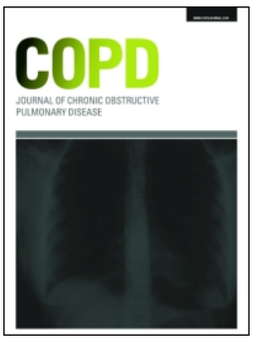

COPD: Journal of Chronic Obstructive Pulmonary Disease

ISSN: 1541-2555 (Print) 1541-2563 (Online) Journal homepage: http://www.tandfonline.com/loi/icop20

REM Sleep Imposes a Vascular Load in COPD Patients Independent of Sleep Apnea

Grote L, Sommermeyer D, Ficker JH, Randerath W, Penzel T, Fietze I, Sanner B, Hedner J & Schneider H

To cite this article: Grote L, Sommermeyer D, Ficker JH, Randerath W, Penzel T, Fietze I, Sanner B, Hedner J & Schneider H (2017): REM Sleep Imposes a Vascular Load in COPD Patients Independent of Sleep Apnea, COPD: Journal of Chronic Obstructive Pulmonary Disease, DOI: 10.1080/15412555.2017.1365119

To link to this article: http://dx.doi.org/10.1080/15412555.2017.1365119

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2017, VOL. 0, NO. 0, 1–8
https://doi.org/10.1080/15412555.2017.1365119

Taylor & Francis
Taylor & Francis Group

REM Sleep Imposes a Vascular Load in COPD Patients Independent of Sleep Apnea

Grote L, MD[a,b], Sommermeyer D, PhD[a,c], Ficker JH, MD [d], Randerath W, MD[e], Penzel T, PhD[f], Fietze I, MD[f], Sanner B, MD[g], Hedner J, MD[a], and Schneider H, MD[b]

[a]Center for Sleep and Wakefulness Disorders, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [b]Department of Respiratory and Critical Care Medicine, Johns Hopkins University, Baltimore, USA; [c]ochschule Mannheim - University of Applied Sciences, Department of Information Technology, Mannheim, Germany; [d]Department of Respiratory Medicine, Allergology and Sleep Medicine, Klinikum Nuremberg/ Paracelsus Medical University, Nuremberg, Germany; [e]Department of Pulmonary Medicine, Bethanien Hospital, Solingen, Germany; [f]Department of Cardiology, University Hospital Charité, Berlin, Germany; [g]Department of Pulmonary Medicine, Bethesda Hospital, Wuppertal, Germany

ABSTRACT

Arterial stiffness, a marker for cardiovascular risk, is increased in patients with Chronic Obstructive Pulmonary Disease (COPD) and Obstructive Sleep Apnea (OSA). The specific influence of both on arterial stiffness during sleep is unknown. Nocturnal arterial stiffness (Pulse Propagation Time (PPT) of the finger pulse wave) was calculated in 142 individuals evaluated for sleep apnea: 27 COPD patients (64.7 ± 11y, 31.2 ± 8 kg/m^2), 72 patients with cardiovascular disease (CVD group, 58.7 ± 13y, 33.6 ± 6 kg/m^2) and 43 healthy controls (HC group 49.3 ± 12y, 27.6 ± 3 kg/m^2). Sleep stage related PPT changes were assessed in a subsample of COPD patients and matched controls (n = 12/12). Arterial stiffness during sleep was increased in COPD patients (i.e. shortened PPT) compared to healthy controls (158.2 ± 31 vs. 173.2 ± 38 ms, p = 0.075) and to patients with CVD (161.4 ± 41 ms). Arterial stiffening was particular strong during REM sleep (145.9 ± 28 vs. 172.4 ± 43 ms, COPD vs. HC, p = 0.003). In COPD, time SaO_2 < 90% was associated with reduced arterial stiffness (Beta +1.7 ms (1.1–2.3)/10 min, p < 0.001). Sleep apnea did not affect PPT. In COPD, but not in matched controls, arterial stiffness increased from wakefulness to REM-sleep (ΔPPT-8.9 ± 10% in COPD and 3.7 ± 12% in matched controls, p = 0.021). Moreover, REM-sleep related arterial stiffening was correlated with elevated daytime blood pressure (r = −0.92, p < 0.001) and increased myocardial oxygen consumption (r = −0.88, p < 0.01). Hypoxia and REM sleep modulate arterial stiffness. In contrast to healthy controls, REM sleep imposes a vascular load in COPD patients independent of sleep apnea indices, intermittent and sustained hypoxia. The link between REM-sleep, vascular stiffness and daytime cardiovascular function suggests that REM-sleep plays a role for increased cardiovascular morbidity of COPD patients.

ARTICLE HISTORY
Received 1 December 2016
Accepted 1 August 2017

KEYWORDS
REM sleep; COPD; arterial stiffness; cardiovascular risk; blood pressure; nocturnal hypoxia

Abbreviations

AHI	Apnea Hypopnea Index
ATC	Anatomical Therapeutical Chemical
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CHF	Chronic Heart Failure
CV	Cardiovascular
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
FEV	Functional Expiratory Volume
GLM	General Linear Model
HC	Healthy Controls
HR	Heart Rate
LTOT	Long-Term Oxygen Therapy
MBP	Mean Blood Pressure
NREM	Non Rapid Eye Movement
N1-N3	NREM sleep stages 1–3
ODI	Oxygen Desaturation Index
PP	Pulse Pressure
PPT	Pulse Propagation Time
R	Regression Coefficient
REM	Rapid Eye Movement
RPP	Rate Pressure Product
SBP	Systolic Blood Pressure
T < 90% T < 90%	Time of oxygen saturation < 90%
VC	Vital Capacity
WHO	World Health Organization

Introduction

Patients with Chronic Obstructive Pulmonary Disease (COPD) suffer from increased cardiovascular (CV) risk (1,2). While common risk factors such as age, cigarette smoking and increased systemic inflammation are involved, the coexistence of obstructive sleep apnea has been recently identified as additional risk factor for increased morbidity and mortality in patients with COPD (3). However, the mechanism for this excess risk in patients with COPD remains unclear (4).

