

## RESEARCH ARTICLE

# Long-term variations of arterial stiffness in patients with obesity and obstructive sleep apnea treated with continuous positive airway pressure

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## Abstract

### Background

Obstructive sleep apnea (OSA) is associated with cardiovascular co-morbidities and mortality. Arterial stiffness is an independent predictor of cardiovascular risk and mortality, and is influenced by the presence of OSA and related comorbidities. There is a paucity of data regarding long-term evolution of arterial stiffness in CPAP-treated OSA patients. *We aimed to prospectively study long term PWV variations and determinants of PWV deterioration.*

### Methods

In a prospective obese OSA cohort, at time of diagnosis and after several years of follow-up we collected arterial stiffness measured by carotid-femoral pulse wave velocity (PWV), clinical and metabolic parameters, and CPAP adherence. *Univariate and multivariate analyses were performed in order to determine contributing factors.*

### Results

Seventy two OSA patients (men: 52.8%, median age: 55.8 years and median BMI of 38.5 kg/m<sup>2</sup>) with a prevalence of hypertension: 58.3%, type 2 diabetes: 20.8%, hypercholesterolemia: 33.3%, current or past smoking: 59.7%, were evaluated after a median follow-up of 7.4 [5.8; 8.3] years. Over the period of follow-up, the median increase in PWV was 1.34 [0.10; 2.37] m/s. In multivariate analysis, the increase in PWV was associated with older age (10 extra years was associated with a 5.24 [1.35; 9.12] % increase in PWV) and hypertension (a significant increase in PWV of 8.24 [1.02; 15.57] %). No impact of CPAP adherence on PWV evolution was found.

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**Competing interests:** LM. Galerneau, S. Bailly, I. Jullian-Desayes, M. Joyeux-Faure, M. Benmerad, MR. Bonsignore have no conflict of interest.

**Abbreviations:** AHI, apnea-hypopnea index; BP, Blood pressure; BPV, BP variability; COPD, chronic obstructive pulmonary disease; CPAP, Continuous positive airway pressure; ESS, Epworth Sleepiness Scale; FEV1, Forced Expiratory Volume in the first second of forced expiration; FVC, Forced Vital Capacity; hsCRP, high-sensitivity C-reactive protein; OSA, Obstructive sleep apnea; PWV, Pulse wave velocity; SaO<sub>2</sub>, Mean nocturnal oxygen saturation; TLC, Total lung capacity.

## Conclusion

PWV progression in CPAP-treated OSA patients is mainly related to pre-existing cardio-metabolic comorbidities and not influenced by CPAP adherence. In this high cardiovascular risk population, it is crucial to associated weight management and exercise with CPAP treatment.

## Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete obstruction of the upper airway during sleep, resulting in chronic intermittent hypoxia and sleep fragmentation. OSA is highly prevalent in obese patients with cardio-metabolic comorbidities. [1] The association between OSA and cardiovascular diseases has been clearly demonstrated, OSA being considered as an independent risk factor for cardiovascular and metabolic co-morbidities and mortality. [2–4] Continuous positive airway pressure (CPAP), the first line therapy for OSA, was reported to reduce the incidence of late cardiovascular events in patients with severe OSA in cohort observational studies. [5] However, in the largest recent randomized controlled trials, CPAP treatment did not reduce mortality or the occurrence of late cardiovascular events in intention to treat analyses. [6,7]

Arterial stiffness is an early independent predictor of cardiovascular risk and secondary occurrence of late incident cardiovascular events. [8–10] The gold standard measure of arterial stiffness is carotid-femoral pulse wave velocity (PWV). [11–13] A 1m/s increase in pulse wave velocity is associated with a 15% increase in mortality independently of other usual cardiovascular risk factors. Arterial stiffness has been suggested as having a dose-response relationship with indices of OSA severity. [8,14–16]

Arterial stiffness increases with age and blood pressure levels (BP); [17] and is linked with chronic conditions such as metabolic syndrome, [18] diabetes, [19] or chronic obstructive pulmonary disease (COPD). [20] All these conditions, which contribute to the lifelong increase in arterial stiffness, are highly prevalent in OSA patients. [21] The deterioration in arterial stiffness over time is sustained by intermediary mechanisms such as sympathetic over-activity, endothelial dysfunction, oxidative stress and systemic inflammation that are enhanced by OSA. [12,22]

There remains a debate regarding improvement in arterial stiffness under CPAP treatment. A recent meta-analysis [11] suggested an improvement but data were obtained from non-randomized studies assessing short term CPAP interventions with small sample sizes. [11,14] To date, no study has reported long term variations of arterial stiffness in CPAP-treated OSA patients. The goal of the current study was to prospectively assess the changes in PWV and their determinants in OSA patients treated by CPAP for at least four years (median duration of follow-up 7.5 years).

## Materials and methods

### Design and study population

Obese patients referred for sleep apnea to the Sleep department of Grenoble Alpes University Hospital between 2007 and 2010 were included in a prospective cohort study. These patients were re-examined after at least 4 years of CPAP treatment, with cardio-metabolic assessments including arterial stiffness. Hypertension was defined following the ESC/ESH guidelines. [23]

At inclusion, patients were aged from 20 to 75 years with a body mass index (BMI)  $> 30$  kg/m<sup>2</sup>. Patients with central apnea were excluded.

The study was conducted in accordance with good clinical practice requirements in Europe, French law, ICH E6 recommendations, and the Helsinki Declaration (1996 and 2000). The protocol was approved by an independent Ethics Committee (Comité de Protection des Personnes, Grenoble, France, IRB0006705) and registered on the ClinicalTrials.gov site (NCT02623088). All patients gave their written informed consent.

