Sleep and Breathing (2019) 23:201–208
https://doi.org/10.1007/s11325-018-1683-x

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Arterial stiffness alteration and obstructive sleep apnea in an elderly cohort free of cardiovascular event history: the PROOF cohort study

Emilia Sforza[1] · Sandrine Millasseau[1] · David Hupin[1] · Jean-Claude Barthélémy[1] · Frédéric Roche[1]

Received: 2 September 2017 / Revised: 5 June 2018 / Accepted: 8 June 2018 / Published online: 26 June 2018

Abstract

Introduction Several studies suggest in middle-aged subjects a relationship between arterial stiffness, a cardiovascular risk marker, and moderate to severe obstructive sleep apnea (OSA). No extensive data are present in older subjects. This study explores this association in a sample of healthy older subjects suffering OSA.

Methods A total of 101 volunteers aged 75.3 ± 0.7 years were examined at the hospital sleep center. Each subject was assessed for medical history, body mass index and 24-h blood pressure measures, biological blood samples, and home polygraphy in 2002–2003 (P2) as well as in 2009–2010 (P4). Arterial stiffness was also assessed using carotid-femoral and carotid-radial pulse wave velocity (cfPWV and crPWV) during P4 examination.

Results The total group consisted of 59 women and 42 men with a mean apnea-hypopnea index (AHI) of 17.8 ± 12.1 and a mean oxygen desaturation index (ODI) of 9.8 ± 8.9. No-OSA (AHI < 15) represented 50% of the sample, and severe cases (AHI > 30) 17%. No significant differences had been founded between men and women for blood pressure, cfPWV, and crPWV. Considering the severity of the AHI, no significant differences between groups were present for PWV and blood pressure values. No difference for PWV was present for subjects with and without hypertension. No correlation was found between PWV value and AHI and ODI values at P2 or between P2 and P4 visits. cfPWV was higher in patients demonstrating incident hypertension during the follow-up.

Conclusions In this sample of older subjects, PWV is not affected by AHI and ODI but was associated with incident hypertension. These results may suggest potential protective and adaptive mechanisms in older sleep apnea patients.

Clinical trial registrations NCT 00759304 and NCT 00766584.

Keywords Obstructive sleep apnea · Elderly · Arterial stiffness · Hypertension

Abbreviations

AHI	apnea-hypopnea index
BMI	body mass index
CPAP	continuous positive airway pressure
HT	hypertension
HDL	high-density lipoprotein cholesterol
LDL	low-density lipoprotein cholesterol
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
P2	clinical visits of the cohort between 2002 and 2003
P4	clinical visits of the cohort between 2009 and 2010
PWV	pulse wave velocity
cfPWV	carotid-femoral pulse wave velocity
crPWV	carotid-radial pulse wave velocity
SaO_2	oxygen saturation
TRG	plasma triglycerides

Introduction

Obstructive sleep apnea (OSA) is a very common sleep-related disorder affecting 24% of men and up to 9% of women aged 30 to 60 years [1], with a greater prevalence in the elderly [2–4]. Several studies have proposed a direct causal relationship between OSA and hypertension (HT) [5], diabetes [6] as well as cardiovascular diseases [7]. Patients with OSA have a 1.5 times

✉ Frédéric Roche
frederic.roche@univ-st-etienne.fr

[1] Service de Physiologie Clinique et de l'Exercice, CHU Nord, Saint-Etienne, EA SNA EPIS 4607, Faculté de Médecine Jacques Lisfranc, Université de Lyon, Université Jean Monnet, 42023 Saint-Etienne, France

higher relative risk of all-cause mortality compared to patients without OSA with the same comorbidities [8]. Several mechanisms may be involved in OSA-related cardiovascular risk [8], including intermittent hypoxia, sympathetic activation, metabolic dysfunction, and inflammatory processes. Moreover, other factors may be considered such as endothelial dysfunction [9], vascular remodeling [10], accelerated progression of atherosclerosis [11], and cardiovascular disorders [12]. We know that arterial stiffness plays a key role in atherosclerosis [13, 14], with high arterial stiffness being associated with a higher risk of cardiovascular disorders [15]. While many methods exist to evaluate arterial stiffness, pulse wave velocity (PWV) is the one the most worldwide recommended.

Recent data stress the role of PWV as an emerging cardiovascular risk marker implicated in heart and vascular complications of OSA [16–20]. Moreover, it is now considered as an accepted independent predictor of cardiovascular morbidity and/or mortality [21, 22], particularly for patients having HT [23], diabetes [24], and in older adults [25].