CONTACT L. Grote, MD, PhD, Prof. ludger.grote@lungall.gu.se Center for Sleep and Wakefulness Disorders, Sahlgrenska Academy, University of Gothenburg, Box 402, 413 45 Gothenburg, Sweden.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/icop.
The corresponding author (LG) takes responsibility for the content of the manuscript, including the data and analysis.
Funding sources of the study
This study was supported by the following funding sources: The Swedish Heart and Lung Foundation (HLF 20110445, 20120429 and 20130488), the German Ministry for Education and Science (BMBF), the National Institute of Health (R01 HL105546), and Weinmann Geräte für Medizin GmbH & Co.KG. Prior Abstract presentation: Not applicable

Assessment of arterial stiffness is an established method to examine mechanisms involved in the development of CV dysfunction in COPD (4,5,6,7). Arterial stiffness reflect structural properties and varies with functional changes of sympathetic vascular activity such as exercise, adrenergic drugs and hypoxia (8,9). Recently, REM sleep has been shown to be associated with marked increased alpha-adrenergic sympathetic activity of the arterial vascular bed, potentially increasing arterial stiffness (10). REM sleep is also known to be associated with worsening of sustained and/or intermittent hypoxia in both COPD and sleep apnea patients (11,12). While hypoxic vasodilation of the arterial vascular bed may reduce cardiac load (13), intermittent hypoxia has been shown to increase peripheral resistance and arterial stiffness (14,15,16,17). Yet the specific influence of sleep related hypoxia and sympathetic activation on CV dysfunction in patients with COPD remains unknown.

In the current study, we examined arterial stiffness during sleep in a convenient sample of COPD and non-COPD patients who were evaluated for the coexistence of obstructive sleep apnea. We hypothesized that arterial stiffness increases with the degree of intermittent hypoxia, and that this increase in arterial stiffness is greater in patients with COPD compared to controls with and without comorbid CV disease. Furthermore, we hypothesized that REM sleep imposes a CV load that is greater in patients with COPD compared to controls. Therefore, we conducted a subset analysis in carefully matched COPD and non-COPD patients to determine the effect of sleep stages on arterial stiffness and daytime cardiac function.

Method

Study settings

The cohort and the pulse wave analysis methodology have been reported in detail before (18,19,20). Six hundred and thirty one patients from five clinical sleep centers in Germany (Nuremberg, Solingen, Berlin, Wuppertal) and Sweden (Göteborg) were referred for a sleep diagnostic test for suspected sleep disordered breathing. Only patients investigated with standard polysomnography without atrial fibrillation or PAP treatment were eligible for the current study (n = 361). The study was conducted according to the amended Declaration of Helsinki and the protocol had been approved by local ethic committees (e-supplement). Oral and written informed consent was obtained.

Study subjects and controls

We identified 27 individuals with clinically diagnosed stable COPD (no exacerbation within pat 4 weeks and not on long-term oxygen therapy). Information on COPD diagnosis was obtained by the pulmonary physician from patient history, the physical status, the concomitant medication, additional information from the hospital chart/the referral as well as from pulmonary function test data (Table 1) where COPD was defined as FEV1/VC ratio below the 5th percentile of population-based predicted values for age and sex (Global Lung Initiative 2012 reference data base (21)). Those individuals without COPD, yet with CV disease (at least hypertension) and treated with at least one drug (according to Anatomical Therapeutic Chemical (ATC) code class C), were classified as "CVD-group" (n = 72). Subjects without CVD, not prescribed CV medication and lifelong non-smoking history were identified as "Healthy controls" (HC, n = 43) (see flowchart in Figure 1). Pulmonary function test data were used to exclude COPD in the HC and CVD groups (Table 1).

A subsequent sleep stage based analysis of arterial stiffness was performed in 12 COPD patients (2 females) and 12 matched controls (4 females) recruited from the groups stated above (Figure 1). Matching criteria included age (±3 years), Body Mass Index (BMI) (±3 kg/m^2), and sleep apnea severity (Apnea Hypopnea Index (AHI) of ±5 events/hr for AHI < 15/hr, ±10 events/hr for AHI > 15–50 events/hr and ±15 for AHI>50 events/hr) and overnight mean saturation in COPD individuals < 95%.

Overnight pulse wave analysis

A modified pulse oximeter was applied during standard polysomnography (Somnolab, Weinmann, Hamburg, Germany). As described elsewhere (18,20), Pulse Propagation Time (PPT) was computed as the time difference between the maximum of the reflection (diastolic) wave t_{refl} and the time point of the maximum of the systolic pulse wave t_{main} (Figure 1, e-supplement). PPT, referred to as "arterial stiffness", and hypoxic measures (oxygen desaturation index (ODI) 4%, time below oxygen saturation <90% (T<90%)) were analyzed as means over the entire night and in the sleep stages NREM/REM and wakefulness within the sleep period. Data were computed for Rapid Eye Movement (REM) sleep, Non REM stages 1, 2, and 3 (N1, N2, and N3, respectively) as well as during wakefulness (wake). PPT is given both in milliseconds (ms) and in percentage of the value obtained during wakefulness (defined as 100%).

Assessment of sleep and breathing

Sleep stages and breathing events were scored according to American Academy of Sleep Medicine criteria (22) including the alternative hypopnea criteria. Intermittent hypoxia was defined as ODI4% whereas sustained hypoxia was defined as T<90%. In the sleep stage based analysis, T<90% was calculated for NREM and REM sleep. In addition, ODI2% was calculated as a measure of intermittent hypoxia for each sleep stage based on our previous findings of a strong association with cardiovascular dysfunction (18,19).

Assessment of cardiovascular risk factors

Comorbidities as well as concomitant medication were assessed by clinical interview and hospital medical charts/information from the referral. Office blood pressure (SBP/DBP) and heart rate (HR) were determined during supine rest (23). Mean blood pressure (MAP) and pulse pressure (PP) were calculated. The Rate Pressure Product (RPP), a measure of cardiac load/myocardial oxygen demand, was calculated according to the formula: RPP = HR*SBP (24). Fasting lipids and smoking status were determined.

Table 1. Anthropometric and clinical characteristics in patients with COPD (n = 27) and 2 non-COPD control groups (n = 115). Shown are means ± standard deviation.