### Sleep study and sleepiness assessment

Overnight polysomnography (PSG) was used to diagnose OSA and characterize severity. [24–26] The apnea-hypopnea index (AHI) was calculated as the number of apnea and hypopnea events per hour of sleep. Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS). [27] Mean nocturnal oxygen saturation (SaO<sub>2</sub>) and time spent under 90% of SaO<sub>2</sub> were also collected in order to characterize sleep apnea severity. Overnight sleep studies were scored according to international guidelines. [28]

### Arterial stiffness assessment

Carotid-femoral PWV, a validated measure of arterial stiffness, was assessed for each patient [12,13] using a Complior device (Alam Medical<sup>®</sup>, France). [29] Carotid-femoral PWV is the ratio on distance to transit time between two pressure waves recorded transcutaneously at carotid and femoral arterial sites. The distance travelled by the pulse wave was measured with an external tape-measure across the body surface. For the 30 min-long PWV measurements the subject was fasted and rested and in an elongated supine position. Two electrodes were placed one on the carotid artery and the other on the femoral artery until a quality signal was obtained, characterized by a clear rise of the systolic curve and a smooth diastolic curve for at least 10 seconds. At least two PWV measurements were systematically done. The mean value between the two measurements was retained if the difference between measurements was less than 0.5 m/s. When the difference was above 0.5 m/s, a third measurement was made and the median value of the three measurements was used.

### Metabolic and inflammatory biomarkers

On waking, after 10 hours fasting, a peripheral blood sample was drawn. Fasting glucose, HbA1c, serum insulin, lipids, and high-sensitivity C-reactive protein (hsCRP) levels were measured using standard procedures.

### Respiratory function

Arterial blood gas measurements and pulmonary function tests (measured using Medisoft<sup>®</sup> devices) were performed. Significant airway obstruction was defined as FEV<sub>1</sub>/FVC  $< 70\%$ , according to standard definitions. [30]

### CPAP treatment

According to French and international recommendations, [31] patients with moderate or severe OSA were treated with CPAP. [2,32] Adherence was defined as a mean CPAP use of at least 4 hours per night. [33] CPAP adherence used for data analysis was corresponding to objective compliance measured in the 3 to 6 months preceding follow-up visit.

## Follow-up

After 4 to 9 years of follow-up, new measurements of the same parameters as at baseline were done, except for PSG.

## Statistical analysis

Statistical analyses were performed with SAS v9.4 software (SAS Institute Inc., Cary, NC, United States). A p-value < 0.05 was considered as significant. Continuous data are presented as median and interquartile range (IQR) and categorical data as frequency and percentage. A comparison of the main quantitative variables at baseline and at follow-up was performed using a non-parametric Mann-Whitney test. A non-parametric Wilcoxon signed-rank test was used to compare the PWV before and after CPAP use. Due to the non-normality of PWV values, a log-transformation was performed and a log-linear mixed effect model with a patient random effect adjusted for the delay between the two measurements was used to analyze the evolution in arterial stiffness. A univariate analysis between PWV and potentially contributing factors was performed to select variables for the multivariate model. Variables with a p-value less or equal to 0.20 were retained and introduced into the multivariate analysis in association with predefined clinically relevant variables. Adjustment for age, sex and CPAP treatment. Due to the log transformation of the PWV, the final estimate presented in the multivariate analysis corresponded to 100\*Beta (where beta was a parameter of the log-linear model and can be directly interpreted as the percent of increase or decrease in the PWV at follow-up). Due to the low number of missing values, a simple imputation method was used to impute missing data: quantitative variables were imputed using the median and qualitative variables were imputed using the most frequent value.

## Results

### Patient characteristics

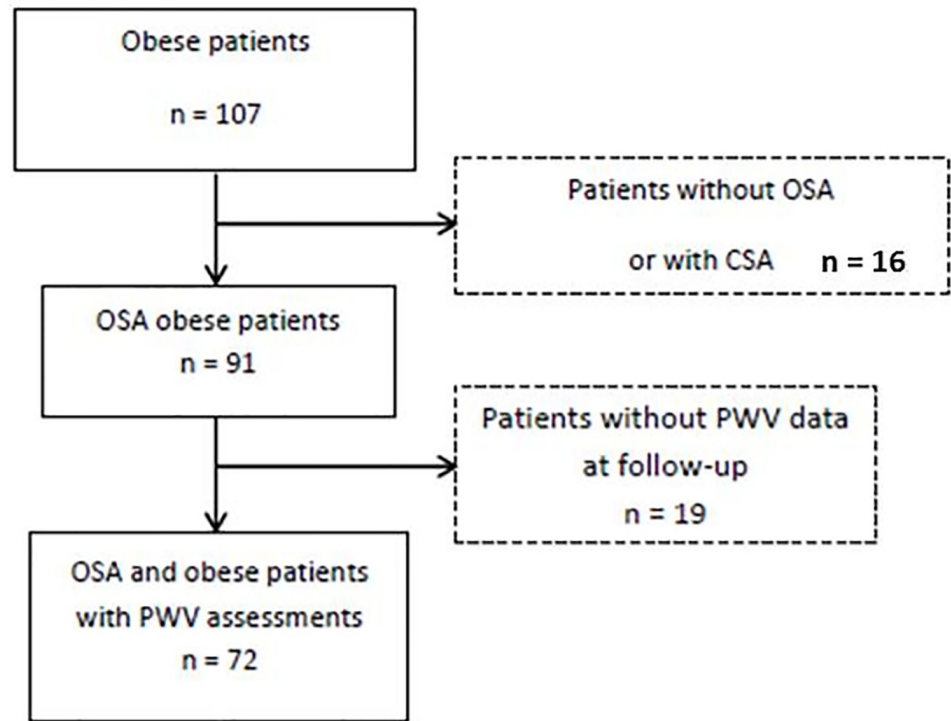
As shown in the study flowchart ([Fig 1](#)), 107 obese patients were initially included in this prospective cohort. Among them, 91 were followed and treated for OSA and for 72 patients PWV was reassessed at long-term.

