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The effect of chronic carbon monoxide exposure on hs-CRP, CIM thickness and PEF in furnacemen

[Kalorifercilerde kronik karbon monoksit maruziyetinin hs-CRP, KIM kalınlığı ve PEF hızı üzerine olan etkisi]

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ABSTRACT

Objective: The relationship of atherosclerosis, carotid intima media thickness, high sensitive C-reactive protein and the airway narrowness in patients who were exposed to chronic carbon monoxide was evaluated.

Materials and Methods: Forty seven healthy non-smoker male furnacemen who have been working at least ten years, and 48 non-smoker healthy men were enrolled to the study. The body mass index, blood pressure, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, carotid intima media thickness, carboxyhemoglobin, high sensitive C-reactive protein and peak expiratory flow velocity of both groups were evaluated.

Results: Carboxyhemoglobin ($p < 0.001$), high sensitive C-reactive protein ($p < 0.001$) and carotid intima media thickness ($p < 0.001$) levels were found to be higher in furnaceman group. While the carotid intima media thickness ($p < 0.001$), carboxyhemoglobin ($p < 0.001$) and high sensitive C-reactive protein ($p < 0.001$) values were observed significantly higher, the peak expiratory flow percentage was significantly lower in furnaceman group ($p < 0.001$). There was a statistically significant correlation between age and carboxyhemoglobin ($p < 0.004$); carboxyhemoglobin and high sensitive C-reactive protein levels ($p < 0.001$); carboxyhemoglobin level and working years ($p < 0.001$); high sensitive C-reactive protein values and working years ($p < 0.001$); peak expiratory flow percentage and carboxyhemoglobin level ($p < 0.001$), peak expiratory flow percentage and working years ($p < 0.001$), peak expiratory flow percentage and age ($p < 0.007$); high sensitive C-reactive protein levels and exposure year ($p < 0.001$), carotid intima media thickness and exposure year ($p = 0.035$) in furnaceman group.

Conclusion: Chronic carbon monoxide exposure increases high sensitive C-reactive protein and carotid intima media thickness in the course of time and lays the groundwork for atherosclerosis and also decreases the peak expiratory flow velocity probably via obstructing the airways.

Keywords: Carotid intima media thickness, high sensitive C-reactive protein, atherosclerosis, peak expiratory flow velocity, furnaceman

Conflict of interest: The authors declare that they have no conflict of interests, not supported or funded by any Drug Company.

ÖZET

Amaç: Bu çalışmamızda kronik karbon monoksite maruz kalan kişilerde ateroskleroz, karotis intima media kalınlığı, yüksek sensiviteli C-reaktif protein ve hava yolu darlığı ilişkisini inceledik.

Materyal ve Metot: En az 10 yıl boyunca çalışan sağlıklı, sigara içmeyen 47 kalorifer yakan erkek görevlisi (çalışma grubu) ve yaşça uyuşan 48 sağlıklı erkek (kontrol grubu) çalışmaya alındı. Her iki grup için vücut kitle indeksi, kan basıncı, total kolesterol, trigliserid, düşük dansiteli lipoprotein kolesterol, yüksek dansiteli lipoprotein kolesterol, karotis intima media kalınlığı, karboksihemoglobin seviyesi, yüksek sensiviteli C-reaktif protein, ekspiratuvar tepe akım hızı değerleri ölçüldü.