Variable	COPD (n = 27)	CVD (n = 72)	HC (n = 43)	Between group analysis*	Post hoc analysis COPD vs CVD	Post hoc analysis COPD vs HC
Females	33%	38%	30%	n.s.	n.s.	n.s.
Age (years)	64.7 ± 11	58.7 ± 13	49.3 ± 12	<0.001	0.03	<0.001
Body Mass Index (kg/m2)	31.2 ± 8	33.6 ± 6	27.6 ± 3	<0.001	n.s.	0.013
Office Systolic Blood Pressure (mmHg)	134.5 ± 18	137.6 ± 20	128.5 ± 16	0.04	n.s.	n.s.
Office Mean Arterial Pressure (mmHg)	98.9 ± 11	100.3 ± 13	97.5 ± 11	n.s.	n.s.	n.s.
Office Diastolic Blood Pressure (mmHg)	80.2 ± 10	81.7 ± 12	82.0 ± 9	n.s.	n.s.	n.s.
Pulse (beats/minute)	75.5 ± 16	71.5 ± 9	74.2 ± 11	n.s.	n.s.	n.s.
Pulse Pressure (mmHg)	56.2 ± 15	55.9 ± 16	46.5 ± 12	0.003	n.s.	0.012
Rate Pressure Product (bpm*mmHg)	10259 ± 2863	9850 ± 1993	9505 ± 1701	n.s.	n.s.	n.s.
Current/previous smoker	58%	28%	0%	0.001	0.023	0.001
Mean Pack Years	19.9 ± 25	6.4 ± 13	0	<0.001	<0.001	<0.001
Total Cholesterol (mg/dl)	208.4 ± 26	203.6 ± 42	217.3 ± 44	0.008	n.s.	n.s.
High Density Lipoprotein (mg/dl)	51.4 ± 17	48.8 ± 11	48.4 ± 13	n.s.	n.s.	n.s.
			Comorbidities (percentage of patients)			
Arterial Hypertension	74%	100%	0%	<0.001	0.001	<0.001
Pulmonary Hypertension	4%	2%	0%	n.s.	n.s.	n.s.
Chronic Heart Failure	19%	13%	0%	<0.023	n.s.	<0.003
Coronary Artery Disease	15%	17%	0%	0.019	n.s.	0.009
TIA/Stroke	4%	7%	0%	n.s.	n.s.	n.s.
Diabetes Mellitus	19%	29%	0%	<0.001	n.s.	0.03
Hyperlipidemia	20%	44%	16%	0.007	n.s.	n.s.
Medication (percentage of patients)						
Betablocker	30%	43%	0%	<0.001	n.s.	0.001
Renin Angiotensin Blocker	41%	60%	0%	<0.001	n.s.	<0.001
Diuretics	34%	20%	0%	0.002	n.s.	<0.001
Calcium Channel Bockers	7%	36%	0%	<0.001	0.05	n.s.
Lipid lowering drugs	19%	31%	0%	0.001	n.s.	0.018
Antidiabetic drugs (including insulin)	11%	22%	0%	0.051	n.s.	0.025
			Sleep, sleep disordered breathing and nocturnal hypoxia			
Total sleep time (h)	5.0 ± 1.3	5.2 ± 1.2	5.1 ± 1.2	n.s.	n.s.	n.s.
REM sleep %	12.3 ± 9	13.8 ± 7	13.9 ± 8	n.s.	n.s.	n.s.
Total arousal index (n/h)	12.2 ± 14	15.8 ± 18	18.2 ± 15	n.s.	n.s.	n.s.
Apnea Hypopnea Index (n/h)	14.1 ± 16	20.4 ± 19	13.8 ± 16	n.s.	n.s.	n.s.
Oxygen Desaturation Index 4% (n/h)	14.4 ± 18	18.9 ± 18	9.8 ± 15	0.003	n.s.	n.s.
Mean overnight SaO_2 (%)	93.1 ± 3	94.5 ± 3	95.9 ± 2	<0.001	<0.024	<0.001
Minimum overnight SaO_2 (%)	80.9 ± 6	80.4 ± 6	85.7 ± 5	<0.001	n.s.	0.008
Time in overnight SaO_2 <90% (min)	74.9 ± 127	32.3 ± 70	8.0 ± 22	<0.001	0.002	<0.001
Time in REM sleep SaO_2 <90% (min)	7.3 ± 17	4.6 ± 8	1.1 ± 3	0.021	n.s.	0.008
Time in NREM SaO_2 <90% (min)	47.3 ± 84	22.8 ± 53	5.9 ± 19	0.002	0.046	0.002
Time in Wake SaO_2 <90% (min)	23.0 ± 41	4.8 ± 16	1.2 ± 2	<0.001	<0.001	<0.001
AHI≥15 n/h	29.6%	52.8%	34.9%	0.051	0.04	n.s.
			Pulmonary function data			
FVC (l)	2.75 ± 0.67	3.51 ± 1.14	4.31 ± 0.95	<0.001	0.003	<0.001
FVC % predicted	78 ± 19	94 ± 14	97 ± 12	<0.001	<0.001	<0.001
FEV_1 (l)	1.49 ± 0.45	2.79 ± 0.88	3.49 ± 0.79	<0.001	<0.001	<0.001
FEV_1% predicted	51 ± 26	96.4 ± 16	95.6 ± 12	<0.001	<0.001	<0.001
FEV_1/FVC	0.54 ± 0.12	0.83 ± 0.08	0.81 ± 0.07	<0.001	<0.001	<0.001

COPD = Chronic Obstructive Pulmonary Disease, CVD = Cardiovascular Disease, AHI = Apnea Hypopnea Index, FVC = Forced Vital Capacity, FEV_1 = Forced Expiratory Volume in the first second, HC = Healthy Controls, bpm = beats per minute, mg = milligram, n = number, h = hour, mmHg = millimeter Mercury

* = Between group analysis by ANOVA-, Kruskal Wallis-, or Chi^2 -test

Data analysis and statistics

Descriptive statistics are presented as mean ± standard deviation. Statistical significance was set at $p < 0.05$, two tailed. Between group differences were tested by ANOVA, Student t-test, Kruskal Wallis test, or the Chi-square test (for equally/not equally distributed data and distributions, respectively). Within group differences were tested by means of the paired t-test or the Wilcoxon Signed Rank test. Post hoc between group comparisons were corrected with the Bonferroni method. Pearson´s and Spearmans correlation analysis assessed associations between PPT and daytime CV measures (e.g. blood pressure) as well as measures of nocturnal hypoxia. Significant predictors