Studies conducted so far on arterial stiffness and OSA were performed on middle-aged patients with moderate-to-severe OSA syndrome. Since prevalence of OSA increases with age, it would be interesting to examine if arterial stiffness is also elevated in elderly patients with OSA but otherwise healthy. The aims of the present study were three-fold: (1) assess if an association is present between arterial stiffness and OSA in a large group of older subjects with minimal health disease, homogenous for age and free of previous vascular diseases; and (2) establish which metabolic, vascular, or polygraphic factor might explain this association (3) to determine whether changes in the severity of sleep apnea over 7 years or the onset of hypertension are associated with an alteration in the pulse wave velocity.

Methods

Subjects

The study population was recruited from the PROOF (PROgnostic indicator OF cardiovascular and cerebrovascular events) cohort [26], a longitudinal population-based cohort study. The PROOF study recruitment consists in 1011 volunteers aged ≥65 years and living in the city of Saint-Etienne (France) between 1998 and 2001. The methods of the baseline and follow-up assessments in the PROOF and SYNAPSE (a sub-study focusing on sleep disorders) studies have been described previously [27]. Briefly, at inclusion, 1011 participants were examined with medical (face-to-face) interview and neurological and cardiological examinations. Three years later, an ancillary study (SYNAPSE) was performed to address the association between OSA and morbidity. To this end, ambulatory blood pressure monitoring, home polygraphic study, and vascular examination were performed between 2002 and 2003 (P2) followed by a 7-year follow-up to record cardiovascular and cerebrovascular morbidity (P4: 2009–2010). Only 854 participants aged 68.0 ± 0.9 years accepted to participate to the SYNAPSE ancillary study while the study was proposed to the whole group. At the study entry, subjects did not have myocardial infarction history, cardiac arrhythmias, pacemaker, stroke, any diagnosed neurological and psychiatric disease, type 1 diabetes, and chronic obstructive pulmonary disease as assessed by clinical, biological, and instrumental measures. At the third evaluation, 275 participants refused polygraphy, while 519 accepted respiratory examination. The fourth (P4) evaluation allowed us the examination of 374 participants. At this point, reasons for the following lose were as follows: death (8.8%), end of participation (10%), relocation out of Saint Etienne town (6.5%), starting continuous positive airway pressure therapy (CPAP) (4.4%), and refusal of nocturnal polygraphy (24.6%). For the current study, only subjects with full clinical evaluation, blood samples to assess metabolic dysfunctions, vascular examination including ambulatory blood pressure at P2 and P4, and arterial stiffness measurement (realized at P4 only for logistical reasons) were considered. The final group consisted of 101 subjects aged 75.3 ± 0.7 years (59 women and 42 men).

The University Hospital and the local Ethics Committee (CCPRB Rhone-Alpes Loire) approved the PROOF as well as the SYNAPSE Study. The National Committee for Information and Liberty (CNIL) gave also at this time consent for data collection. All subjects gave their written consent prior to participation in the study.

Detailed clinical assessment was focused on cardiovascular and cerebrovascular diseases, HT, diabetes, dyslipidemia, and self-report medications and medical prescription. Smoking and habitual alcohol intake (more than 40 g of alcohol consumed per day on average) were self-reported. Subjects were recognized as "normotensives" when they did not report any history of HT or antihypertensive medication or did not show a mean systolic blood pressure > 135 mmHg and a mean diastolic pressure > 85 mmHg on ambulatory blood pressure monitoring.

All medications were not discontinued during the study. Height and weight were measured, and body mass index (BMI) calculated as weight/height squared (kg/m^2).

Measurement of metabolic risk factors

Blood was collected the morning after at-home polygraphic recording. Glycemia, total cholesterol, high-density lipoprotein cholesterol (HDL), calculated low-density lipoprotein cholesterol (LDL), and triglycerides (TRG) were then assessed (Roche Diagnostics).

Normal ranges for those parameters were set as follows: serum TRG (< 1.5 g/L), serum cholesterol (< 2 g/L), serum LDL (< 1.60 g/L), serum HDL (< 0.40 g/L), serum glycemia (0.70–1.05 g/L).