Bulgular: Her iki grubun yaş, body mass index, kan basıncı, total cholesterol, triglyceride, low-density lipoprotein cholesterol ve high-density lipoprotein cholesterol değerleri birbirleriyle benzer bulundu. Kalorifercilerde karboksihemoglobin, yüksek sensiviteli C-reaktif protein ve karotis intima media kalınlığı ($p < 0.001$) değerleri daha yüksek bulunurken ekspiratuvar tepe akım hızı yüzdeleri daha düşük bulundu ($p < 0.001$). Kalorifercilerde yaş ve karboksihemoglobin arasında ($p < 0.004$); karboksihemoglobin ve yüksek sensiviteli C-reaktif protein seviyeleri ($p < 0.001$); karboksihemoglobin seviyesi ve çalışma yılları ($p < 0.001$); yüksek sensiviteli C-reaktif protein değerleri ve çalışma yılları ($p < 0.001$); ekspiratuvar tepe akım hızı yüzdesi ve karboksihemoglobin seviyesi ($p < 0.001$), ekspiratuvar tepe akım hızı yüzdesi ve çalışma yılları ($p < 0.001$), ekspiratuvar tepe akım hızı yüzdesi ve yaş ($p < 0.007$); yüksek sensiviteli C-reaktif protein değerleri ve karnmonoksite maruziyet süresi ($p < 0.001$), karotis intima media kalınlığı ve maruziyet yılları ($p = 0.035$) arasında istatistiksel olarak anlamlı bir korelasyon vardı.

Sonuç: Kronik karbon monoksit maruziyeti zamanla yüksek sensiviteli C-reaktif protein ve karotis intima media kalınlığını artırarak ateroskleroza zemin hazırlamakta ve ayrıca hava yollarında daralma yaparak ekspiratuvar tepe akım hızında azalmaya neden olmaktadır.

Anahtar Kelimeler: Karotis intima media kalınlığı, yüksek duyarlı C-reaktif protein, ateroskleroz, ekspiratuvar tepe akım hızı, kaloriferci

Çıkar çatışması: Yazarlar çıkar çatışması bulunmadığını, hiçbir ilaç firması tarafından desteklenmediklerini beyan ederler.

Introduction

Carbon monoxide (CO) is a colorless, odorless, tasteless, non-irritating gas, which occurs due to incomplete burning of carbon containing materials, and can easily be absorbed by the lungs. CO, which creates COHb by connecting to hemoglobin, may cause several clinical problems from specific appearances to coma leading to hypoxia in several organs, starting with the myocardium [1,2]. Chronically, CO intoxication usually occurs in people who are in long term contact with CO due to their profession. The exact diagnosis of intoxication is possible by determination of high COHb levels [3]. Our information on the effects of chronic CO exposure on the respiratory system, cardiovascular system, and atherosclerosis is limited, and data resulting from human and animal tests do not correspond [4,5].

Carotid intima media thickness (CIMT) provides information regarding future cardiovascular happenings and is accepted as the marker of generalized atherosclerosis [6]. C-reactive protein (CRP) is an acute phase reactant that shows the dimension and progression of coronary and extra coronary atherosclerosis [7]. In order to use CRP at the diagnosis of cardiovascular diseases, a more sensitive measurement is needed. For this, high sensitivity C-reactive protein (hs-CRP) measurement methods were developed [8].

It is known that air pollution, smoking, and being exposed to gases that cause airway inflammation decrease peak expiratory flow (PEF) values [9]. Being chronically exposed to CO at moderate levels without acute intoxication is especially observed in barbecue workers (grill-kebab chefs), machine operators, firemen, furnacemen (who run coal or foil oil in to the furnaces especially in residential apartments to keep apartments warm during winter season in Turkey) and mine workers, who do not have enough air circulation in their working environment [10].

The period to be found in environment with CO, the greatness of closed environment, the ventilation condition of closed environment and the construction time of measurement influenced those varieties.

Almost every apartment employs a furnaceman in Turkey. Although, a few amount of apartment houses are heated with fuel-oil, mostly used coal in winter. At south east of Turkey the furnaceman run coal five months per year. In that period they work approximately three hours in a closed environment without sufficient air circulation per a day. In present study, we tried to demonstrate the effects of chronic exposure to CO on the respiratory system, cardiovascular system, and atherosclerosis among furnacemen by measuring TC, HDL-C, TG, LDL-C, hs-CRP, COHb, environment CO, CIMT and PEF. Besides we evaluate the relationship between chronic CO exposures, atherosclerosis and airway obstruction in healthy furnacemen from Turkey.