At inclusion, patients had a median age of 55.8 [47.4; 62.0] years, 52.8% were men, with a median (IQR) BMI of 38.5 [35.4; 43.1] kg/m<sup>2</sup>. Median (IQR) AHI at diagnosis was 36.1 [23.3; 75.2] events/hour. Patients with hypertension (58.3%), had type 2 diabetes (20.8%) and were current or former smokers (59.7%). Baseline data concerning medical history, comorbidities, arterial blood gases, biological parameters, sleep studies and pulmonary function tests are shown in [Table 1](#). The comparison between imputed and non-imputed datasets is available in [S1 Table](#) of the online supplement.

### Follow-up

The median duration of follow-up was 7.5 years. At baseline, the median value of PWV was 9.7 m/s. At the follow-up PWV assessment, the median value was 10.5 m/s corresponding to a median increase of 1.34 m/s over the follow-up period. There was a significant difference of PWV between and after CPAP use (p<0.01).

CPAP adherence of at least 4 hours/night was recorded for 72% of the patients and the median adherence to CPAP was 6.4 [5.1; 7.5] hours per night ([Tables 2 & 3](#)). The medications being used at the time of the follow-up visit are shown in [S2 Table](#) of the online supplemental material.



**Fig 1. Study flow chart.** CSA, central sleep apnea; OSA, obstructive sleep apnea; PWV, pulse wave velocity.

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## Determinants of arterial stiffness deterioration

**Univariate analysis.** A ten year increase in age was associated with a 7.36% increase in PWV ( $p < 0.01$ ). High blood pressure at baseline was associated with a 12.63% increase in PWV compared to normotensive patients ( $p < 0.01$ ) and having diabetes was associated with a 13.75% increase in PWV compared to patients without diabetes ( $p < 0.01$ ). There was no association between changes in PWV results over the years and BMI or indices of OSA severity at baseline. CPAP adherence was not linked to change in PWV. (Fig 2).

**Multivariate analysis.** After adjustment for follow-up duration, age, gender, hypertension, diabetes, COPD, and CPAP adherence PWV was shown to increase significantly more in CPAP-treated OSA patients with hypertension ( $p = 0.03$ ). A trend close to significance was apparent for type 2 diabetic patients ( $p = 0.08$ ) and with airway obstruction ( $p = 0.11$ ). The multivariate analysis did not demonstrate a long-term impact of CPAP adherence on PWV evolution ( $p = 0.54$ ). (Fig 3).

## Discussion

To our knowledge, this is the first study assessing long-term variations (median follow-up 7.5 years) of arterial stiffness in obese OSA CPAP-treated patients. During this period, the median PWV increase under CPAP was 1.34 m/s. In multivariate analysis, PWV progression was significantly dependent of age and hypertensive status. Neither indices of OSA severity at diagnosis nor CPAP adherence contributed significantly to the long-term trajectory of arterial stiffness.

Sleep apnea is known to impact vascular age. [14,34,35] We should compare our obese OSA population (median age 55 years) to the same age group in the general population, they

**Table 1. Study population characteristics at baseline.**

| <b>Anthropometric and biological characteristics</b>                  |                  |
|---|------------------|
| Age, (years)  | 55.8 [47.4–62]   |
| Men   | 38 (52.8)        |
| BMI, (kg/m <sup>2</sup> )   | 38.5 [35.4–43.1] |
| Hypertension, n (%)   | 42 (58.3)        |
| Stroke, n (%)   | 3 (4.2)          |
| Diabetes mellitus, n (%)  | 15 (20.8)        |
| Hypercholesterolemia, n (%)   | 24 (33.3)        |
| Smoking, n (%)  | 40 (59.7)        |
| SBP, (mmHg)   | 132 [122–140]    |
| DBP, (mmHg)   | 79.5 [70–85]     |
| HbA1c, (%)  | 5.8 [5.5–6.3]    |
| Fasting blood Glucose, (mmol/l)                                       | 5.7 [5.3–6.2]    |
| Insulinemia, (μU/ml)  | 8.7 [6.4–13.3]   |
| hsCRP, (mg/l)   | 4.2 [2.1–8.9]    |
| <b>Respiratory function</b>   |                  |
| FVC, (% of predicted value)   | 99 [84–106]      |
| FEV <sub>1</sub> , (% of predicted value)                             | 92 [82–103]      |
| FEV <sub>1</sub> / FVC, (%)   | 80.6 [75.5–84.1] |
| FEV <sub>1</sub> / FVC < 70%, n (%)                                   | 7 (10.1)         |
| TLC, (% of predicted value)   | 103.5 [96.5–114] |
| PaCO <sub>2</sub> , (kPa)   | 5.3 [5–5.6]      |
| PaO <sub>2</sub> , (kPa)  | 10.2 [9.6–11.2]  |
| <b>Sleep disordered breathing</b>                                     |                  |
| Epworth Sleepiness Scale  | 12 [8–16]        |
| AHI, (/hour)  | 36.1 [23.3–75.2] |
| Mean nocturnal SpO <sub>2</sub> , (%)                                 | 92 [89–94]       |
| Sleep time spent with SpO <sub>2</sub> < 90%, (% of total sleep time) | 11 [2–43]        |
| <b>PWV (m/s)</b>  | 9.7 [8.5–10.7]   |

Categorical variables are expressed as a percentage and quantitative variables as the median (IQR). AHI, apnea hypopnea index; BMI, body mass index; DBP, diastolic blood pressure; FEV<sub>1</sub>, Forced Expiratory Volume of the first second of forced expiration; FVC, Forced Vital Capacity; HbA1c, Glycated hemoglobin; PaCO<sub>2</sub>, partial pressure of carbon dioxide; PaO<sub>2</sub>, partial pressure of oxygen; PWV, Pulse Wave Velocity; SBP, systolic blood pressure; SpO<sub>2</sub>, oxygen saturation; TLC, Total lung capacity.