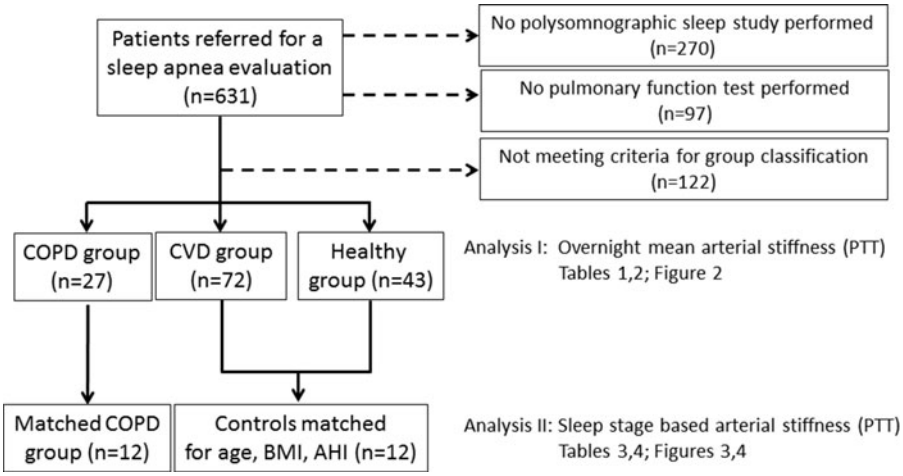

Figure 1. Study flow chart. From a pool of polysomnographic sleep studies two analyses have been performed in the current study: Analysis 1 targteted overnight PPT in 142 patients divided in 3 subgroups; analysis 2 targeted sleep stage based PPT analysis performed in 12 COPD patients and 12 matched controls.

of arterial stiffness in univariate analysis (age, blood pressure, gender, comorbidities, sleep variables) were used in General Linear Models (GLM) to explore independent predictors of overnight PPT as a measure of arterial stiffness. The analysis was divided into the three subgroups (COPD, CV disease and healthy controls) and followed thereby the study inclusion criteria described above. Numbers of individuals included in the analysis are stated in the result section. Analyses were performed using IBM-SPSS (version 22.0, Chicago, USA).

Results

Anthropometric and clinical characteristics are shown in Table 1. CV and metabolic comorbidities were more prevalent in COPD patients and in the CVD group. Compared to healthy controls, the degree of sustained hypoxia (mean oxygen saturation and T < 90%) was greater in the COPD group and slightly elevated in the CVD group. Clinical significant sleep apnea (AHI ≥ 15) occurred in approximately a third of COPD patients (29.6%). Lung function test performed in COPD patients showed pathological values compared to normal values in the CVD and HC groups (Table 1).

Mean overnight PPT varied over the three patient groups (ANOVA, p = 0.098) and PPT tended to be shorter in COPD patients compared to healthy controls (158.2 ± 31 vs. 173.2 ± 38 ms, p = 0.075), while PPT in patients with CVD (161.4 ± 41 ms) did not differ from PPT in the COPD group. Arterial stiffening was particular strong during REM sleep in COPD patients (145.9 ± 28 vs. 172.4 ± 43 ms, COPD vs. HC, p = 0.003). In COPD patients, sustained hypoxia, assessed as time of oxygen saturation <90% (T < 90%) during the entire sleep period, correlated strongly with PPT (Figure 2). In GLM analysis, T < 90% T < 90% negatively predicted arterial stiffness in both, COPD and HC patients (Table 2), whereas AHI or ODI as measures of apnea related intermittent hypoxia did not. Moreover, independent predictors of overnight mean PPT included established CV risk factors like age, BMI, and blood pressure.

For the subgroup analysis of sleep stage based PPT changes, the COPD and control groups were well matched with regard to anthropometric and clinical data (Table 3). The changes observed in arterial stiffness over the different sleep stages are exemplified in one recording example of a patient with COPD (Figure 2, e-supplement). For the entire group, PPT analysis by sleep stages followed two different patterns in COPD and control subjects (Figure 3, PPT-% change from wakefulness level (reference 100%)): First, arterial stiffness decreased (= PPT increased) from wake to deep sleep (N3) (% change in PPT 8.5 ± 7%, p = 0.002) as well as from light to deep sleep (N1 to N3) ΔPPT 6.6 ± 9, p = 0.044) in controls but not in COPD patients

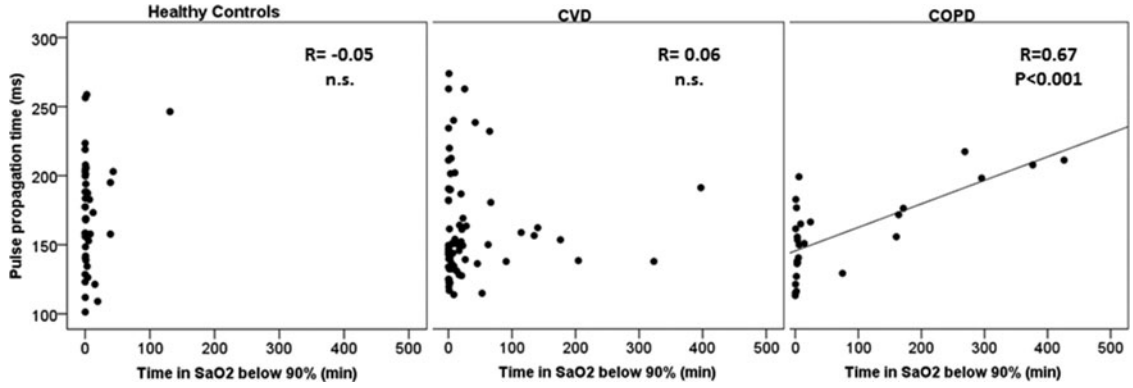

Figure 2. Association between pulse propagation time (PPT in milliseconds) and time below 90% oxygen saturation (in minutes) for the three study groups: Healthy Controls group, Cardiovascular Disease group (CVD) and Chronic Obstructive Pulmonary Disease group (COPD). Spearmen rho correlation factor (R) and significance level are shown.