Measurement of arterial stiffness

Arterial stiffness was determined during daytime by carotid-femoral pulse wave velocity (cfPWV) and carotid-radial PWV (crPWV) with a Complior device (Alam Medical, St Quentin Fallavier, France). PWV was determined from the time taken by the pulse wave generated by the contracting heart to travel between two arterial sites. This measure provides information about the mechanical arterial system proprieties. Higher PWV, a marker of higher arterial stiffness, corresponds to lower great vessel distensibility and compliance. Three pulse transducers were fixed on the skin over the right common carotid artery, over the radial artery, and over the femoral artery. The Complior device automatically measured the time delay between the feet of the simultaneous recorded pulse waves and averaged over 10 consecutive cycles. Carotid-femoral (cf PWW) and carotid-radial PWW (crPWW) were then calculated as the direct surface distance between arterial site measurements divided by the time delay. A PWV > 12 m/s was defined as higher than a normal value [28]. Reference values were also used according to standard criteria [29].

Ambulatory home polygraphy

Ambulatory night recording was done using a polygraphic system (HypnoPTT, Tyco Healthcare, Puritan Bennett, USA) allowing measurement of tracheal sounds, of 1 lead electrocardiography allowing pulse transit time measurement, of nasal pressure and respiratory efforts as well as the determination of body position. Oxygen saturation (SaO_2) was also measured using pulse oximetry. All subjects completed the St. Mary's Hospital questionnaire to minimize potential overestimation of sleep duration. All recordings were manually scored after visual inspection for respiratory events and nocturnal SaO_2 according to the Chicago criteria [30]. Hypopnea was defined as a 50% or greater reduction in airflow from the baseline value lasting ≥ 10 s and associated with at least 3% oxygen desaturation and apnea was validated in the absence of airflow on the nasal cannula lasting for ≥ 10 s. A progressive increase in pulse transit time and respiratory efforts allowed definition of an obstructive episode. The absence of rib cage movements associated with validated apnea defined a central event. The apnea-hypopnea index (AHI) was calculated as the average number of apneas and hypopneas per hour of recording. Nocturnal hypoxemic load was evaluated according to the following: mean SaO_2, percentage of time spent with a $SaO_2 \leq 90\%$; minimum SaO_2 recorded during sleep (minimum SaO_2) as well as oxygen desaturation index (ODI: number of episodes/h with a SaO_2 level fell by 3% or more). Autonomic respiratory-related and total autonomic arousal indices were calculated using pulse transit time monitoring after visual correction. An AHI > 15 with at least 50% of events scored as obstructive was considered diagnostic of OSA and subjects were subsequently stratified as no-OSA (AHI < 15), mild-to-moderate (15 ≥ AHI < 30), and severe (AHI ≥ 30) [31].

Statistical analysis

The results are presented percentages for categorical variables and as mean ± SD for continuous variables. Statistical significance was assessed by Student's t test for continuous variables as well as by Chi-square test for categorical variables. ANOVA was used to assess differences between no-OSA, mild-to-moderate, and severe OSA. Statistical significance was set at $p \leq 0.05$. Pearson's correlation coefficient was done to assess the potential factors explaining the PWV values, i.e., BMI, AHI, indices of hypoxemia, autonomic activation, HT, and metabolic values. The same type of analysis was done to test the relationship between the PVW at P4 and the evolution of the polygraphic parameters (evolution in 7 years of the AHI, the ODI, the average SaO2, and the time passed under 90%). Finally, a comparison of PVW was made between patients still normotensive at P4 and hypertensive treated patients or newly diagnosed ones at P4. Data had been analyzed using the Statistical Package for the Social Sciences version 17 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Clinical or anthropometric, metabolic, and polygraphic data for the general population at the 7-year follow-up visit are shown in Table 1. The group consisted of 101 subjects (58% women) with a mean age of 75.3 ± 0.7 years. Type 2 diabetes was found in 7% of cases, dyslipidemia in 28%, HT in 67%, smoking in 4%, and taking alcohol in 42%. As per the study design, no patient had history of cardiovascular events. For the total group, the mean AHI was 17.8 ± 12.1, the mean ODI 9.8 ± 8.9, and the mean autonomic activation 13.3 ± 9.5. As expected, men had higher BMI as well as the proportion of subjects taking alcohol regularly. AHI and ODI were also significantly higher in men. Men had a higher prevalence of HT without significant difference in cfPWV and crPWV (Table 2).