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**Table 2. Data at the follow-up PWV assessment.**

|  |                  |
|--|------------------|
| Follow-up time, (years)                                  | 7.5 [5.8–8.3]    |
| PWV, (m/s)   | 10.5 [9.6–12.7]  |
| Patients adherent to CPAP, n (%)                         | 52 (72.2)        |
| Adherence to CPAP, (hours per night)                     | 6.4 [5.1–7.5]    |
| PWV increase during the complete follow-up period, (m/s) | 1.34 [0.10–2.37] |
| PWV increase per year, (m/s per year)                    | 0.19 [0.01–0.36] |

Categorical variables are expressed as percentage and quantitative variables as median (IQR). PWV, Pulse Wave Velocity.

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**Table 3. Comparison between baseline and follow-up values.**

| Variable                 | Baseline          | Follow-up         | P    |
|--------------------------|-------------------|-------------------|------|
| BMI (kg/m <sup>2</sup> ) | 38.5 [35.4; 43.1] | 38.4 [34.3; 41.9] | 0.19 |
| SBP (mmHg)               | 132 [122; 140]    | 132 [122; 138]    | 0.44 |
| DBP (mmHg)               | 79.5 [70; 85]     | 74 [68; 81]       | <.01 |
| hsCRP (mg/l)             | 5.8 [5.5; 6.3]    | 5.9 [5.7; 6.5]    | 0.61 |
| Fasting Glucose (mmol/l) | 5.7 [5.3; 6.2]    | 6.1 [5.4; 7]      | 0.02 |
| Insulinemia (μU/ml)      | 8.7 [6.4; 13.3]   | 12.2 [7.9; 16.7]  | 0.08 |
| hsCRP (mg/l)             | 4.2 [2.1; 8.9]    | 4.1 [1.7; 5.8]    | 0.22 |
| PaCO <sub>2</sub> (kPa)  | 5.3 [5; 5.6]      | 4.9 [4.6; 5.2]    | <.01 |
| PaO <sub>2</sub> (kPa)   | 10.2 [9.6; 11.2]  | 11 [10.1; 11.8]   | <.01 |
| Epworth Sleepiness Scale | 12 [8; 16]        | 7 [4; 10]         | <.01 |

BMI, body mass index; hs-CRP, high sensitivity C-reactive protein; DBP, diastolic blood pressure; PaCO<sub>2</sub>, partial pressure of carbon dioxide; PaO<sub>2</sub>, partial pressure of oxygen; SBP, systolic blood pressure.

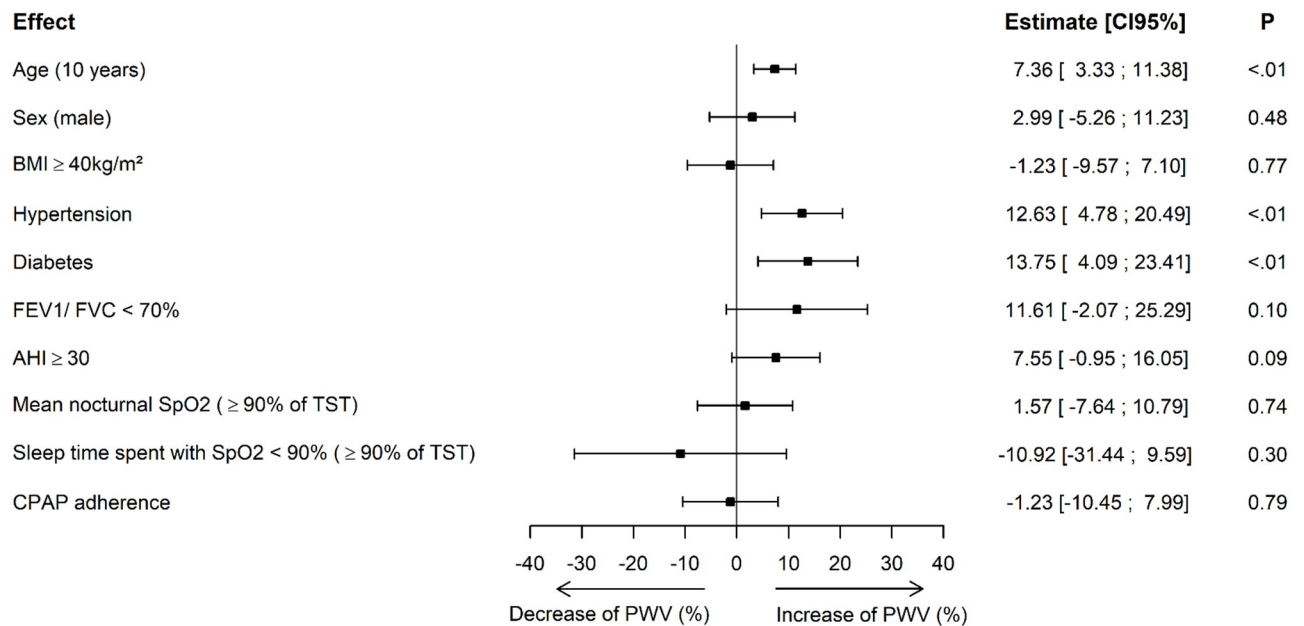
P: p value for the non-parametric Mann-Whitney test.

