

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

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### ABSTRACT

**Objective:** To assess the carotid and brachial arteries' intima-media thicknesses (IMTs) in cases with intermittent (obstructive sleep apnoea syndrome (OSAS)) and continuous (chronic obstructive pulmonary disease (COPD)) hypoxaemia together with other confounding demographic and biochemical factors.

**Methods:** The study was prospectively performed on 197 patients allocated in three groups: 80 with severe OSAS, 80 with 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 control group ( $p < 0.001$ ). Similarly, levels of haemoglobin, haematocrit, cholesterol, triglycerides, low-density lipoproteins (LDL), C-reactive protein and D (domain)-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 ( $p < 0.001$ ), hemoglobin ( $p = 0.004$ ) and LDL ( $p = 0.001$ ) levels were higher in the OSAS group. Except the right carotid IMT, which was increased significantly in OSAS patients, IMT measurements were similar in the 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 apnoea

### INTRODUCTION

Hypoxaemia occurs continuously in chronic obstructive pulmonary disease (COPD) and intermittently (only nocturnally) in obstructive sleep apnoea 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 and 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 also the risk factors related to abnormal IMT values may differ notably between various populations (6). Ultrasonographic diagnosis of increased IMT can assist the decision for treatment and monitoring of preventive therapy.

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Intima-media thicknesses of carotid and brachial arteries can be useful for the prediction and evaluation of the atherosclerotic process and for early detection of subsequent complications (7). Therefore, identification of the risk factors for IMT is crucial for slowing the progression of the atherosclerotic disease and enhancement of the effectiveness 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 is 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.

## SUBJECTS AND 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 who attended the chest diseases department of Van Yuksek Ihtisas Training and Research Hospital between February 2013 and May 2013 were prospectively enrolled in this case-control study, and those who met the inclusion criteria were allocated in one of the following three groups: Group 1 = 80 patients with severe OSAS, Group 2 = 80 patients with severe COPD and Group 3 = 37 healthy controls

The patients were clinically diagnosed with OSAS and COPD at different times. The clinical history was investigated, and physical examination, chest roentgenogram, electrocardiography, monitoring 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  $\geq 220$  mmHg, acute coronary syndrome, stroke, ischemic heart disease and major systemic diseases, 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 and diabetes mellitus), smoking habits, diurnal and nocturnal oxygen saturations,

durations of hypoxaemic periods, ejection fractions, carotid intima-media thickness (C-IMT) measurements, and 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 was defined as 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 1-week intervals or currently taking antihypertensive treatment. Diagnosis of OSAS was confirmed after an overnight sleep study performed in the hospital. An apnoea/hypopnea index (AHI)  $> 5$  was consistent with OSAS, and patients with severe OSAS (AHI  $\geq 30$ ) 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 (FEV1 / FVC  $< 70$ ) with a change in FEV1  $< 200$  ml and 12% in the bronchodilator test. Patients with severe COPD were diagnosed with FEV1  $< 50\%$ .

### 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. IMT 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 four consecutive sites at intervals of 1 mm, and the average of four measurements was used for analysis. The average value was obtained from values obtained from the right and left common carotid arteries. 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 analyses

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–Whitney *U*-tests. One-way analysis of variances test was performed 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 the Pearson chi-square test. The 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 Groups 1, 2 and 3 are  $48.1 \pm 10.4$ ,  $58.3 \pm 8.9$  and  $47.6 \pm 9.7$ , respectively ( $p > 0.001$ ). In addition to age, the groups displayed significant differences in terms of gender ( $p < 0.001$ ), pulmonary artery pressure ( $p < 0.001$ ) and smoking habit ( $p < 0.001$ ).

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

## 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 was observed (7–9, 13, 14). Hypoxaemia and systemic inflammatory reactions resulting from OSAS and COPD can be linked to the progression of atherosclerosis and increased risk of cardiovascular morbidity (13–15). Up to now, it was demonstrated that a continuous positive airway pressure therapy course over four months could reduce carotid IMT in patients with severe OSAS free of existing cardiovascular diseases versus healthy controls (16, 17). In the present study, only right carotid artery IMT was found to be increased in the OSAS group compared to the 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 hypoxaemia in OSAS) seems to be as effective as continuous hypoxaemia (in the case of COPD) with respect to its effect on IMT. This may result from the fact that nocturnal hypoxaemia is probably more important in terms of oxidative stress than daily hypoxaemia. We assessed brachial arteries bilaterally in

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)	<i>p</i> value
Age (years)		48.1 ± 10.4	58.3 ± 8.9	47.6 ± 9.7	p1vs2 < 0.001 p1vs3 = 0.784 p2vs3 < 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-square test. COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HT = hypertension; OSAS = obstructive sleep apnoea syndrome; PAP = pulmonary artery pressure; \*: statistically significant.

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	p1vs2 = 0.706 p1vs3 < 0.001 p2vs3 < 0.001
Left C-IMT (mm)	0.60 ± 0.10	0.70 ± 0.20	0.40 ± 0.10	p1vs2 = 0.144 p1vs3 < 0.001 p2vs3 < 0.001
Right B-IMT (mm)	0.30 ± 0.10	0.40 ± 0.15	0.20 ± 0.10	p1vs2 = 0.724 p1vs3 < 0.001 p2vs3 < 0.001
Left B-IMT (mm)	0.30 ± 0.10	0.3 ± 0.1	0.10 ± 0.10	p1vs2 = 0.647 p1vs3 < 0.001 p2vs3 < 0.001
Hb (g/dl)	16.3 ± 2.0	15.6 ± 2.4	14.9 ± 1.6	p1vs2 = 0.049 p1vs3 = 0.001 p2vs3 = 0.082
Hct	48.5 ± 6.7	47.9 ± 7.7	44.9 ± 5.0	p1vs2 = 0.599 p1vs3 = 0.010 p2vs3 = 0.030
LDL (mg/ml)	124.3 ± 36.8	105.8 ± 37.6	111.5 ± 32.0	p1vs2 = 0.001 p1vs3 = 0.079 p2vs3 = 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	p1vs2 < 0.001 p1vs3 = 0.010 p2vs3 = 0.548
TG (mg/ml)	189.5 ± 110.0	123.5 ± 87.5	97.0 ± 76.0	p1vs2 < 0.001 p1vs3 < 0.001 p2vs3 = 0.014
CRP (mg/ml)	0.62 ± 0.64	0.92 ± 1.0	0.40 ± 0.41	p1vs2 = 0.001 p1vs3 = 0.001 p2vs3 < 0.001
D-dimer (mg/ml)	123.0 ± 91.0	141.0 ± 153.0	110.0 ± 77.0	p1vs2 = 0.008 p1vs3 = 0.559 p2vs3 = 0.086
EF (%)	62.50 ± 5.00	60.00 ± 5.50	65.00 ± 8.0	p1vs2 < 0.001 p1vs3 = 0.052 p2vs3 < 0.001
Oxygen saturation (%)	87.0 ± 5.0	85.0 ± 6.0	97.0 ± 2.0	p1vs2 < 0.001 p1vs3 < 0.001 p2vs3 < 0.001

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

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 the 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, the analysis of biochemical and respiratory parameters has shown that issues such as hemoglobin, 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 the 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 are increased in both OSAS and COPD patients compared with the healthy control subjects. However, the IMT measurements did not display a 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.

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