Table 2. Independent predictors of mean overnight Pulse Propagation Time (PPT) obtained in 3 different General Linear Models for (a) 27 COPD patients, (b) 72 CVD patients and (c) 43 healthy controls. Beta values indicate the numerical influence on PPT for each factor listed in the table.

	Beta value: Influences on PPT in ms (Mean and 95% CI)			Statistics		
Covariate	COPD	CVD	Healthy Controls	COPD	CVD	Healthy Controls
Age	−1.1 (−1.9 – −0.3)	−1.6 (−2.1 – −1.0)	−2.0 (−2.7 – −1.0)	0.003	<0.001	<0.001
BMI	n.s.	1.9 (0.7–3.0)	n.s.	—	0.001	—
Systolic BP	n.s.	0.6 (0.2–1.0)	n.s.		0.004	—
Diastolic BP	−1.2 (−2.2–−0.2)	−1.8 (−2.5 – −1.1)	n.s.	<0.05	<0.001	—
Time SaO_2 <90% (10 min)	1.7 (1.1–2.3)	n.s.	4.7 (0.9–8.5)	<0.001	—	0.015
Intercept	303 (188–417)	261 (190–331)	316 (212–420)	<0.001	<0.001	<0.001

Non-significant factors tested in the model: Arterial hypertension, diabetes mellitus, total cholesterol, and Oxygen Desaturation Index 4% or Apnea Hypopnea Index
NA = not applicable, n.s. = not significant.

(ΔPPT 1.3 ± 12% and 4.9 ± 9%, n.s., respectively). Second, COPD patients decreased PPT significantly from wakefulness to REM sleep whereas controls increased PPT values slightly when compared to wakefulness (ΔPPT −8.9 ± 10% in COPD and 3.7 ± 12% in matched controls, between group difference p = 0.021). Third, REM sleep PPT was lower in COPD patients compared with controls (% of awake PPT 91 ± 12% vs. 108 ± 12%, between group difference p = 0.019). Changes in PPT by sleep stage did not associate with pulmonary function (FVC/VC ratio), the amount of intermittent hypoxia (ODI 2% for NREM and REM sleep), or sustained hypoxia (mean SaO_2 or time of SaO_2 < 90%) (Figure 3, e-supplement).

Finally, REM sleep related arterial stiffening was associated with elevated systolic and mean blood pressure, pulse pressure, and signs of increased myocardial oxygen consumption (RPP) only in the COPD group (Table 4, Figure 4). Intermittent or sustained nocturnal hypoxia did not associate significantly with daytime hemodynamic variables in this case control sub-study.

Table 3. Anthropometric and clinical data in patients with COPD and matched controls. Shown are means ± standard deviation.

Parameter	Matched COPD patients (n = 12)	Matched controls (n = 12)	Statistics
	Anthropometric and clinical data		
Females	33%	17%	n.s.
Age (years)	62.6 ± 8	62.3 ± 11	Matching variable
Body Mass Index (kg/m^2)	32.8 ± 7	33.1 ± 6	Matching variable
Office Systolic Blood Pressure (mmHg)	138.3 ± 24	144.7 ± 20	n.s.
Office Mean Arterial Pressure (mmHg)	102.1 ± 16	104.4 ± 14	n.s.
Office Diastolic Blood Pressure (mmHg)	83.9 ± 14	84.2 ± 13	n.s.
Pulse (beats/minute)	79.7 ± 14	75.3 ± 18	n.s.
Pulse Pressure (mmHg)	54.4 ± 17	60.6 ± 14	n.s.
Heart Pressure Product (bpm∗mmHg)	10978 ± 2943	11135 ± 4203	n.s.
Current or previous smoker	75%	33%	n.s.
Mean Pack Years	30.4 ± 28	10.8 ± 17	0.056
Total Cholesterol (mg/dl)	207.3 ± 30	196.5 ± 21	n.s.
High Density Lipoprotein (mg/dl)	48.3 ± 11	53.8 ± 17	n.s.
	Comorbidities (percentage of patients)		
Arterial Hypertension	75%	92%	n.s.
Pulmonary Hypertension	0%	0%	n.s.
Chronic Heart Failure	42%	0%	0.02
Coronary Artery Disease	17%	25%	n.s.
TIA/Stroke	8%	8%	n.s.
Diabetes Mellitus	25%	42%	n.s.
Hyperlipidemia	42%	33%	n.s.
	Medication (percentage of patients)		
Betablocker	33%	50%	n.s.
Renin Angiotensin Blocker	33%	66%	n.s.
Diuretics	42%	17%	n.s.
Calcium Channel Bockers	17%	42%	n.s.
Lipid lowering drugs	25%	42%	n.s.
Antidiabetic drugs (including insulin)	17%	33%	n.s.
	Sleep related hypoxia and breathing disorders		
Apnea Hypopnea Index (n/h)	20.1 ± 20	23.0 ± 21	Matching variable
Oxygen Desaturation Index 4% (n/h)	20.4 ± 22	19.4 ± 21	n.s.
NREM Oxygen Desaturation Index 2% (n/h)	25.1 ± 24	27.1 ± 24	n.s.
REM Oxygen Desaturation Index 2% (n/h)	36.6 ± 35	29.8 ± 17	n.s.
Mean overnight SaO_2(%)	90.7 ± 3	94.5 ± 3	0.002
Minimum overnight SaO_2 (%)	78.4 ± 4	80.4 ± 9	n.s.
Time in overnight SaO_2 <90% (min)	150.3 ± 157	28.6 ± 41	0.023
Time in REM SaO_2 <90% (min)	11.6 ± 23	4.8 ± 5	n.s.
Time in NREM SaO_2 <90% (min)	94.0 ± 104	20.4 ± 34	0.036
Time in Wake SaO_2 <90% (min)	44.5.6 ± 53	3.3 ± 5	0.021