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probably show greater arterial stiffness at baseline, as assessed by PWV. The Arterial Stiffness Collaboration [36] reported a median ( $\pm$  2 SD) PWV of 8.1 (6.3–10.0) m/s for the 50–59 year age group in the healthy population compared to 9.7 [8.5; 10.7] in our study population. A 1 m/s increase in aortic PWV corresponds to a 15% increase in all-cause mortality after adjustment for confounders. [8] This association between OSA and elevated measurements of arterial stiffness had been previously described independently of BP [15,37] or metabolic syndrome. [38] However, in a recent individual patient meta-analysis, [39] we showed that cross-sectional elevated arterial stiffness in patients with OSA is mainly driven by the conventional cardiovascular risk factors; age, BP and the presence of diabetes, while apnea severity indices had limited influence. The current data extend these results by demonstrating that long-term OSA treatment by CPAP does not check the progression in arterial stiffness.

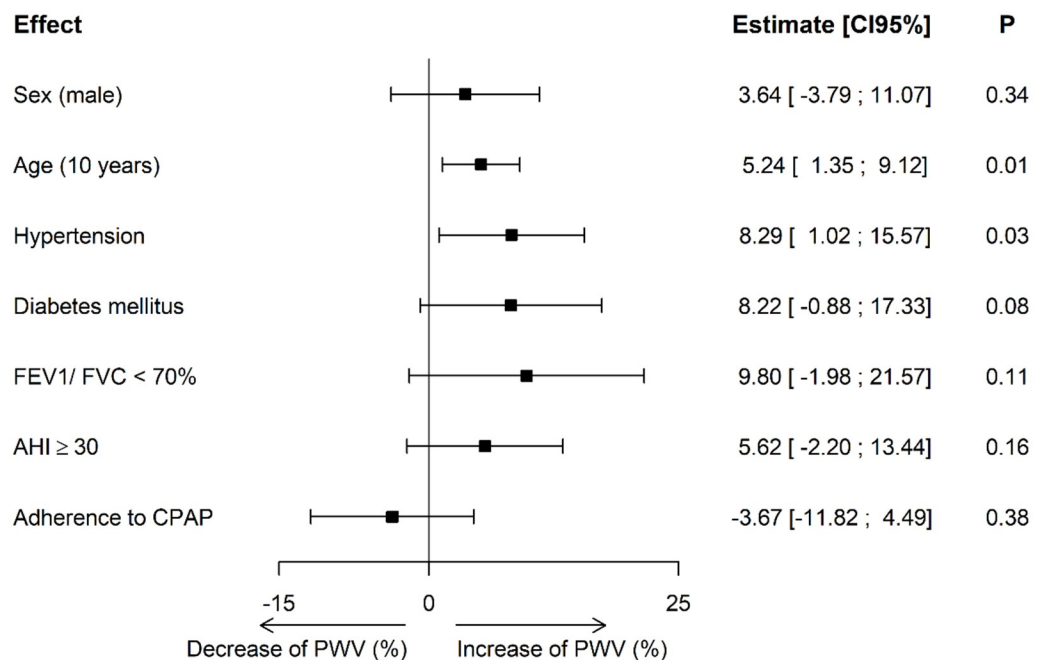
A PWV decrease after CPAP initiation had been reported in several mostly small sample size, uncontrolled and short-term studies. [11] The largest study with a long-term follow-up showed that PWV decreased significantly over the first 6 months of treatment and then gradually increased between 6 and 24 months. [40] As in our study this late increase in PWV might be explained not only by age-related progression in arterial stiffness but also by the long-term burden of uncontrolled co-morbidities.

Hypertension is the main condition associated with PWV progression, with a reciprocal relationship between the two. [36,41–43] Severe OSA and hypertension are both associated with an increase in arterial stiffness, with cumulative effects when the two diseases coexist [14,34,44,45] In morbidly obese OSA patients CPAP has been shown to produce a small but significant reduction in blood pressure in relatively short term randomized controlled trials. [46] The SAVE study showed a non-significant systolic blood pressure difference between CPAP-treated and usual care groups of <1.0 mmHg over a mean follow-up of 3.7 years. [47] Further data on mean BP and visit-to-visit BP variability (BPV) over the first 24-months of the SAVE study have recently been reported. [48] The initial reduction in visit-to-visit BPV and mean BP was lost after 12 months and was associated with a decrease in CPAP adherence. These results are in accordance with our findings, suggesting that non-sustained reductions in mean BP and the relatively small potential effect size of CPAP are not enough to counteract the development of comorbidities and limit arterial stiffness progression. CPAP adherence was relatively high in our study population but no reduction in PWV values was observed. The



**Fig 2. Univariate analysis.** BMI, body mass index; FEV1, Forced Expiratory Volume in the first second of forced expiration; FVC, Forced Vital Capacity; AHI, apnea hypopnea index; TST, total sleep time, CPAP, continuous positive airway pressure. Interpretation: An increase of ten years in age is associated with a 7.36% increase in PWV. Having high blood pressure at baseline was associated with a 12.63% increase in PWV compared to normotensive patients. Having diabetes was associated with a 13.75% increase in PWV compared to patients without diabetes.

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**Fig 3. Multivariate analysis.** FEV1, Forced Expiratory Volume of the first second of forced expiration; FVC, Forced Vital Capacity; AHI, apnea hypopnea index; CPAP, continuous positive airway pressure. Interpretation: A 10-year increase in age was associated with a 5.24% increase in PWV. Compared to the baseline PWV value of the multivariate model, this is associated to a significant increase of 0.35m/s of PWV for 10-year age increase. Having hypertension at baseline was associated to a significant increase in PWV of 8.24%.

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follow-up long term assessment did not include a PSG as CPAP efficiency was evaluated by the index of residual events downloaded from the CPAP software's. It is unexpected that the severity of OSA changed dramatically as there was no significant change in BMI (38.5 [35.4; 43.1] versus 38.4 [34.3; 41.9] for baseline and follow-up respectively; [Table 3](#)).