Material and Method

Subjects

The present study was conducted in Emergency and Cardiology Departments of Medical School of Gaziantep University, Turkey, from 10th November, 2008 to 21st April 2008. The protocol was conducted in accordance with the Helsinki Declaration and the Ethical Approval was obtained (06-2008/116). Forty-seven male (study group) furnacemen working in apartments and run furnaces (that works with coal) for at least 10 years, and 48 non-smokers (smoking status was evaluated by self-report) healthy male volunteers (control group) were gathered for this study. For the study group, all the participators were recruited from different apartment where they run coal for at least 20 hours per week. For the control group, the volunteers were collected from our hospital personnel (18 technicians, 17 doctors, 2 ambulance drivers, and 11 security guards). Exclusion criteria included smoking, history of any cardiovascular disease including coronary arterial diseases, valvular heart disease, myocardial or pericardial diseases, arrhythmia, and diabetes mellitus. Also, anyone with infection or autoimmune diseases, neoplastic diseases, kidney/lung/liver diseases, major depression, and history of major surgery were excluded.

The heights and weights of all participants were recorded, and the the body mass index (BMI) were calculated by dividing the weight into the square of the height (kg/m^2) and the blood pressure (BP) measurements were recorded after a rest of 10 minutes and the average of 3 BP measurements with an interval of 5 minutes.

Blood collection and biochemical parameters

The venous blood samples were taken from the antecubital vein of the subjects while lying in the supine position after a 12-h fasting state.

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) levels are measured by the enzymatic colorimetric method with a Beckman DU-7 spectrometer (Roche-Hitachi, Mannheim, Germany; Beckman, Fullerton, CA, USA). And the low-density lipoprotein cholesterol (LDL-C), was calculated by the Friedewald's formula. High sensitive C-reactive protein (hs-CRP) levels were measured by using CardioPhase hs-CRP (Dade Behring Inc. Newark, DE, USA) kits. carboxyhemoglobin (COHb) level was examined by Masimo Rainbow SET Radical-7 Pulse CO-Oximeter (Masimo, USA) device from tip of finger. The environment CO level was determined by using GMI GT-40 (GMI, Scotland) device.

Carotids intimae media thickness measurement *(CIMT)*

Carotids intimae media thickness measurement at the evaluation of atherosclerosis is a non-invasive method. CIMT not only determines the early diagnosis of athe-

rosclerosis. The measurement of the CIMT is performed by a physician, who did not know the clinical data of the participants by using a 12 MHz linear transducer (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway). For the CIMT, the distal plain edge of the carotis artery at the neck was examined. The distance between lumen-intimae and the media-adventitia was measured for CIMT. At the measurement, the thickness of the wall that was far to the probe was determined. For every area, measurement was performed at 3 different points, and the average was taken for calculations.

Peak expiratory flow measurement (PEF)

Peak expiratory flow is the maximum expiratory flow speed due to a forced expiration after a forced inspiration. The PEF measurement is defined as liters per minute, and is used for measuring the range of great airway obstructions. Values are determined according to height and age [9]. The PEF measurements were performed with a PEF-meter (Personel Best, Respironics New Jersey NC, USA) by asking the persons to put the device in their mouths and blow with all their power after a deep breath while standing and after the PEF-meter needle was brought to zero. Of the 3 measurements, which were made following each other, the one with the highest value was taken.

Statistics

Mean values of parameters were compared using Analysis of Variance (ANOVA) using the SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized by using mean ±standard deviations and qualitative data were summarized by using percentages. Relationships between variables were made using the Pearson correlation test. A value of $p < 0.05$ was considered statistically meaningful.

Results

Forty-seven male furnaceman (average age: 35.3 ±3.9 years) that had been running furnace for at least 10 years (average occupation time: 12.1 ±2.4 years) and 48 non smoker, male healthy volunteers (average ages: 34.7 ±6.5 years) were gathered for this study. The average of measured CO level at working places was 64.53 ±21.38 ppm (43-85 ppm). CO level that was measured with the same machine in the environment was 0 ppm.