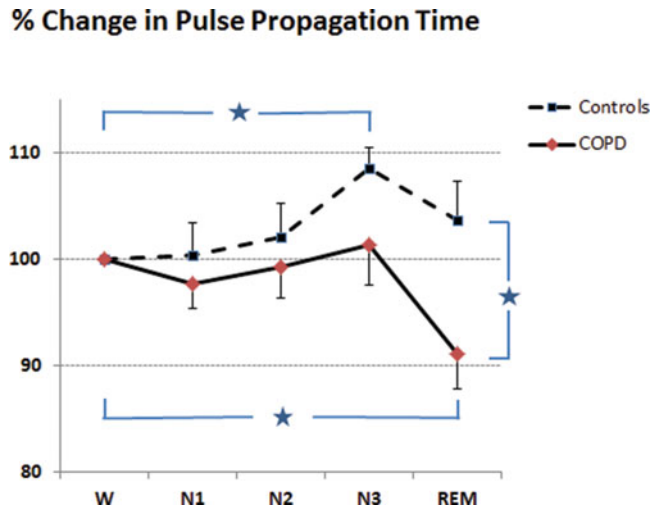

Figure 3. Percentage of change in pulse propagation time (PPT, mean and standard error of the means (SEM)) from wakefulness (= 100%) in patients with COPD and matched non-COPD controls. Asterix indicate significant differences (all $p < 0.05$): Within group increase in PPT from wake to N3 (non-COPD controls) and PPT decrease from wake to REM (COPD patients); between group difference in REM sleep PPT between COPD patients and non-COPD controls. N1, N2, N3 and REM indicate the sleep stages NREM1-3 and REM. Please note, a decrease in PPT corresponds to an increase in arterial stiffness and vice versa.

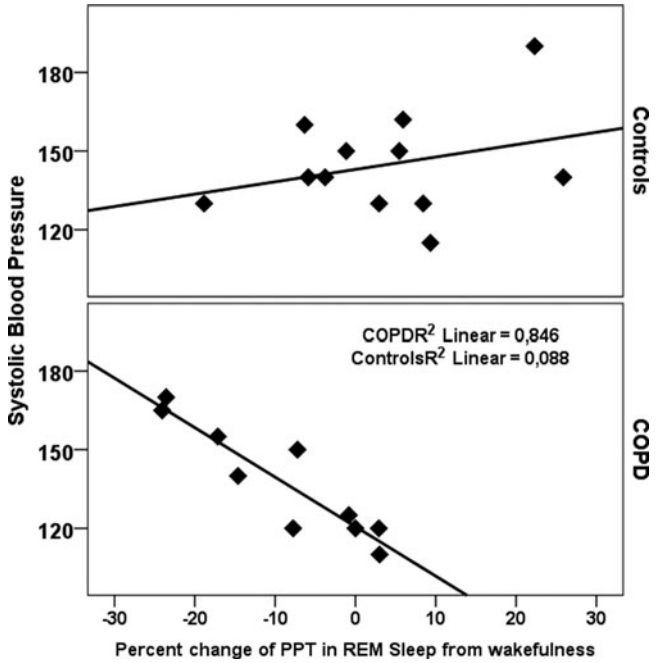

Figure 4. Association between the change in arterial stiffness (PPT) from wakefulness to REM sleep and daytime systolic blood pressure at rest in COPD patients and matched controls.

Discussion

We report three major findings: First, we found that hypoxia and REM sleep modulate overnight arterial stiffness in COPD and healthy controls. Second, in contrast to healthy controls, REM sleep increased arterial stiffness in COPD patients independent of sleep apnea indices, intermittent and sustained hypoxia. Third, the REM-sleep dependent increases of arterial stiffness, and not measures of hypoxia, predicted daytime arterial blood pressure and myocardial oxygen consumption in patients with COPD. Our data suggest that REM sleep imposes a vascular load in COPD patients independent of sleep apnea indices, intermittent and sustained hypoxia.

The effect of hypoxia during sleep on vascular circulation has been studied extensively both in humans and animal models (25–30). While there is consensus that hypoxia generates vasodilation through release of endothelial vasodilatory substances such as NO (13), the overall effect of hypoxia on arterial stiffness remains unclear. This uncertainty may primarily be due to the extent of counter-regulatory increase of sympathetic nervous system activity in response to hypoxia. Indeed, sympathetic activity during sleep will increase vascular muscle tone and highly likely even arterial stiffness (10,26,31). Depending on the balance between these opposing factors the net effect may be either a relaxation or stiffening of the vascular bed. We found that NREM hypoxia was associated with prolonged PPT values. In contrast, REM sleep hypoxia had no additional effect on PPT. A possible explanation is that, sympathetic nerve activity is known to increase during REM sleep (10,32) independently of hypoxia (33,34). Our data strongly suggest that during REM sleep vasoconstrictive forces dominate over the hypoxic vasodilatory component in COPD patients. Taken together, our data demonstrate that REM sleep imposes a vascular load in COPD patients independent of sustained hypoxia. The COPD patients were recruited from patients with suspected sleep apnea and had similar sleep apnea characteristics when compared to a population based study of individuals with mild airway obstruction (35) and a clinical cohort sample with moderate to severe COPD (36). Several studies have demonstrated that sleep apnea in the absence of COPD is associated with increased vascular stiffness, both during sleep and daytime (14–17). We have demonstrated that intermittent hypoxia had no independent effect on arterial stiffness in COPD. This may indicate that intermittent hypoxia in COPD may not be the major contributor for the increased CV morbidity and mortality.

Our study confirmed a strong association between traditional risk factors of cardiovascular disease (including age, blood pressure, obesity) and overnight PPT as a measure of arterial stiffness (8,9,37). We extended these findings by demonstrating that data in patients with COPD showed that sleep stage related changes in arterial stiffness had a strong linear association with daytime hemodynamic measures like daytime arterial blood pressure and RPP—a measure of myocardial oxygen consumption.

Table 4. Correlations between the change in pulse wave propagation time from wakefulness to REM-sleep and daytime hemodynamic parameters.

	PPT change in % from wakefulness to REM sleep	
Variable	COPD ($n = 10$)	Controls ($n = 12$)
Office SBP	**− .920***	.297
Office MBP	**− .764***	.179
Office DBP	− .326	.059
Office HR	− .453	− .301
Pulse Pressure	**− .835***	− .367
Rate Pressure Product	**− .876***	− .358

* = significance value P is ≤ 0.01

COPD = Chronic Obstructive Pulmonary Disease (n = 10), Controls = age, BMI, and AHI matched patients without COPD (n = 12), SBP = Systolic Blood Pressure, MBP = Mean Blood Pressure, DBP = Diastolic Blood Pressure, HR = Resting Heart Rate, Pulse Pressure = SBP-DBP, Rate Pressure Product = HR*SBP

Vascular stiffening during REM sleep may be an independent predictor of CV morbidity in COPD.