Other acknowledged contributors to arterial stiffness progression are type 2 diabetes or glucose intolerance in pre-diabetic states, [\[19,48\]](#) and metabolic syndrome. [\[49\]](#) Again, OSA and metabolic syndrome synergistically act to increase PWV [\[38\]](#) and type 2 diabetes has a major impact toward increasing arterial stiffness in patients with metabolic syndrome. [\[49,50\]](#) In the present study, the association with type 2 diabetes did not reach significance in multivariate analysis, but this can certainly be explained by an insufficient sample size resulting in lack of statistical power.

The combination of COPD and OSA is called “overlap syndrome” [\[51\]](#) and is associated with a worse prognosis compared to that of patients with only one of the two diseases. [\[52–55\]](#) Our data failed to show an independent association between COPD and high arterial stiffness [\[20,56–58\]](#) and additive effects of COPD on the cardiovascular damage seen in patients with OSA. [\[59\]](#)

## Conclusion and perspectives

There is an increase in PWV over the study period. In multivariate analysis, determinants of PWV progression are old age and hypertension. Optimal management of OSA-associated comorbidities is needed for patients on CPAP treatment [\[60,61\]](#) in order to slow deterioration in arterial stiffness, reduce the occurrence of late cardiovascular events and to improve survival.

## Supporting information

**S1 Table. Comparison between imputed and non-imputed datasets.** AHI, apnea hypopnea index; HbA1c, Glycated hemoglobin; hs-CRP, high sensitivity C-reactive protein; DBP, diastolic blood pressure; FEV1, Forced Expiratory Volume of the first second of forced expiration; FVC, Forced Vital Capacity; SBP, systolic blood pressure; SpO2, oxygen saturation; TLC, total lung capacity.

(DOCX)

**S2 Table. Medication used by patients at the second assessment.**

(DOCX)

**S1 Data.**

(CSV)

**S2 Data.**

(CSV)

**S3 Data.**

(CSV)

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## Author Contributions

**Conceptualization:** Louis-Marie Galerneau, Jean-Christian Borel, Renaud Tamisier, Jean-Louis Pépin.

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**Writing – review & editing:** Jean-Christian Borel, Marie Joyeux-Faure, Renaud Tamisier, Jean-Louis Pépin.

## References

1. Pépin JL, Timsit JF, Tamisier R, Borel JC, Lévy P, Jaber S. Prevention and care of respiratory failure in obese patients. *Lancet Respir Med*. 2016; 4: 407–418. [https://doi.org/10.1016/S2213-2600\(16\)00054-0](https://doi.org/10.1016/S2213-2600(16)00054-0) PMID: 27304558
2. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primer*. 2015; 15015. <https://doi.org/10.1038/nrdp.2015.15> PMID: 27188535
3. Murphy AM, Thomas A, Crinion SJ, Kent BD, Tambuwala MM, Fabre A, et al. Intermittent hypoxia in obstructive sleep apnoea mediates insulin resistance through adipose tissue inflammation. *Eur Respir J*. 2017; 49.
4. Aron-Wisniewsky J, Clement K, Pépin J-L. Nonalcoholic fatty liver disease and obstructive sleep apnea. *Metabolism*. 2016; 65: 1124–1135. <https://doi.org/10.1016/j.metabol.2016.05.004> PMID: 27324067
5. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005; 365: 1046–1053. [https://doi.org/10.1016/S0140-6736\(05\)71141-7](https://doi.org/10.1016/S0140-6736(05)71141-7) PMID: 15781100
6. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med*. 2016; 375: 919–931. <https://doi.org/10.1056/NEJMoa1606599> PMID: 27571048
7. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S, INCOSACT Initiative (International Collaboration of Sleep Apnea Cardiovascular Trialists). Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science. *Circulation*. 2017; 136: 1840–1850. <https://doi.org/10.1161/CIRCULATIONAHA.117.029400> PMID: 29109195
8. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010; 55: 1318–1327. <https://doi.org/10.1016/j.jacc.2009.10.061> PMID: 20338492