Table 3 reports polygraphic as well as metabolic data for subjects stratified according to AHI. No-OSA subjects (AHI < 15) represented 50% of the population, 33% demonstrated mild-to-moderate OSA (≥ 15AHI < 30), and OSA was severe in 17% (AHI ≥30). Comparison analysis did not reveal any significant difference between subgroups. When we

Table 1 Clinical, anthropometric, metabolic, and polygraphic data for the whole group and for women and men separately (mean ± SD)

	Total ($n = 101$)	Women ($n = 59$)	Men ($n = 42$)	p
Age (year)	75.3 ± 0.7	75.3 ± 0.7	75.4 ± 0.8	ns
BMI (kg/m^2)	25.7 ± 7.8	24.6 ± 6.7	27.3 ± 9.0	0.005
Diabetes (%)	7	6	8	ns
Dyslipidemia (%)	28	32	22	0.01
Alcohol (%)	42	30	59	0.005
Smoking (%)	4	4	5	ns
AHI (n/h)	17.8 ± 12.1	15.4 ± 11.0	20.7 ± 13.20	0.03
ODI (n/h)	9.8 ± 8.9	8.0 ± 7.3	12.9 ± 10.5	0.02
Time $SaO_2 < 90\%$ (%)	3.9 ± 6.9	4.1 ± 10.0	3.7 ± 9.2	ns
Minimal SaO_2 (%)	87.7 ± 5.0	87.9 ± 5.2	87.4 ± 4.9	ns
Respiratory AA index (n/h)	13.3 ± 9.5	12.0 ± 8.2	14.9 ± 10.8	ns

BMI body mass index, *AHI* apnea-hypopnea index, *ODI* oxygen desaturation index, *SaO2* oxygen saturation, *AA* autonomic activation, *ns* nonsignificant

P value: Student's *t* test or Chi-square differences between women and men

considered the vascular parameters (Table 4), no significant difference was found between groups for blood pressure and PWV values, except for greater prevalence of HT in severe OSA ($p = 0.01$). Carotid-radial and carotid-femoral distances ($p < 0.001$) were also higher in patients with AHI ≥ 30, despite similar BMI. To assess if the presence of HT could affect arterial stiffness values, an independent Student's *t* test was done between subjects with ($n = 60$) and without ($n = 41$) HT; again, no difference was found for respiratory variables and PWV values of the two arterial segments.

Pearson's correlation analysis did not reveal any association between PWV values and AHI, all indices of hypoxemia (ODI, time spent SaO2 < 90%, and minimal SaO2), blood pressure, BMI, and metabolic data. No significant association was found ($p > 0.05$) between crPWV or cfPWV values (P4) and delta (P4-P2) values of AHI (− 1.3 ± 1.8), ODI (− 0.8 ± 2.1), time $SaO_2 < 90\%$ (0.8 ± 0.9), or minimal SaO_2 (− 0.8 ± 0.6).

Among the normotensive subjects at P2 ($n = 64$), 29 became hypertensive at P4 (25 treated for clinical hypertension and 4 found hypertensive after ambulatory blood pressure measurement). These new hypertensive patients ($n = 29$) had a higher cfPWV compared with still normotensive ($n = 34$) subjects (11.8 ± 2.0 vs 9.5 ± 2.1 m/s; $p < 0.05$). The difference observed between those patients did not reach significance level according to comparison of crPWV (10.3 ± 1.6 vs. 9.3 ± 1.8 m/s; p = ns).

Discussion

In our elderly population over 75 years with no history of cardiovascular events, we examined if there was an association between presence and also OSA severity and arterial stiffness. It is of note that no association was found between AHI and/or ODI and PWV in the elderly. Moreover, diabetes, dyslipidemia, BMI, did not contribute to PWV values. No difference in arterial stiffness values was present between subjects without and with OSA and for mild-moderate and severe OSA cases. Furthermore, the alteration over 7 years of follow up of the respiratory sleep-related disorders parameters did not influence PWV. These results might suggest possible physiological changes in vascular reactivity related to aging. Here, we found a higher carotid-femoral pulse wave velocity in "incident hypertensive patients" compared with still normotensive subjects well reflecting a proper impact of arterial hypertension on arterial elasticity including in the elderly as founded by others.