The results of two groups regarding age, BMI, BP, TC, LDL-C, HDL-C, TG, CIMT, COHb, hs-CRP, and PEF percentage are summarized in Table 1. The clinical attributes, ages, BMI, BP, TC, LDL-C, HDL-C, and TG levels of the furnaceman and the control groups were similar ($p > 0.05$). While the CIMT ($p < 0.001$), COHb ($p < 0.001$) and hs-CRP ($p < 0.001$) values were seen statistically significant high at an advanced level, the PEF percentage was seen statistically significant low at an advanced level in furnacemen group according to the control group ($p < 0.001$).

Relationships between variables are given in Table 2. In Pearson correlation analysis, there was a closely relationship between age and COHb in furnaceman group ($r = 0.416$, $p < 0.004$). However, there was no relationship between age and hs-CRP ($r = 0.213$, $p = 0.150$), age and CIMT ($r = 0.277$, $p = 0.069$).

In furnaceman group, while a statistically significant relation was demonstrated between COHb and hs-CRP levels ($r = 0.844$, $p < 0.001$), COHb level and working years ($r = 0.657$, $p < 0.001$); there was not a correlation between COHb and CIMT levels ($r = 0.174$, $p = 0.259$). In furnaceman group, Pearson correlation displayed a significant relationship between hs-CRP and working years ($r = 0.505$, $p < 0.001$), however, there was no significant relationship between hs-CRP and CIMT ($r = 0.266$, $p = 0.081$).

The correlation between PEF percentage and COHb level ($r = 0.593$, $p < 0.001$), PEF percentage and working years ($r = 0.579$, $p < 0.001$), PEF percentage and age ($r = 0.386$, $p < 0.007$) were statistically related in furnaceman group. The more the working years, age and COHb level increased the more decreasing quantity of PEF values increased.

In furnaceman group, the measured PEF values (average = 585.2 ±23.7 L/min) were in average, 38.2 L/min, lower than the reference values (average = 623.4 ±10.4 L/min) that was determined according to the age and height of the persons. As for in control group, the measured PEF values (average = 622.9 ±15.8 L/min) were in average, 7.1 L/min, lower than the reference values (average = 630 ±12 L/min). PEF values of the control group were corresponded with the reference values.

In both groups, it was observed that the higher the COHb level was, the higher the difference (relationship) between the measured PEF values and the reference PEF values got. The statistically comparison of outcomes between groups were summarized in Table 2.

Discussion

Chronic exposure generally occurs in smokers, traffic policemen, and toll station clerks on highways, tunnel and bridge workers, and workers of parking houses, machine operators, firemen, miner and grill-kebab chefs [10]. In this study, COHb, hs-CRP and CIMT levels were individually found to be higher in the furnacemen group. Even though, COHb and hs-CRP correlation was demonstrated, there was no association between raised COHb and CIMT as well as hs-CRP and CIMT. There was significant association between COHb and reduced PEF.

Kocasoy and his colleagues [11] compared the COHb level in box officer of İstanbul Bosporus Bridge in the morning (smoker/non-smoker the average COHb: %0.67/1.99) and in the evening (smoker/non-smoker the average COHb %1.25/3.23); the values measured in the evening was higher. In Bahrain [12], the COHb values

Table 1. The comparison of lipid profile, age, CIMT, COHb, hs-CRP and PEF percentage in groups