9. Mitchell GF, Hwang S-J, Vasani RS, Larson MG, Pencina MJ, Hamburg NM, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010; 121: 505–511. <https://doi.org/10.1161/CIRCULATIONAHA.109.886655> PMID: 20083680
10. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertens Dallas Tex* 1979. 2001; 37: 1236–1241.
11. Vlachantoni I-T, Dikaiakou E, Antonopoulos CN, Daskalopoulou SS, Petridou ET. Effects of continuous positive airway pressure (CPAP) treatment for obstructive sleep apnea in arterial stiffness: a meta-analysis. *Sleep Med Rev*. 2013; 17: 19–28. <https://doi.org/10.1016/j.smrv.2012.01.002> PMID: 22575367
12. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006; 27: 2588–2605. <https://doi.org/10.1093/eurheartj/ehl254> PMID: 17000623
13. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens*. 2012; 30: 445–448. <https://doi.org/10.1097/HJH.0b013e32834fa8b0> PMID: 22278144
14. Phillips CL, Butlin M, Wong KK, Avolio AP. Is obstructive sleep apnoea causally related to arterial stiffness? A critical review of the experimental evidence. *Sleep Med Rev*. 2013; 17: 7–18. <https://doi.org/10.1016/j.smrv.2012.03.002> PMID: 22658640
15. Doonan RJ, Scheffler P, Lalli M, Kimoff RJ, Petridou ET, Daskalopoulos ME, et al. Increased arterial stiffness in obstructive sleep apnea: a systematic review. *Hypertens Res Off J Jpn Soc Hypertens*. 2011; 34: 23–32. <https://doi.org/10.1038/hr.2010.200> PMID: 20962788
16. Chung S, Yoon I-Y, Lee CH, Kim J-W. The association of nocturnal hypoxemia with arterial stiffness and endothelial dysfunction in male patients with obstructive sleep apnea syndrome. *Respir Int Rev Thorac Dis*. 2010; 79: 363–369.
17. McEniery CM, Yasmin null, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR, et al. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol*. 2005; 46: 1753–1760. <https://doi.org/10.1016/j.jacc.2005.07.037> PMID: 16256881
18. Koivisto T, Hutri-Kähönen N, Juonala M, Aatola H, Kööbi T, Lehtimäki T, et al. Metabolic syndrome in childhood and increased arterial stiffness in adulthood: the Cardiovascular Risk In Young Finns Study. *Ann Med*. 2011; 43: 312–319. <https://doi.org/10.3109/07853890.2010.549145> PMID: 21284533
19. Prenner SB, Chirinos JA. Arterial stiffness in diabetes mellitus. *Atherosclerosis*. 2015; 238: 370–379. <https://doi.org/10.1016/j.atherosclerosis.2014.12.023> PMID: 25558032
20. Vivodtzev I, Tamsier R, Baguet J-P, Borel JC, Levy P, Pépin J-L. Arterial stiffness in COPD. *Chest*. 2014; 145: 861–875. <https://doi.org/10.1378/chest.13-1809> PMID: 24687708
21. Lévy P, Bonsignore MR, Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. *Eur Respir J*. 2009; 34: 243–260. <https://doi.org/10.1183/09031936.00166808> PMID: 19567607
22. Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, et al. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. *Circulation*. 2008; 117: 2270–2278. <https://doi.org/10.1161/CIRCULATIONAHA.107.741512> PMID: 18413499
23. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens*. 2018; 36: 1953–2041. <https://doi.org/10.1097/HJH.0000000000001940> PMID: 30234752
24. International Classification of Sleep Disorders 3rd ed. American Academy of Sleep Medicine. 2014.
25. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014; 146: 1387–1394. <https://doi.org/10.1378/chest.14-0970> PMID: 25367475
26. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med*. 2012; 8: 597–619. <https://doi.org/10.5664/jcsm.2172> PMID: 23066376
27. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991; 14: 540–545. <https://doi.org/10.1093/sleep/14.6.540> PMID: 1798888

28. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, et al. AASM Scoring Manual Updates for 2017 (Version 2.4). *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med*. 2017; 13: 665–666. <https://doi.org/10.5664/jcsm.6576> PMID: 28416048
29. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension*. 1995; 26: 485–490. <https://doi.org/10.1161/01.hyp.26.3.485> PMID: 7649586
30. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: The GOLD Science Committee Report 2019. *Eur Respir J*. 2019.
31. Société de Pneumologie de Langue Française, Société Française d'Anesthésie Réanimation, Société Française de Cardiologie, Société Française de Médecine du Travail, Société Française d'ORL, Société de Physiologie, et al. [Recommendations for clinical practice. Obstructive sleep apnea hypopnea syndrome in adults]. *Rev Mal Respir*. 2010; 27: 806–833. <https://doi.org/10.1016/j.rmr.2010.05.011> PMID: 20863987
32. Gay P, Weaver T, Loube D, Iber C, Positive Airway Pressure Task Force, Standards of Practice Committee, et al. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. *Sleep*. 2006; 29: 381–401. <https://doi.org/10.1093/sleep/29.3.381> PMID: 16553025
33. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc*. 2008; 5: 173–178. <https://doi.org/10.1513/pats.200708-119MG> PMID: 18250209
34. Drager LF, Bortolotto LA, Figueiredo AC, Silva BC, Krieger EM, Lorenzi-Filho G. Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. *Chest*. 2007; 131: 1379–1386. <https://doi.org/10.1378/chest.06-2703> PMID: 17494787
35. Pépin J-L, Tamisier R, Baguet J-P, Lévy P. Arterial health is related to obstructive sleep apnea severity and improves with CPAP treatment. *Sleep Med Rev*. 2013; 17: 3–5. <https://doi.org/10.1016/j.smrv.2012.11.002> PMID: 23219181
36. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: “establishing normal and reference values”. *Eur Heart J*. 2010; 31: 2338–2350. <https://doi.org/10.1093/eurheartj/ehq165> PMID: 20530030
37. Drager LF, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: an emerging risk factor for atherosclerosis. *Chest*. 2011; 140: 534–542. <https://doi.org/10.1378/chest.10-2223> PMID: 21813534
38. Drager LF, Bortolotto LA, Maki-Nunes C, Trombetta IC, Alves MJNN, Fraga RF, et al. The incremental role of obstructive sleep apnoea on markers of atherosclerosis in patients with metabolic syndrome. *Atherosclerosis*. 2010; 208: 490–495. <https://doi.org/10.1016/j.atherosclerosis.2009.08.016> PMID: 19762024
39. Joyeux-Faure M, Tamisier R, Borel J-C, Millasseau S, Galerneau L-M, Destors M, et al. Contribution of obstructive sleep apnoea to arterial stiffness: a meta-analysis using individual patient data. *Thorax*. 2018. <https://doi.org/10.1136/thoraxjnl-2018-211513> PMID: 30032122
40. Saito T, Saito T, Sugiyama S, Asai K, Yasutake M, Mizuno K. Effects of long-term treatment for obstructive sleep apnea on pulse wave velocity. *Hypertens Res Off J Jpn Soc Hypertens*. 2010; 33: 844–849. <https://doi.org/10.1038/hr.2010.77>
41. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013; 31: 1281–1357. <https://doi.org/10.1097/01.hjh.0000431740.32696.cc> PMID: 23817082
42. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA*. 2012; 308: 875–881. <https://doi.org/10.1001/2012.jama.10503> PMID: 22948697
43. Lin X, Chen G, Qi J, Chen X, Zhao J, Lin Q. Effect of continuous positive airway pressure on arterial stiffness in patients with obstructive sleep apnea and hypertension: a meta-analysis. *Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol—Head Neck Surg*. 2016; 273: 4081–4088. <https://doi.org/10.1007/s00405-016-3914-8> PMID: 26861547
44. Tsioufis C, Thomopoulos K, Dimitriadis K, Amfilochiou A, Tousoulis D, Alchanatis M, et al. The incremental effect of obstructive sleep apnoea syndrome on arterial stiffness in newly diagnosed essential hypertensive subjects. *J Hypertens*. 2007; 25: 141–146. <https://doi.org/10.1097/HJH.0b013e32801092c1> PMID: 17143185
45. Tavil Y, Kanbay A, Sen N, Ulukavak Ciftçi T, Abaci A, Yalçın MR, et al. The relationship between aortic stiffness and cardiac function in patients with obstructive sleep apnea, independently from systemic