Several studies performed on clinical OSA populations showed an increase in cfPWV with OSA severity reversed by CPAP [32, 33]. Elevated PWV has also been associated to increased left ventricular afterload, ventricular hypertrophy [34], and impaired coronary perfusion [35], which seems to be reversed by CPAP [36]. However, other studies showed inconsistent results regarding the relationship between OSA with changes in PWV. This is probably related to differences in the examined population, in sample size, and the absence of evaluation of other factors (obesity and metabolic factors for example). In a 7.7-year longitudinal meta-analysis of 15,877 subjects [37], the predictive ability of cfPWV was higher in young patients and in subjects with higher cardiovascular risk factors at baseline such as hypertension, diabetes, renal diseases, and coronary vascular diseases. In the study of Wang et al. [38], a meta-analysis considering 736 patients with OSA and 424 healthy participants was done; they found that OSA patients had higher PWV compared to controls, but again only in moderate to severe cases. Similar results were reported by a recent French meta-analysis involving 901 participants [39] in which the authors did not find any association between PWV

Table 2 Vascular and arterial stiffness data for the total group and for women and men (mean ± SD)

	Total	Women	Men	*p*
Baseline SBP (mmHg)	131.5 ± 16.4	129.3 ± 16.6	134.9 ± 15.7	ns
Baseline DBP (mmHg)	85.1 ± 14.6	85.9 ± 14.6	83.9 ± 14.6	ns
SBP 24 h (mmHg)	115.5 ± 11.8	115.5 ± 12.3	116.2 ± 11.2	ns
DBP 24 h (mmHg)	85.7 ± 7.9	85.5 ± 8.1	86.0 ± 7.7	ns
HT (%)	67	62	73	0.01
Carotid-radial PWV (m/s)	9.9 ± 1.5	9.7 ± 1.5	10.2 ± 1.5	ns
Carotid-femoral PWV (m/s)	11.7 ± 2.6	11.7 ± 2.9	11.6 ± 2.3	ns
Carotid-radial distance (mm)	650.2 ± 41.8	632.4 ± 33.5	675.2 ± 39.5	< 0.001
Carotid femoral distance (mm)	622.1 ± 43.1	602.4 39.7	649.8 ± 1.1	< 0.001
Carotid-radial transit time (ms)	66.3 ± 9.6	63.2 ± 3.4	67.5 ± 3.9	ns
Carotid-femoral transit time (ms)	55.1 ± 12.1	57.9 ± 7.9	58.8 ± 9.1	ns

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HT* hypertension, *PWV* pulse wave velocity, *ns* nonsignificant

P value: Student's *t* test or Chi-square differences between women and men

and AHI and ODI, obesity, with age and clinical blood pressure being the most important contributors. Bruno and coworkers [40] found that a significantly higher PWV was present only in patients cumulating OSA and associated cardiovascular risk. It appears in our population that incident hypertension (treated or not) is associated with an alteration of the aortic elasticity measured by the velocity of the pulse wave between the carotid and the femoral arteries.

The assessment of cofactors contributing to increased cardiovascular risk in OSA represents an interesting background, particularly in older subjects in whom the presence of OSA increases with age in parallel with an increase in metabolic dysfunction, obesity, and HT. The most interesting finding of our study is the lack of association between arterial stiffness and OSA, neither AHI nor ODI correlated with PWV. In addition, potential cofactors of vascular risk, i.e., diabetes, dyslipidemia, obesity, alcohol intake, and smoking, did not affect PWV and were not correlated with indices of OSA severity. We must remind that intermittent nocturnal hypoxemia, more than AHI, plays a key role in the occurrence of cardiovascular consequences via inflammatory pathway activation, increased sympathetic tone, and impaired endothelium-dependent vasodilatation [41]. In our sample, the severity of hypoxemia was low, a finding that may suggest the interference of protective and adaptative mechanisms to reduce vascular morbidity and mortality in elderly OSA [42].

Our study has methodological strengths: the relatively large number of participants, an important proportion of women, the inclusion of biological analysis, the use of the reference tool to assess arterial stiffness, and the absence of major metabolic and vascular disease that may affect PWV measurement. We should remind that differences with previous studies in middle-aged patients might be related to differences in the definition of AHI threshold

Table 3 Clinical, anthropometric, metabolic, and polygraphic data for the three groups of subjects stratified according to the apnea-hypopnea index (mean ± SD)

