023 and < 0.001, respectively), VLF (P = 0.006 and < 0.001), and LF (P < 0.001 and < 0.001) (Table 5). However, no relation with HF was found. Adjusted multivariate regressions showed that diurnal and nocturnal LF% (P = 0.001 and < 0.001), HF% (P = 0.001 and < 0.001), and LF/HF ratio (P = 0.001 and < 0.001) were also significantly related to the AAI.

In the high AAI tertile, Ptot (P < 0.05), VLF (P < 0.05), and LF (P < 0.05) were higher than in the other two tertiles during nighttime, whereas HF was unaltered (Figure 3A). LF% and the LF/HF ratio (P < 0.05 and < 0.05) were also higher in the intermediate and high AAI tertile. In daytime, LF (P < 0.05), the LF/HF ratio (P < 0.05), and LF% (P < 0.05) remained higher in the high AAI tertile than in the low AAI tertile (Figure 3B).

Discussion

Our results show that sleep fragmentation (AAI) is related to BP, particularly diurnal BP, in a large population of elderly volunteers. Higher AAI is associated with higher BP, which carries a higher risk of 24 h hypertension, independently of other major confounders such as sleep-disordered breathing (SDB), hypoxaemic load, sex, BMI, diabetes, hypercholesterolaemia, and self-reported sleep duration and quality. Autonomic arousal index is also related to elevated diurnal normalized low-frequency (LF%) power and the low-to-high-frequency ratio (LF/HF ratio) derived from HRV, suggesting that diurnal rise in sympathetic activity could contribute to diurnal elevation in BP and the risk of hypertension. Our findings further suggest that using autonomic markers such as PTT to assess sleep fragmentation could add relevant clinical information about hypertension risk in the elderly.
Pulse transit time is a validated tool to assess sleep fragmentation and sympathetic activation

Several environmental circumstances and diseases, including noise, pain, LM/RLS, bruxism, and SDB, are known to stimulate autonomic activity during sleep. This autonomic activation, accompanied or not by cortical arousals, is associated with concomitant changes in physiological parameters that depend on the ANS. Autonomic activation leads to increased heart rate (decreased RR), BP surges, and elevated systemic vascular resistance. Based on these physiological changes, PTT has been used to detect these events. Although PTT correlated to oesophageal pressure, and could be used to characterize respiratory efforts during apnoeas and hypopnoeas, Pitson et al. demonstrated a strong relationship between abrupt dips in PTT and cortical microarousals during sleep. Moreover, PTT reactivity was not specific to respiratory events, as shown by the weak association between AAI and AHI. Pulse transit time dip was therefore proposed as useful for detecting both respiratory- and non-respiratory-related autonomic arousals during sleep. In our study, subjects presented with frequent respiratory-related autonomic activation, but also non-respiratory sleep fragmentation (Table 1). Non-respiratory sleep fragmentation could have various causes in an elderly population, and fragmented sleep due to spontaneous awakenings was reported to increase over the lifespan.

Sleep and hypertension risk

Sleep has been well established as essential for cardiovascular control, as shorter sleep duration has been associated with a rise in sympathetic activity as well as higher risks for hypertension, coronary heart disease, and stroke. Nevertheless, short sleep duration was reported to increase hypertension risk in a middle-aged population but not in an elderly population. Our results show an independent positive relationship between sympathetic sleep fragmentation and 24 h BP in an elderly population (OR in the high AAI tertile of 1.70, 95% CI: 1.04–2.80). Surprisingly, a multivariate analysis showed a significant relationship between BP and AAI in the day but not at night. In a model of healthy adults exposed to both intermittent hypoxia and sleep fragmentation, BP rose significantly during daytime. These experiments provided relatively short-term exposures to sleep fragmentation. In real life, sleep problems and disorders that impact either the quality or quantity of sleep are associated with intermediary mechanisms that favour the development of hypertension. Sleep-related hypertension is often masked in the early stages as a non-dipping status. Thereafter, a chronic increase in sympathetic activity secondarily leads to daytime hypertension. Overall, these results concur with several studies on the consequences of a noisy environment and PLM/RLS for hypertension risk. In the HYENA cohort, which examined exposure to nighttime aircraft noise near airports, a 10 dB increase in exposure was
associated with an OR of 1.14 (95% CI: 1.01–1.29) after adjusting for major confounders. Concerning the PLM/RLS, OR for the association between hypertension and RLS has been reported at from 1.36 (95% CI: 1.14–1.61) to 1.5 (95% CI: 0.9–2.40). Moreover, Morrell et al. showed that a sleep fragmentation index based on sleep awakenings and shifts to sleep stage 1 was related to a diurnal systolic BP rise of ~3 mmHg in a population without SDB. Taken together, these studies and ours support the idea that sleep disruptions, whether