- hypertension. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2007; 20: 366–372. <https://doi.org/10.1016/j.echo.2006.09.005> PMID: 17400115
46. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *JAMA*. 2015; 314: 2280–2293. <https://doi.org/10.1001/jama.2015.16303> PMID: 26624827
  47. Van Ryswyk E, Anderson CS, Barbe F, Loffler KA, Lorenzi-Filho G, Luo Y, et al. Effect of CPAP on Blood Pressure in Obstructive Sleep Apnea with Cardiovascular Disease. *Am J Respir Crit Care Med*. 2019. <https://doi.org/10.1164/rccm.201811-2200LE> PMID: 30849229
  48. Cecelja M, Chowienzyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. *Hypertension*. 2009; 54: 1328–1336. <https://doi.org/10.1161/HYPERTENSIONAHA.109.137653> PMID: 19884567
  49. Pietri P, Vlachopoulos C, Vyssoulis G, Ioakeimidis N, Stefanadis C. Macro- and microvascular alterations in patients with metabolic syndrome: sugar makes the difference. *Hypertens Res Off J Jpn Soc Hypertens*. 2014; 37: 452–456. <https://doi.org/10.1038/hr.2013.148> PMID: 24173360
  50. Safar ME, Balkau B, Lange C, Protogerou AD, Czernichow S, Blacher J, et al. Hypertension and vascular dynamics in men and women with metabolic syndrome. *J Am Coll Cardiol*. 2013; 61: 12–19. <https://doi.org/10.1016/j.jacc.2012.01.088> PMID: 23287369
  51. Malhotra A, Schwartz AR, Schneider H, Owens RL, DeYoung P, Han MK, et al. Research Priorities in Pathophysiology for Sleep-disordered Breathing in Patients with Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Research Statement. *Am J Respir Crit Care Med*. 2018; 197: 289–299. <https://doi.org/10.1164/rccm.201712-2510ST> PMID: 29388824
  52. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med*. 2010; 182: 325–331. <https://doi.org/10.1164/rccm.200912-1869OC> PMID: 20378728
  53. Zamarrón C, García Paz V, Morete E, del Campo Matías F. Association of chronic obstructive pulmonary disease and obstructive sleep apnea consequences. *Int J Chron Obstruct Pulmon Dis*. 2008; 3: 671–682. <https://doi.org/10.2147/copd.s4950> PMID: 19281082
  54. Stone IS, Barnes NC, Petersen SE. Chronic obstructive pulmonary disease: a modifiable risk factor for cardiovascular disease? *Heart Br Card Soc*. 2012; 98: 1055–1062. <https://doi.org/10.1136/heartjnl-2012-301759> PMID: 22739636
  55. Lee HM, Lee J, Lee K, Luo Y, Sin DD, Wong ND. Relation between COPD severity and global cardiovascular risk in US adults. *Chest*. 2012; 142: 1118–1125. <https://doi.org/10.1378/chest.11-2421> PMID: 22518027
  56. McAllister DA, Maclay JD, Mills NL, Mair G, Miller J, Anderson D, et al. Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007; 176: 1208–1214. <https://doi.org/10.1164/rccm.200707-1080OC> PMID: 17885263
  57. Weir-McCall JR, Struthers AD, Lipworth BJ, Houston JG. The role of pulmonary arterial stiffness in COPD. *Respir Med*. 2015; 109: 1381–1390. <https://doi.org/10.1016/j.rmed.2015.06.005> PMID: 26095859
  58. Vanfleteren LEGW, Spruit MA, Groenen MTJ, Bruijnzeel PLB, Taib Z, Rutten EPA, et al. Arterial stiffness in patients with COPD: the role of systemic inflammation and the effects of pulmonary rehabilitation. *Eur Respir J*. 2014; 43: 1306–1315. <https://doi.org/10.1183/09031936.00169313> PMID: 24311762
  59. Shiina K, Tomiyama H, Takata Y, Yoshida M, Kato K, Nishihata Y, et al. Overlap syndrome: additive effects of COPD on the cardiovascular damages in patients with OSA. *Respir Med*. 2012; 106: 1335–1341. <https://doi.org/10.1016/j.rmed.2012.05.006> PMID: 22705293
  60. Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, et al. CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med*. 2014; 370: 2265–2275. <https://doi.org/10.1056/NEJMoa1306187> PMID: 24918371
  61. Vivodtzev I, Tamsier R, Croteau M, Borel J-C, Grangier A, Wuyam B, et al. Ventilatory support or respiratory muscle training as adjuncts to exercise in obese CPAP-treated patients with obstructive sleep apnoea: a randomised controlled trial. *Thorax*. 2018. <https://doi.org/10.1136/thoraxjnl-2017-211152> PMID: 29463621