Association of Intermittent and Continuous Hypoxaemia with Carotid and Brachial Arterial Intima-media Thicknesses

S Asker[1], M Asker[2], M Ozgokce[3], B Ozbay[4]

ABSTRACT

Objective: We hypothesized that the effect of intermittent and continuous hypoxia on carotid and brachial artery intima-media thicknesses (IMTs) may be similar. We aimed to assess the carotid and brachial arteries' IMTs in cases with intermittent [obstructive sleep apnea syndrome] (OSAS) and continuous (chronic obstructive pulmonary disease) [COPD] hypoxemia together with other confounding demographic and biochemical factors.

Methods: The study was prospectively performed on 197 patients allocated in three groups: 80 patients with severe OSAS, 80 severe COPD patients and 37 healthy controls. These groups were compared in terms of demographics, biochemical markers and IMTs of the right and left carotid and brachial arteries.

Results: Carotid and brachial arterial IMTs were found to be higher in both patient groups than the contro group ($p < 0.001$). Similarly, levels of haemoglobin, haematocrit, cholesterol, triglycerides, LDL, CRP and D-dimer were significantly increased in patient groups. Oxygen saturations ($p < 0.001$) and ejection fractions ($p = 0.001$) were found to be worse and D-dimer levels ($p = 0.010$) were elevated more prominently in COPD patients; whereas, cholesterol ($p < 0.001$), haemoglobin ($p = 0.004$) and LDL ($p = 0.001$) levels were higher in OSAS group. Except the right carotid IMT, which was increased significantly in OSAS patients, IMT measurements were similar in OSAS and COPD groups ($p < 0.001$).

Conclusion: We have shown that both intermittent and continuous hypoxia result in remarkable alterations in carotid-IMT and brachial-IMT. Further prospective trials are warranted to confirm and extend these findings including the biochemical markers, which may aid in the diagnosis and follow-up of patients suffering from hypoxaemia.

Keywords: Brachial artery, carotid intima-media thickness, chronic obstructive pulmonary disease, common carotid artery, sleep apnea

---

[1]Department of Chest Diseases, [2]Department of Cardiology, Van Yuksek Ihtisas Training and Research Hospital, Van, Turkey, [3]Department of Radiology, Van Regional Training and Research Hospital, Van, Turkey and [4]Department of Chest Diseases, Mugla University Faculty of Medicine, Mugla, Turkey.

Correspondence: Dr Selvi Asker, Department of Chest Diseases, Van Yuksek Ihtisas Training and Research Hospital, 65100, Van, Turkey. Tel: +905052514704;
Fax: +904322121954. E-mail: selviasker@yahoo.com

INTRODUCTION

Hypoxaemia occurs continuously in chronic obstructive pulmonary disease (COPD) and intermittently (only nocturnally) in obstructive sleep apnea syndrome (OSAS) patients (1). Hypoxaemia can cause endothelial dysfunction and alterations, which subsequently give rise to atherosclerosis and cardiovascular disease (2, 3).

Intima media thickness (IMT) is an indicator of atherosclerosis and may be linked with coronary heart disease and stroke (4). The IMT ranges between 0.25–1.5 mm, while values > 1.0 mm are often regarded as abnormal (5, 6). However, not only the 'normal' range or 'abnormal' values, but the risk factors related with abnormal IMT values may differ notably between various populations (6). Ultrasonographic diagnosis of increased IMT can assist the decision for treatment and monitorization of preventive therapy.

Intima media thicknesses of carotid and brachial arteries can be useful for prediction and evaluation of atherosclerotic process and for early detection of following complications (7). Therefore, identification of the risk factors for IMT is crucial for slowing the progression of the atherosclerotic disease and enhancement of the effectivity of treatment before symptoms prevail. Furthermore, any correlations between IMT and biochemical markers remain to be elucidated (2, 5).

We hypothesized that the effect of intermittent and continuous hypoxia on carotid and brachial artery IMTs may be similar. The objective of the current study was to compare the alterations of carotid and brachial arterial IMTs in patients with OSAS and COPD and to investigate any differences in terms of demographic, respiratory and laboratory parameters.