Figure 3  Heart rate variability according to autonomic arousal index tertiles in (A) nocturnal and (B) diurnal periods (mean ± standard error). Ptot, total power; VLF, very low-frequency power; LF, low-frequency power; HF, high-frequency power; LF%, normalized low-frequency power; HF%, normalized high-frequency power; LF/HF ratio, low-to-high-frequency power ratio.

caused by environmental factors or several infraclinical neurological disorders, could alter cardiovascular control, thereby increasing hypertension risk. In SDB, other factors could be implicated, such as hypoxaemia or intrathoracic pressure swing during respiratory events. Hypoxaemia can also interact with autonomic activity to alter BP control. Nevertheless, regardless of whether the impact on diurnal BP is mediated by hypoxaemic load or by intrathoracic pressure swing as well, our results indicate that systolic BP regulation could also be influenced by sleep-dependent events related to sleep fragmentation independently of other known confounders in SDB.

### Sympathetic overactivity and hypertension

There is considerable evidence to suggest that the ANS plays a fundamental role in hypertension development and maintenance. The sympathetic sleep overactivity reported in our study and its diurnal BP control dysfunction supports this proposal. However, the question remains as to how this sleep disruption induces a rise in systolic BP during wakefulness. Intrinsin brain factors and vascular mechanisms could be implicated. First, several studies have demonstrated an inappropriate increase in sympathetic activity in patients with essential hypertension and pre-hypertension using HRV, microneurography, and plasma catecholamine measurements. Decreased baroreflex sensitivity, which induces inappropriate sympathetic overactivity, is currently proposed as a central mechanism for ANS dysfunction in hypertension, particularly in systolic BP control. This is supported by electric field stimulation of the human carotid sinus, resulting in a sustained reduction in BP and sympathetic nerve activity in resistant hypertensive patients. In our study, we hypothesized that alterations of the baroreflex control could have provoked a rise in diurnal sympathetic activity, and consequently in systolic BP. The second proposal concerns peripheral mechanisms: the sympathetic outflow goes towards not only splanchic, hind limb, and cardiac territories, but also towards the renal territory, and the sympathetic system plays a major role in regulating vascular resistance as well as cardiac and renal functions. Recurrent sympathetic arousal during sleep could therefore contribute to hypertension by increasing vascular resistance and cardiac function, altering endothelial function, inducing cardiac and vascular remodelling, and/or altering renal sodium and water homeostasis. Furthermore, diurnal sympathetic flow and BP are dependent on the wake central command, and elevated sympathetic activity and sleepiness were found to be correlated. In our study, the highest AAIm tertile showed not only the most elevated BP, but also the most daytime sleepiness.

### Limitations and strengths

We did not use polysomnography to assess sleep architecture. This is a potential limitation, as in elderly individuals, slow-wave sleep duration is predictive of incident hypertension. However, we used ambulatory monitoring in a large prospective population of elderly subjects in ecological conditions at home that more realistically reflect the burden of autonomic activation in real-life conditions compared with in-lab polysomnography. Another strength of this study is the examination of underlying mechanisms, showing for the first time in an elderly population the dose–response relationship between AAIm and relative indices of sympathetic activity derived from HRV. Moreover, HRV analysis has been demonstrated reliable in assessing autonomic activity, Nevertheless, regardless of whether the impact on diurnal BP is mediated by hypoxaemic load or by intrathoracic pressure swing as well, our results indicate that systolic BP regulation could also be influenced by sleep-dependent events related to sleep fragmentation independently of other known confounders in SDB.

### Perspectives

Whatever the origin of sleep disruptions (respiratory-related or not), PTT monitoring derived from simple nocturnal ambulatory parameters (requiring only ECG and pulse oximetry devices) adds relevant clinical information regarding the risk of elevated systolic BP. Moreover, although continuous positive airway pressure treatment (CPAP) reduced the incident hypertension risk by normalizing sleep continuity and reducing hypoxaemic load in SDB, Norman et al. demonstrated that improving oxygen saturation alone, without treating sleep fragmentation, may be insufficient to counteract BP elevation. By extension, cardiovascular tools estimating sleep fragmentation, including PTT, are potentially useful to assess therapeutic interventions intended to reduce sleep fragmentation in the presence of sleep disorders.