There are several strengths and limitations to the current study. This is to our knowledge the first study addressing the changes of arterial stiffness during sleep in COPD patients. Our approach to identify COPD patients and controls, all based on pulmonary function test data, with and without CV disease provided three well defined subsamples allowing for the analysis of different comorbid influences on arterial stiffness. Moreover, we successfully matched COPD and non-COPD control patients in order to identify vascular stiffness pattern during REM sleep. Another strength resides in a careful matching of individuals in the sub-study. Our method to calculate arterial stiffness by an oximeter based pulse wave propagation time analysis has been validated against applanation tonometry of the radial artery and assessment of aortic pulse wave velocity (18, data on file). Indeed, pulse wave analysis has previously been applied for vascular function assessments in COPD and OSA patients (38–40). Third, our study used comprehensive investigations for cardiovascular risk status comparable to Framingham and EU SCORE CV risk classifications (18).

Limitations include the lack of a population based healthy control group and the limited number of COPD patients. Our study is therefore more likely to underestimate the true disease impact of COPD on the cardiovascular system. In our case control sub-analysis, the clinical characteristics of the COPD patients and their matched controls differed with regard to smoking status and CHF prevalence (Table 3). However, our analysis revealed no systematic change in arterial stiffness by CHF disease status. Lastly, the mechanisms or the causal relationship between sleep related changes in arterial stiffness in COPD could not be investigated with the current study design. Methods which can assess local or systemic sympathetic activity during NREM and REM sleep may be used in future studies.

The present work has several important clinical implications. First, the data strongly suggest that sleep imposes a specific load to the cardiovascular system in COPD and this influence may provide diagnostic information for CV risk estimation in COPD. Further mechanistic studies are needed to fully understand NREM and REM specific modulations of arterial stiffness in COPD and other chronic conditions characterized by hypoxia and inflammation. Second, the results suggest a potential vasorelaxing effect of sustained hypoxia during sleep. If the observed changes in PPT are associated with significant hemodynamic consequences, it may explain the deleterious effects of hypoxia on mortality and morbidity in patients with COPD. Third, assessment of PPT by finger pulse oximetry has a number of advantages like robustness, feasibility, non-invasiveness and validated use during sleep. The diagnostic potential for utilizing sleep for cardiovascular monitoring is given.

In conclusion, REM sleep imposes a vascular load in COPD patients independent of sleep apnea indices, intermittent and sustained hypoxia. REM sleep was associated with strong arterial stiffening only in COPD patients suggesting that mechanisms other than hypoxia may affect the CV system. The link between REM-sleep and daytime cardiovascular function suggests that REM-sleep plays a role for increased cardiovascular morbidity of COPD patients. Future studies exploring overnight PPT may provide new insights in the early identification of harmful CV outcome in COPD.

Acknowledgments

Contribution: The corresponding author (LG) takes responsibility for the content of the manuscript, including the data and analysis. All co-authors except for HS were involved in the collection of data. LG and HS planned and performed the data analysis, they also wrote the first draft of the manuscript. All co-authors reviewed the data and were involved in the preparation of the final manuscript.

Funding sources of the study: This study was supported by the Swedish Heart and Lung Foundation (HLF 20110445, 20120429 and 20130488), the German Ministry for Education and Science (BMBF), the National Institute of Health (R01 HL105546), and Weinmann Geräte für Medizin GmbH&Co.KG.

Declaration of interest

1. Dr. Grote reports personal fees from Weinmann GMBH and grants from the Swedish Heart and Lung Foundation during the conduct of the study; personal fees from Resmed, Philips, Mundipharma, and Breas as well as grants from the Resmed and Philips Foundations outside the submitted work.
2. Dr. Hedner reports grants from ResMed, grants from Phillips Respironics, payments related to speaker activities from AstraZeneca, Novartis, Takeda and Jazz Pharmaceuticals outside the submitted work.
3. Dr. Fietze reports personal fees from Somnomed and grant support from Heinen and Löwenstein, Philips, Resmed, Weinmann and Hoffrichter.
4. Dr. Penzel is shareholder of The Siestagroup GmbH and Advanced Sleep Research. His institution has received grants from Cidelec, Apnex, Imthera, Itamar, Nomics, Heinen and Löwenstein, Philips, Resmed, Weinmann.
5. Dr. Randerath reports personal fees from Inspire, personal fees from Philips Respironics, personal fees from Resmed, personal fees from Weinmann, outside the submitted work.
6. Dr. Sanner reports grants from Weinmann outside the submitted work.
7. Dr. Ficker reports personal fees from Weinmann during the conduct of the study.
8. Dr. Schneider reports personal fees from Linde Healthcare, TNI Medical, Fisher & Paykel Healthcare, InSleep, Philipps Respironics, Apnex. My institution has received grants from Imthera, Resmed, InSleep, TNI Medical and Fisher & Paykel Healthcare.
9. Dr. Sommermeyer has nothing to disclose.

ORCID

Ficker JH http://orcid.org/0000-0002-7175-5852

References

1. Müllerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: Systematic literature review. Chest. 2013; 144(4):1163–1178.
2. Sin Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. Proc Am Thorac Soc. 2005; 2(1):8–11.
3. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patientswith chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med. 2010; 182(3):325–331.
4. Maclay JD, MacNee W. Cardiovascular disease in COPD: mechanisms. Chest. 2013; 143(3):798–807.