	Study Group (n = 47)	Control Group (n = 48)	P
Age (Year)	35.3 ±3.9	34.7 ±6.5	>0.05
BMI (Kg/m)	24.6 ±5.9	25.4 ±6.0	**>0.05**
BP (mmHg)	125.8 ±15.2/79.4 ±12.6	124.5 ±13.7/77.3 ±11.3	**>0.05**
TC (mg/dL)	169.0 ±31.8	169.0 ±31.9	**>0.05**
LDL-C (mg/dL)	101.5 ±26.1	99.5 ±32.8	**>0.05**
HDL-C (mg/dL)	39.8 ±8.4	39.2 ±15.2	>0.05
TG (mg/dL)	159.1 ±78.8	164.9 ±72.7	**>0.05**
CIMT (mm)	1.11 ±0.32	0.91 ±0.11	<0.001
COHb (%)	4.5 ±1.5	2.0 ±1.1	<0.001
hs-CRP (mg/L)	3.2 ±2.1	1.1 ±0.8	<0.001
PEF (%)	93 ±3.3	98.5 ±1.8	<0.001

[1]Measured PEF (L/min) /Reference value (L/min) ×100,
BMI: Body Mass Index, BP: Blood Pressure, TC: Total Cholesterol, TG: Triglyceride, LDL-C: Low Density Lipoprotein Cholesterol, HDL-C: High Density Lipoprotein Cholesterol, CIMT: Carotids Intimae Media Thickness, COHb: Carboxy-hemoglobine, hs-CRP: high sensitive C-reactive Protein, PEF: Peak Expiratory Flow

Table 2. Statistical results of age, working years, CIMT, COHb, hs-CRP levels and PEF percentages

	Study Group (n = 47)		Control Group (n = 48)	
	p	r	p	r
Age and COHb level	0.004	*0.416*	0.092	0.257
Age and hs-CRP level	0.150	0.213	0.912	0.017
Age and CIMT	0.069	0.277	0.770	0.045
COHb level and hs-CRP	<0.001	0.844	0.002	0.427
COHb level and CIMT	0.259	0.174	0.152	0.210
COHb level and working year	*<0.001*	*0.657*	_	_
hs-CRP level and CIMT	0.081	0.266	0.413	0.121
hs-CRP level and working year	*<0.001*	*0.505*	_	_
CIMT and working year	0.150	0.213	_	_
COHb level and PEF percentage	<0.001	0.593	<0.001	0.798
Working year and PEF perc.	*<0.001*	*0.579*	_	_
Age and PEF percentage	*0.007*	*0.386*	0.460	0.109

BMI: Body Mass Index, BP: Blood Pressure, TC: Total Cholesterol
LDL-C: Low Density Lipoprotein Cholesterol, HDL-C: High Density Lipoprotein Cholesterol
TG: Triglyceride, CIMT: Carotids Intimae Media Thickness, COHb: Carboxy-hemoglobine
hs-CRP: high sensitive C-reactive Protein, PEF: Peak Expiratory Flow
rrelation between CRP level and CIMT was not significant.

of 100 grill-kebab chiefs measured in the evening (smoker/non-smoker the average COHb: %6.2/8.1) was found higher than the values measured in the morning (smoker/non-smoker the average COHb: %2.4/3.8). In the present study the average COHb values of smoker group (%4.5 ±1.5) were higher than the values of non-smoker group (%2.0 ±1.1).

The outcomes between atherosclerosis and CO exposure are changeable. Wald [13] and his colleagues studied the COHb values in 1085 voluntary smokers. In that study it was determined that the atherosclerosis risk in patients who had more than 5%COHb value was 21 times higher than the patients who had COHb value lower than 3%. In Astrup [14] and his colleagues study, cholesterol and lipid accumulation were detected in aorta of rabbit that were exposed to chronic CO. Pathologically; atherosclerotic thickness was seen in aorta and renal artery of rabbits. Similar outcome was determined by Al [10] and his colleagues' study that was carried out on grill-kebab chiefs. Our results supported those outcomes. However, atherosclerotic changes were not detected in Sorhaug [15], Penn [16], Smith [17] and their colleagues' that were carried out on mouse, cocks and epidemiological studies respectively.