METHODS

Study Design: This study was approved by the local Institutional Review Board (2013/1) and performed with respect to the principles of the Helsinki Declaration. Written informed

consent was obtained from all patients prior to participation in the study. A total of 1000 patients that applied to the chest diseases department of our institution between February 2013 and May 2013 were prospectively enrolled in this case-control study and the ones that met the inclusion criterias were allocated in one of the following three groups: Group 1 = eighty severe OSAS patients; Group 2 = eighty severe COPD patients; Group 3 = thirty-seven controls.

The patients had clinical diagnoses of OSAS and COPD at different times. The clinical history was investigated and physical examination, chest roentgenogram, electrocardiography, monitorization of blood pressure, echocardiography and ultrasound examinations were carried out. The control subjects were devoid of any systemic or cardiovascular disease with normal laboratory results. Exclusion criteria were systolic blood pressure ≥ 220 mmHg, acute coronary syndrome, stroke, ischaemic heart disease, major systemic disease such as renal insufficiency, malignancy, liver disease, insulin-dependent diabetes mellitus and depression.

Outcome Parameters: Age, gender, pulmonary artery pressures, co-existing diseases (*eg* hypertension, diabetes mellitus), smoking habits, diurnal and nocturnal oxygen saturations and durations of hypoxemic periods and ejection fractions carotid intima media thickness (C-IMT) measurements, brachial intima media thickness (B-IMT) measurements were noted.

Serum levels of haemoglobin, haematocrit, cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), C-reactive protein (CRP) and D (domain) -dimer were recorded and compared between groups.

Hypertension is a systolic blood pressure of > 140 mmHg and/or a diastolic blood pressure of > 90 mmHg derived from the mean of three measurements in at least three visits at one-week intervals or under antihypertensive treatment. Diagnosis of OSAS was confirmed after an overnight sleep study performed in the hospital. An apnea/hypopnea index (AHI) > 5 was consistent with OSAS and patients with severe OSAS (AHI ≥30) were included in the study

(8, 9). Chronic obstructive pulmonary disease was substantiated with past or current smoking history (> 20 pack years), clinical assessment, as well as pulmonary function tests demonstrating an airflow obstruction (FEV_1 / FVC < 70) with a change in FEV_1 < 200 mL and 12% in the bronchodilator test. Severe COPD patients were diagnosed with FEV_1 < 50%.

Ultrasound measurements: Patients participated in the current study were evaluated by high-resolution ultrasound (Logiq 9 system, GE Medical Systems, Milwaukee, WI, USA) and a 7.5 MHz linear array transducer was used in this purpose. Intima-media thicknesse measurement was performed *via* B-mode ultrasonography. A location 1 cm proximal to the carotid bifurcation was identified and the IMT of the distant wall was assessed between the lumen–intima interface and the media–adventitia interface (10). The IMT measurement was obtained on 4 consecutive sites at intervals of 1-mm and the average of 4 measurements was used for analysis. The average value was obtained from values obtained from right and left CCAs. The measurements were performed manually on images obtained during the sonographic scanning (11). Assessments were performed by a single experienced radiologist blinded to the data (12).

Statistical analysis: Data were analysed using the Statistical Package for Social Sciences 19.0 for Windows (SPSS Inc., Chicago, IL, USA). Parametric tests were used for data with normal distribution and non-parametric tests were applied to data of questionably normal distribution. Independent groups were compared with Independent-samples *t*-test and Mann-Whiney U-tests. One-way analysis of variance (ANOVA) test was used to compare groups of independent continuous variables and Bonferroni *post hoc* analysis was used for multiple comparison tests. The distribution of categorical variables in both groups was compared using Pearson Chi-squared test. Level of significance was set at $p < 0.05$.

RESULTS

Table 1 demonstrates the demographical, biological, haematological and respiratory characteristics of the studied population. The mean ages for Group 1, 2 and 3 are 48.1 ± 10.4, 58.3 ± 8.9 and 47.6 ± 9.7, respectively ($p > 0.001$). In addition to age, three groups displayed significant differences in terms of gender ($p < 0.001$), pulmonary artery pressure ($p < 0.001$) and smoking habit ($p < 0.001$).

Table 1. Comparative demographic and clinical data of the studied population in three groups.