5. Mills NL, Miller JJ, Anand A, Robinson SD, Frazer GA, Anderson D, et al. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. Thorax. 2008; 63(4):306–311.
6. Vivodtzev I, Tamisier R, Baguet JP, Borel JC, Levy P, Pépin JL. Arterial stiffness in COPD. Chest. 2014; 145(4):861–875.
7. Maclay JD, McAllister DA, Mills NL, Paterson FP, Ludlam CA, Drost EM, et al. Vascular dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009; 15; 180(6):513–520.
8. Van Bortel LM, Duprez D, Starmans-Kool MJ, Safar ME, Giannattasio C, Cockcroft J, et al. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. Am J Hypertens. 2002; 15(5):445–452.
9. Chirinos JA. Arterial stiffness: basic concepts and measurement techniques. J Cardiovasc. Transl Res. 2012; 5(3):243–255.
10. Lavie P, Schnall RP, Sheffy J, Shlitner A. Peripheral vasoconstriction during REM sleep detected by a new plethysmographic method. Nat Med 2000; 6:606.
11. Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med. 1985; 6(4):651–661.
12. Biselli PJ, Grossman PR, Kirkness JP, Patil SP, Smith PL, Schwartz AR, et al. The Effect of Increased Lung Volume in Chronic Obstructive Pulmonary Disease on Upper Airway Obstruction during Sleep. J Appl Physiol 1985; 2015; 5:jap.00455.2014.
13. Halliwill JR. Hypoxic regulation of blood flow in humans. Skeletal muscle circulation and the role of epinephrine. Adv Exp Med Biol. 2003; 543:223–36.
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(1):7–18.
15. Scholze A, Lamwers S, Tepel M, Sanner BM. Nasal continuous positive airway pressure: influence on digital volume pulse in obstructive sleep apnoea patients. Eur Respir J. 2012; 39(5):1127–1135.
16. Jelic S, Bartels MN, Mateika JH, Ngai P, DeMeersman RE, Basner RC. Arterial stiffness increases during obstructive sleep apneas. Sleep. 2002; 25(8):850–855.
17. Wons AM, Kohler M. Established vascular effects of continuous positive airway pressure therapy in patients with obstructive sleep apnoea-an update. J Thorac Dis. 2015; 7(5):912–919.
18. Sommermeyer D, Zou D, Eder DN, Hedner J, Ficker JH, Randerath W, et al. The use of overnight pulse wave analysis for recognition of cardiovascular risk factors and risk: a multicentric evaluation. J Hypertens. 2014; 32(2):276–285.
19. Grote L, Sommermeyer D, Zou D, Eder DN, Hedner J. Oximeter-based autonomic state indicator algorithm for cardiovascular risk assessment. Chest. 2011; 139(2):253–259.
20. Sommermeyer D, Zou D, Ficker JH, Randerath W, Fischer, C, Penzel T, et al. Detection of cardiovascular risk from a photoplethysmographic signal using a matching pursuit algorithm. Med Biol Eng Comput. 2016 Jul; 54(7):1111–1121.
21. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MSM, Zheng J, Stocks J. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Resp J 2012; 40: 1324–1343
22. Iber C, Ancoli-Israel S, Chesson A, Quan S, for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. 1st ed. American Academy of Sleep Medicine, Westchester, IL; 2007.
23. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, et al. european society of hypertension working group on blood pressure monitoring. european society of hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens. 2003; 21(5):821–848.
24. White WB. Heart rate and the rate-pressure product as determinants of cardiovascular risk in patients with hypertension. Am J Hypertens. 1999; 12:50S–55S.
25. Coccagna G, Mantovani M, Brignani F, Parchi C, Lugaresi E. Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnia with periodic breathing. Bull Physiopathol Respir. 1972; 8(5):1159–1172.
26. Hedner J, Ejnell H, Sellgren J, Hedner T, Wallin G. Is high and fluctuating muscle nerve sympathetic activity in the sleep apnoea syndrome of pathogenetic importance for the development of hypertension? J Hypertens Suppl. 1988; 6(4):S529–S531.
27. Schneider H, Schaub CD, Andreoni KA, Schwartz AR, Smith PL, Robotham JL, et al. Systemic and pulmonary hemodynamic responses to normal and obstructed breathing during sleep. J Appl Physiol 1985; 1997 Nov;83(5):1671–1680.
28. Schneider H, Schaub CD, Chen CA, Andreoni KA, Schwartz AR, Smith PL, et al. Neural and local effects of hypoxia on cardiovascular responses to obstructive apnea. J Appl Physiol 1985. 2000; 88(3): 1093–1102.
29. Fletcher EC. Invited review: Physiological consequences of intermittent hypoxia: systemic blood pressure. J Appl Physiol 1985. 2001; 90(4):1600–1605.
30. Fletcher EC, Levin DC. Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease. The effect of short- and long-term oxygen. Chest. 1984; 85(1):6–14.
31. Zou D, Grote L, Eder DN, Peker Y, Hedner J. Obstructive apneic events induce alpha-receptor mediated digital vasoconstriction. Sleep. 2004; 27(3):485–489.
32. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med. 1993 Feb 4; 328(5):303–307.
33. Trinder J, Kleiman J, Carrington M, Smith S, Breen S, Tan N, et al. Autonomic activity during human sleep as a function of time and sleep stage. J Sleep Res. 2001; 10(4):253–264.
34. Herscovici S, Pe'er A, Papyan S, Lavie P. Detecting REM sleep from the finger: an automatic REM sleep algorithm based on peripheral arterial tone (PAT) and actigraphy. Physiol Meas. 2007 Feb; 28(2): 129–140
35. Sanders MH, Newman AB, Haggerty CL, Redline S, Lebowitz M, Samet J, et al. Sleep Heart Health Study. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. Am J Respir Crit Care Med. 2003 Jan 1; 167(1):7–14.
36. Soler X, Gaio E, Powell FL, Ramsdell JW, Loredo JS, Malhotra A, et al. High Prevalence of Obstructive Sleep Apnea in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2015;12(8):1219–1225.
37. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. European society of hypertension; european society of cardiology. 2007 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). Blood Press. 2007; 16(3): 135–232.
38. Clarenbach CF, Stoewhas AC, van Gestel AJ, Latshang TD, Lo Cascio CM, Bloch KE, et al. Comparison of photoplethysmographic and arterial tonometry-derived indices of arterial stiffness. Hypertens Res. 2012; 35(2):228–233.
39. Millasseau SC, Kelly RP, Ritter JM, Chowienczyk PJ. Determination of age-related increases in large artery stiffness by digital pulse contour analysis. Clin Sci (Lond) 2002; 103(4):371–377.
40. Gunarathne A, Patel JV, Hughes EA, Lip GY. Measurement of stiffness index by digital volume pulse analysis technique: clinical utility in cardiovascular disease risk stratification. Am J Hypertens 2008; 21(8):866–872.