	No-OSA (*n* = 50)	≥ 15AHI < 30 (*n* = 33)	AHI > 30 (*n* = 18)	*p*
BMI (kg/m ^{2})	25.7 ± 8.0	25.1 ± 7.0	27.1 ± 9.0	ns
Diabetes (%)	7	6	8	ns
Dyslipidemia (%)	28	32	22	0.01
Alcohol (%)	42	30	59	0.005
Smoking (%)	4	4	5	ns
AHI (n/h)	7.5 ± 3.5	22.2 ± 4.5	37.2 ± 7.0	< 0.001
ODI (n/h)	4.0 ± 2.5	10.8 ± 4.3	24.1 ± 10.1	< 0.001
Time SaO_2 < 90% (%)	2.0 ± 7.7	4.4 ± 9.5	8.5 ± 12.9	0.041
Minimal SaO_2 (%)	89.4 ± 4.6	87.4 ± 4.9	83.6 ± 4.1	< 0.001
Respiratory AA index (n/h)	8.6 ± 4.7	14.3 ± 8.0	25.2 ± 11.9	< 0.001

BMI body mass, *AHI* apnea-hypopnea index, *ODI* oxygen desaturation index, *SaO2* oxygen saturation, *AA* autonomic arousal, *ns* nonsignificant. *P* value: ANOVA

Table 4 Vascular and arterial stiffness data for no-OSA, mild-moderate, and severe OSA cases (±SD)

	No-OSA < 15	> 15AHI < 30 9)	AHI > 30	*P*
Baseline SBP (mmHg)	129.1 ± 13.3	129.6 ± 14.5	128.3 ± 11.5	ns
Baseline DBP (mmHg)	75.5 ± 11.8	76.9 ± 7.0	77.9 ± 6.3	ns
SBP 24 h (mmHg)	115.5 ± 11.8	115.0 ± 12.3	116.2 ± 11.2	ns
DBP 24 h (mmHg)	85.7 ± 7.9	85.4 ± 8.1	86.0 ± 7.7	ns
HT (%)	67	62	73	0.01
Carotid-radial PWV (m/s)	9.9 ± 1.5	9.7 ± 1.5	10.2 ± 1.5	ns
Carotid-femoral PWV (m/s)	11.7 ± 2.6	11.6 ± 2.9	11.6 ± 2.3	ns
Carotid-radial distance (mm)	650.2 ± 41.8	632.4 ± 33.6	675.2 ± 39.5	< 0.001
Carotid femoral distance (mm)	622.1 ± 43.1	612 ± 31.0	655.2 ± 38.0	< 0.001
Carotid-radial transit time (ms)	66.3 ± 9.6	63.2 ± 3.4	67.5 ± 3.9	ns
Carotid-femoral transit time (ms)	55.1 ± 12.1	57.9 ± 7.9	58.8 ± 9.1	ns

OSA obstructive sleep apnea, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HT* hypertension, *PWV* pulse wave velocity, *ns* nonsignificant. *P* value: ANOVA

to define OSA. If we applied the current guidelines proposed by American studies [1, 2] defining OSA by the presence of an AHI > 5, the majority of our subjects will be OSA subjects, with only 15 subjects having an AHI < 5 inducing an overestimation of the real OSA risk and a methodological bias. For this reason, we applied the recent published criteria [33] for older populations that allow a better description of the presence of OSA. The longitudinal nature of our study is also a highlight. Some limitations of the study need to be underlined. One limitation of the study is that we examined a group of elderly subjects with homogenous age and without major health disease that preclude the comparison with clinically older samples. Secondly, only about 10% of the original population was examined in the current study suggesting a survivorship bias that may have conferred risk protection in the subjects who were studied. Moreover, the PWV measurements were done during daytime, and only at the P4 examination, which is considered less sensitive than nocturnal measurements [18]. However, it is evident that nocturnal assessment is not possible when larger samples are considered.

Conclusion

In the present study, there was no association between PWV and OSA in a sample of elderly volunteers free of cardiovascular event history and with different degrees of sleep-disordered breathing. The low severity of nocturnal hypoxemia and the presence of potential protective mechanisms with aging might explain this lack of association. Large-scale longitudinal epidemiological studies in older subjects are now requested to confirm our results.

Acknowledgments The authors of this study would like to thank all the study participants and Delphine Maudoux for her help in data acquisition as well as Arnauld Garcin.

Funding French Minister of Health provided financial support in the form of PHRC 1998 and 2001 funding (funding of salaries and clinical research devices). The sponsor had no role in the design or conduct of this research.

Compliance with ethical standards

The University Hospital and the local Ethics Committee (CCPRB Rhone-Alpes Loire) approved the PROOF as well as the SYNAPSE Study. The National Committee for Information and Liberty (CNIL) gave also at this time consent for data collection. All subjects gave their written consent prior to participation in the study.

Conflicts of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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