		Group 1 (n = 80) (OSAS)	**Group 2 (n = 80) (COPD)**	**Group 3 (n = 37) (Healthy controls)**	***p*-value**
Age (years)		48.1 ± 10.4	58.3 ± 8.9	47.6 ± 9.7	p1 *vs* 2 < 0.001 p1 *vs* 3 = 0.784 p2 *vs* 3 < 0.001
Gender	Female	24 (30%)	27 (33.8%)	27 (73%)	< 0.001*
	Male	56 (70%)	53 (66.2%)	10 (27%)	
PAP	< 20 mmHg	62 (77.5%)	44 (55%)	37 (100%)	< 0.001*
	≥ 20 mmHg	18 (22.5%)	36 (45%)	0	
DM	No	73 (91.3%)	71 (88.8%)	37 (100%)	0.113
	Yes	7 (8.7%)	9 (11.2%)	0	
HT	No	71 (88.8%)	72 (90%)	37 (100%)	0.112
	Yes	9 (11.2%)	8 (10%)	0	
Smoking	No	52 (65%)	27 (33.8%)	30 (81.1%)	< 0.001*
	Yes	28 (35%)	53 (66.2%)	7 (18.9%)	

Pearson Chi-squared test
(Abbreviations: OSAS = obstructive sleep apnea syndrome; COPD = chronic obstructive pulmonary disease; PAP = pulmonary artery pressure; DM = diabetes mellitus; HT = hypertension; *: statistically significant)

Intima media thicknesses and biochemical parameters in three groups are shown in Table 2. C-IMT, B-IMT, oxygen saturation level, duration of hypoxia duration, ejection fraction as well as serum levels of triglycerides, cholesterol, CRP, D-dimer, haemoglobin, haematocrit and LDL exhibited difference between three groups.

Table 2. Results of IMT measurements, laboratory and respiratory data of three groups.

	Group 1 (n = 80) (OSAS)	**Group 2 (n = 80) (COPD)**	**Group 3 (n = 37) (Healthy controls)**	***p* -value**
Right C-IMT (mm)	0.70 ± 0.15	0.70 ± 0.30	0.40 ± 0.20	p1 vs 2 = 0.706 p1 vs 3 < 0.001 p2 vs 3 < 0.001
Left C-IMT (mm)	0.60 ± 0.10	0.70 ± 0.20	0.40 ± 0.10	p1 vs 2 = 0.144 p1 vs 3 < 0.001 p2 vs 3 < 0.001
Right B-IMT (mm)	0.30 ± 0.10	0.40 ± 0.15	0.20 ± 0.10	p1 vs 2 = 0.724 p1 vs 3 < 0.001 p2 vs 3 < 0.001
Left B-IMT (mm)	0.30 ± 0.10	0.3 ± 0.1	0.10 ± 0.10	p1 vs 2 = 0.647 p1 vs 3 < 0.001 p2 vs 3 < 0.001
Hb (g/dL)	16.3 ± 2.0	15.6 ± 2.4	14.9 ± 1.6	p1 vs 2 = 0.049 p1 vs 3 = 0.001 p2 vs 3 = 0.082
Hct	48.5 ± 6.7	47.9 ± 7.7	44.9 ± 5.0	p1 vs 2 = 0.599 p1 vs 3 = 0.010 p2 vs 3 = 0.030
LDL (mg/mL)	124.3 ± 36.8	105.8 ± 37.6	111.5 ± 32.0	p1 vs 2 = 0.001 p1 vs 3 = 0.079 p2 vs 3 = 0.426
HDL (mg/mL)	39.7 ± 10.3	43.2 ± 41.9	44.3 ± 11.8	0.620
Cholesterol (mg/mL)	204.0 ± 47.4	174.5 ± 48.4	180.0 ± 39.6	p1 vs 2 < 0.001 p1 vs 3 = 0.010 p2 vs 3 = 0.548
TG (mg/mL)	189.5 ± 110.0	123.5 ± 87.5	97.0 ± 76.0	p1 vs 2 < 0.001 p1 vs 3 < 0.001 p2 vs 3 = 0.014
CRP (mg/mL)	0.62 ± 0.64	0.92 ± 1.0	0.40 ± 0.41	p1 vs 2 = 0.001 p1 vs 3 = 0.001 p2 vs 3 < 0.001
D-dimer (mg/mL)	123.0 ± 91.0	141.0 ± 153.0	110.0 ± 77.0	p1 vs 2 = 0.008 p1 vs 3 = 0.559 p2 vs 3 = 0.086
EF (%)	62.50 ± 5.00	60.00 ± 5.50	65.00 ± 8.0	p1 vs 2 < 0.001 p1 vs 3 = 0.052 p2 vs 3 < 0.001
Oxygen saturation (%)	87.0 ± 5.0	85.0 ± 6.0	97.0 ± 2.0	p1 vs 2 < 0.001 p1 vs 3 < 0.001 p2 vs 3 < 0.001