Carotid intima-media thickness was begun to be used in the diagnosis of atherosclerosis frequently [7,18]. The present study is important because of showing the increase of CIMT in furnacemen who were exposed to CO chronically for an average 12.1 ±2.4 years according to the normal person. In spite of CIMT values in furnacemen were higher than the values in control group, it was not statistically meaningful. Nevertheless, the difference values of age, BMI, BP, TC, LDL-C, HDL-C, and TG that affected CIMT did not show a statistically significant correlation between groups. COHb and hs-CRP values in furnaceman were higher than the COHb ve hs-CRP values in control group.

Clinical studies show that hs-CRP is a strong and independent risk factor for stroke, myocardial infarcts and peripheral vascular disease [19]. There are not so many clinical studies investigating the effect of chronic CO exposure on CRP level. Zevin et al [20] did not demonstrate a statistically relation between CRP and CO effect due to smoking. On the other hand Davutoğlu [6] et al found a significant correlation between CO exposure and high level of hs-CRP.

The study carried out by Davutoğlu et al [6] is the first to demonstrate that hs-CRP increases in subjects with chronic CO exposure. In addition, hs-CRP showed significant correlation with CIMT. The mechanism by which chronic CO exposure causes increase in CIMT and hs-CRP level is unclear. CO is known to have direct toxic effects on myocardium. Apart from direct toxic effects of CO to the myocardium, it might stimulate chronic inflammatory process known as key element of atherosclerosis which was shown by increase in hs-CRP level in Davutoğlu et al. studys' [6]. Falsom et al. [21] did not find a strong correlation between hs-CRP level and atherosclerosis on 875 male and 948 female. While, Makita et al. [7] found a correlation between hs-CRP levels, atherosclerosis and plaque formation on 1290 male, they did not find a significant correlation on 766 female. On the contrary, Wang et al. [22] found a significant correlation between hs-CRP level and CIMT on 1665 female, but they did not found the same correlation on 1508 male. In another study [23], a statistically meaningful correlation was demonstrated between CRP level and CIMT in 1051 persons with dislipidemia. In present study the coChronic CO exposure increases the rate of asthma, pneumonia, upper respiratory diseases, chronic obstructive lung disease and pulmonary function failure [24]. Wang JM et al. [25] determined serious pulmonary changes in superhighway worker who were exposed to the tunnel atmosphere for a long time. Sauza et al. [26] found hyperplasia, wall-thickness and inflammation in bronchiole of human who lived in air pollution and smoked.

There are limited studies on the effects of chronic exposure to CO and PEF values in healthy persons. Being chronically exposed to CO reduces the PEF values. It was mentioned that the more the amount of cigarettes and smoking time increased the more the PEF values decreased.

It was also demonstrated in the study of Al et al. [10] that the PEF values of 40 grill- kebab chiefs who worked for a long time were significantly low. Park et al. [27] detected that the PEF values of metal worker were 10-15%lower than the theoretical PEF values of healthy person. In present study the PEF values of furnacemen were lower than the reference PEF values. In study group, the difference between PEF percentage and age, working year, COHb level was statistically significant.

Study Limitations

Whether our results which demonstrate an association between chronic CO exposure and atherosclerosis in terms of CIMT and hs-CRP measurements has a causal relationship needs to be clarified with prospective following studies. Whether a result of present study is confined to furnacemen or can be extended to all subjects with chronic CO exposure need to be evaluated. The difference of working environment and time, difference quality of coal to measure the COHb level in different time is the factors that we could not be able to control. We were not able to control the environment of the study subject and control group because they might be exposed to CO in different ways, such as via air pollution by means of living nearby highways and via passive smoking.

As conclusion, this study involving furnacemen, demonstrated that COHb, CIMT, hs-CRP and PEF values are influenced from chronic exposure to CO. The increase between working years and COHb and hs-CRP valu-

es was proportional. The more working years and COHb values increased, the more PEF 1 values decreased.

Conflict of interest: The authors declare that they have no conflict of interests, not supported or funded by any Drug Company

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