In summary, sleep fragmentation and indices of sympathetic activation were associated with elevated systolic BP and higher risk of systolic hypertension in a large population of elderly volunteers. This result was independent of the influence of SDB, hypoxaemic load, sex, BMI, diabetes, hypercholesterolaemia, and self-reported sleep duration and quality. The proposal is that increased sympathetic activity is maintained during the diurnal period, contributing to BP elevation and hypertension. Furthermore, pulse transit time, a simply measured ambulatory parameter, can be used in an epidemiological approach to assess sympathetic sleep fragmentation, and would be useful in clinical practice for predicting hypertension risk in the elderly.

### Funding

This study was supported by a grant from the French Ministry of Health (PHRC 1998 and PHRC 2002).

### Conflict of interest

None declared.

### References

1. Joyner MJ, Charkoudian N, Wallin BG. Sympathetic nervous system and blood pressure in humans: individualized patterns of regulation and their implications. Hypertension 2010;56:10–16.
2. Young T, Peppard P, Palta M, Ha KM, Finn L, Morgan B, Skatrud J. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Arch Intern Med 1997;157:1746–1752.
3. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897–1904.
Spicuzza L, Bernardi L, Calcitai A, Di Maria GIU. Autonomic modulation of heart rate during obstructive versus central apneas in patients with sleep-disordered breathing. Am J Respir Crit Care Med 2003;167:902–910.

Griefahn B, Brode P, Marks A, Basner M. Autonomic arousals related to traffic noise during sleep. Sleep 2008;31:569–577.

Choufour F, Pichot V, Perchet C, Legrain V, Garcia-Larrea L, Roche F, Bastuji H. Autonomic pain responses during sleep: a study of heart rate variability. Eur J Pain 2011;15:554–560.

Sforza E, Jouzy C, Ibanez V. Time-dependent variation in cerebral and autonomic activity during periodic limb movements in sleep: implications for arousal mechanisms. Clin Neurophysiol 2002;113:883–891.

Huynh N, Kato T, Rompire PH, Okura K, Saber M, Lanfranchi PA, Montplaisir JY, Lavige G. Sleep bruxism is associated to micro-arousals and is an increase in cardiac sympathetic activity. J Sleep Res 2006;15:339–346.

Chaicharn J, Carrington M, Trinder J, Khoo MC. The effects on cardiovascular autonomic control of repetitive arousal from sleep. Sleep 2008;31:93–103.

Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. Sleep 2009;32:589–597.

Wing YK, Zhang J, Ho CK, Au CT, Li AM. Periodic limb movement during sleep is associated with nocturnal hypertension in children. Sleep 2009;32:579–585.

Batool-Anwar S, Malhotra A, Forman J, Winkelman J, Li Y, Gao X. Restless legs syndrome and hypertension in middle-aged women. Hypertension 2011;58:791–796.

Haralabis AS, Dimakopoulou K, Vigna-Taglianti F, Giampolo M, Borgini A, Dudley ML, Pershanen G, Bluhm H, Houthujs D, Babich W, Velanakis M, Katsouyanni K, Jarup L. Acute effects of night-time noise exposure on blood pressure in populations living near airports. Eur Heart J 2008;29:658–664.

Zou D, Grotte L, Radiinski J, Edler DN, Lindblad U, Hedner J. Nocturnal pulse wave attenuation is associated with office blood pressure in a population based cohort. Sleep Med 2009;10:836–843.

Smith RP, Argjol J, Pepin JL, Levy PA. Pulse transit time: an appraisal of current clinical applications. Thorax 1999;54:452–457.

Pitsou D, Chinea N, Kipnis S, Van Herwaaden M, Stradling J. Changes in pulse transit time and pulse rate as markers of arousal from sleep in normal subjects. Clin Sci 1994;87:269–273.

Pepin JL, Delave N, Pin I, Deschaux C, Argjol J, Bost M, Levy P. Pulse transit time improves detection of sleep respiratory events and microarousals in children. Chest 2005;127:722–730.