Kruskal-Wallis Test (*post hoc* test: Bonferroni corrected Mann-Whitney U test $\alpha = 0.017$)
(Abbreviations: OSAS = Obstructive sleep apnea syndrome; COPD = Chronic obstructive pulmonary disease; C-IMT = carotid artery intima media thickness; B-IMT= brachial artery intima media thickness; Hb = haemoglobin; Hct = haematocrit; LDL = low density lipoproteins; HDL = high density lipoproteins; TG = triglycerides; CRP = C-reactive protein; EF = ejection fraction; min = minutes

DISCUSSION

In this study, we attempted to demonstrate whether C-IMT and B-IMT displayed variation among OSAS patients, COPD patients and healthy controls. In addition, levels of haemoglobin, haematocrit, CRP, D-dimer, triglycerides, LDL and cholesterol were studied between OSAS and COPD patients.

Carotid intima media thickness is an early marker of systemic atherosclerosis (5). The intima-media complex consists of endothelial cells, connective tissue and smooth muscle (3). Vascular risk factors result in lipid deposition and provoke intimal hyperplasia and hypertrophy that in-turn causes thickening of the intima-media complex (8, 9). A correlation was demonstrated between C-IMT and traditional vascular risk factors and OSAS was supposed to lead to atherosclerosis, and this was evident as an increase in IMT of carotid artery (7–9, 13, 14). Hypoxaemia and systemic inflammatory reactions ensourcing from OSAS and COPD can be linked with progression of atherosclerosis and increased risk of cardiovascular morbidity (13–15). Up to now, it was demonstrated that a CPAP therapy course over four months could reduce carotid IMT in patients with severe OSAS free of existing cardiovascular diseases *versus* controls (16, 17). In the present study, only right carotid artery IMT was found to be increased in OSAS group than COPD group. Other than this finding, C-IMT and B-IMT measurements yielded similar results. According to our results, we could not demonstrate a noteworthy difference between intermittent and continuous hypoxaemia groups in terms of IMT. In other words, intermittent hypoxia (nocturnal hypoxemia in OSAS) seems to be as effective as continuous hypoxaemia (in case of COPD) with respect to its effect on IMT. This may ensource from the fact that nocturnal hypoxaemia is probably more important in terms of oxidative stres than daily hypoxaemia. We assessed brachial arteries bilaterally in addition to the carotid arteries and to our knowledge, this methodological aspect is original and unique.

Hypoxaemia that occurs in OSAS and COPD may worsen atherosclerosis by means of the impacts on hypertension, diabetes mellitus and dyslipidaemia. In addition, these hypoxaemic disorders can trigger atherosclerosis directly through the systemic inflammatory mechanisms such as activation of leukocytes and vascular smooth muscle cells, oxidative stress, peroxidation of lipids and endothelial dysfunction (15). The present study showed that nocturnal and daily oxygen saturations were significantly worse in COPD patients.

In the present study, analysis of biochemical and respiratory parameters have yielded that issues such as haemoglobin, haematocrit, CRP and D-dimer can undergo noteworthy changes due to hypoxaemia. However, validation and standardization of specific markers that may aid in diagnosis of vascular pathologies requires further sophisticated studies on larger series.

Some limitations of our study must be mentioned. First of all, our sample size is relatively small and definite criteria for selection of patients and ongoing impact of treatments being applied for OSAS and COPD is lacking. Due to ethical considerations, concurrent medications could not be interrupted and this might have an effect on the measurements of carotid and brachial IMTs. Due to these limitations, extrapolations should be made carefully.

Moreover, further randomized, prospective, controlled trials on larger series are necessary for making healthier interpretations. Our findings need to be confirmed by other studies and further studies are obviously required to understand these relationships.