Malik M, Bigger JT, Camm AJ, Kleiger RE, Malliani A, Turina M, Schwartz PJ. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17:354–381.

Barthelemy JC, Pichot V, Lagrange F, Celle S, Kerleroux J, Lacour JR, Roche F. Autonomic nervous system activity and sleep during periodic leg movements in sleep to hypertension, heart disease, and stroke. Sleep Med 2008;9:93–97.

Chouchou F, Pichot V, Dauphinoit V, Celle S, Laurent B, Lacour JR, Kossovsky M, Gaspoz JM, Roche F. Autonomic pain responses during sleep: a study of heart rate variability. Clin Neurophysiol 2008;119:554–560.

Stone KL. Decreased slow wave sleep increases risk of developing hypertension in elderly men. Hypertension 2011;58:596–603.

Jarup L, Babisch W, Houthujs D, Pershanen G, Katsouyanni K, Cadum E, Dudley ML, Sangviny P, Seiffert I, Swart W, Breugelmans O, Bluhm G, Selandar J, Haralabis A, Dimakopoulou K, Sourtzis P, Velanakis M, Vigna-Taglianti F. Hypertension and exposure to noise near airports: the HYENA study. Environ Health Perspect 2008;116:129–133.

Utberg J, Nyström B, Cato N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuro-psychiatric symptoms. Mov Disord 2001;16:1159–1163.

Morrell MJ, Fini L, Kim H, Peppard PE, Badr MS, Young T. Sleep fragmentation, awake blood pressure, and sleep-disordered breathing in a population-based study. Am J Respir Crit Care Med 2002;166:2091–2096.

Tamisier R, Gilmartin GS, Launois SH, Pepin JL, Nespoulet H, Thomas RJ, Levy P, Weiss J. A new model of chronic intermittent hypoxia in humans: effect on ventilation, sleep and blood pressure. J Appl Physiol 2009;107:17–24.

Roche F, Pepin JL, Achour-Crawford E, Tamisier R, Pichot V, Celle S, Maudoux D, Chouchou F, Assoumou HG, Levy P, Barthelemy JC, B, PROOF Study Group. At night, obstructive sleep apnoea is associated with elevated ambulatory blood pressure. Eur Respir J 2012;40:649–656.

Singh JP, Larson MG, Tsui H, Evans JC, O’Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: Insights into pathogenesis of the hypertension: the Framingham heart study. Hypertension 1998;32:293–297.

Grassi G. Sympathetic neural activity in hypertension and related diseases. Am J Hypertens 2010;23:1052–1060.

Bagnoli I. Sympathetic control of the circulation in hypertension: lessons from autonomic disorders. Curr Opin Nephrol Hypertens 2003;12:175–180.

Heusser K, Tank J, Engeli S, Driedrich A, Menne J, Eckert S, Peters T, Sweep FC, Haller H, Pichmaier AM, Luft FC, Jordan J. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. Hypertension 2010;55:619–626.

Hypertens Res. 2012. 35:373–377.

Schiffrin EL. Vascular smooth muscle growth and extracellular matrix deposition: Is there a role for the sympathetic nervous system? J Hypertens 2002;20:179–181.

DiBona GF. Sympathetic nervous system and the kidney in hypertension. J Clin Invest 2009;119:1058–1063.

Guyenet PG. The sympathetic control of blood pressure. Nat Rev Neurosci 2007;8:333–346.

Donadio V, Liguori R, Vetrueno R, Contini M, Elam M, Wallin BG, Karlsson T, Bugiardini E, Baruzzi A, Montagna P. Daytime sympathetic hyperactivity in OSAS is related to excessive daytime sleepiness. J Sleep Res 2007;16:327–332.

Lombardi F, Stein PK. Origin of heart rate variability and turbulence: an appraisal of autonomic modulation of cardiovascular function. Front Physiol 2011;2:95.

Marrin JM, Agusti A, Villar I, Forner M, Nieto D, Carriojo SJ, Bar PJ, Vicente E, Wei Y, Nieto FJ, Jelic S. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA 2012;307:2169–2176.

Norman D, Loredano J, Nelesen RA, Anciels-Israel S, Mills PJ, Ziegler MG, Dimsdale JE. Effects of continuous positive airway pressure versus supplemental oxygen on 24-hour ambulatory blood pressure. Hypertension 2006;47:840–845.