In conclusion, we have found that carotid and brachial arterial IMT is increased in both OSAS and COPD patients compared with the control subjects. However, the IMT measurements did not display significant difference between the COPD and OSAS groups. In other words, intermittent and continuous hypoxia seem to exert similar effects on the vascular wall. This may be due to the fact that nocturnal hypoxia plays a more crucial role on

the vascular oxidative stress leading to atherosclerosis. All in all, IMT seems to be a reliable predictor and index of atherosclerosis and other laboratory indicators that may aid in the diagnosis and monitorization of efficacy of treatment needs for further prospective studies.

ACKNOWLEDGEMENTS

None

REFERENCES

1. Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN et al. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. Stroke 1999; **30:** 841–50.

2. Baguet JP, Hammer L, Levy P, Pierre H, Launois S, Mallion JM et al. The severity of oxygen desaturation is predictive of carotid wall thickening and plaque occurrence. Chest 2005: **128:** 3407–12.

3. Altin R, Ozdemir H, Mahmutyazicioglu M, Kart L, Uzun L, Ozer T et al. Evaluation of carotid artery wall thickness with high-resolution sonography in obstructive sleep apnea syndrome. J Clin Ultrasound 2005; **33:** 80–6.

4. Tavil Y, Kaya MG, Oktar SO, Sen N, Okyay K, Yazici HU et al. Uric acid level and its association with carotid intima-media thickness in patients with hypertension. Atherosclerosis 2008; **197:** 159–63.

5. Sun Y, Lin CH, Lu CJ, Yip PK, Chen RC. Carotid atherosclerosis, intima media thickness and risk factors- an analysis of 1781 asymptomatic subjects in Taiwan. Atherosclerosis 2002; **164:** 89–94.

6. Vicenzini E, Ricciardi MC, Puccinelli F, Altieri M, Vanacore N, Di Piero V et al. Common carotid artery intima-media thickness determinants in a population study. J Ultrasound Med 2007; **26:** 427–32.

7. Silvestrini M, Rizzato B, Placidi F, Baruffaldi R, Bianconi A, Diomedi M. Carotid artery wall thickness in patients with obstructive sleep apnea syndrome. Stroke 2002; **33:** 1782–5.

8. Suzuki T, Nakano H, Maekawa J, Okamoto Y, Ohnishi Y, Yamauchi M et al. Obstructive sleep apnea and carotid artery intima-media thickness. Sleep 2004; **27:** 129–33.

9. Wattanaki K, Boland L, Punjabi NM, Shahar E. Relation of sleep-disordered breathing to carotid plaque and intima-media thickness. Atherosclerosis 2008; **197:** 125–31.

10. Sidhu PS, Desai SR. A simple and reproducible method for assessing intima-media thickness of the common carotid artery. Br J Radiol 1997; **70:** 85–9.

11. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986; **74:** 1399–406.

12. Salonen R, Haapanen A, Salonen JT. Measurement of intima-media thickness of common carotid arteries with high-resolution B-mode ultrasonography: inter and intra-observer variability. Ultrasound Med Biol 1991; **17:** 225–30.

13. Kawamoto R, Ohtsuka N, Ninomiya D, Nakamura S. Association of obesity and visceral fat distribution with intima-media thickness of carotid arteries in middle-aged and older persons. Intern Med 2008; **47:** 143–9.

14. Kotsis VT, Stabouli SV, Papamichael CM, Zakopoulos NA. Impact of obesity in intima media thickness of carotid arteries. Obesity 2006; **14:** 1708–15.

15. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N et al. Mannheim intima-media thickness consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis 2012; **34:** 290–6.

16. Hui DS, Shang Q, Ko FW, Ng SS, Szeto CC, Ngai J et al. A prospective cohort study of the long-term effects of CPAP on carotid artery intima-media thickness in obstructive sleep apnea syndrome. Respiratory Research 2012; **13:** 22.

17. Oyama J, Yamamoto H, Maeda T, Ito A, Node K, Makino N. Continuous positive airway pressure therapy improves vascular dysfunction and decreases oxidative stress in patients with the metabolic syndrome and obstructive sleep apnea syndrome. Clin Cardiol 2012; **35:** 231–6.