

# THE DEPENDENCE BETWEEN URINARY MERCURY CONCENTRATION AND CAROTID ARTERIAL INTIMA-MEDIA THICKNESS IN WORKERS OCCUPATIONALLY EXPOSED TO MERCURY VAPOUR

ANNA SKOCZYŃSKA, RAFAŁ POREĘBA, ALEKSANDRA STEINMENTZ-BECK, HELENA MARTYNOWICZ, ANNA AFFELSKA-JERCHA, BARBARA TURCZYN, ANNA WOJAKOWSKA, and IWONA JĘDRYCHOWSKA

University of Medicine, Wrocław, Poland

Department of Internal Medicine and Occupational Diseases

## Abstract

**Objectives:** Mechanisms of the mercury effect on arterial vessel walls include increased free radicals generation, decreased nitric oxide synthesis and increased reactivity to vasoconstrictors, leading to accelerated development of atherosclerosis and arterial hypertension. The aim of this study was to evaluate the correlation between urinary mercury (Hg-U) concentration and carotid intima-media thickness (IMT) or intraventricular septum diastolic diameter (IVSDD) to find the best markers of mercury cardiovascular toxicity. **Materials and Methods:** The study included 154 workers of a chemical factory using mercury in chlorine production. Urinary mercury concentration was determined by atomic absorption spectrophotometry. Serum lipids were assessed by routine methods using enzymatic assay. Serum total antioxidant status (TAS) was determined by colorimetry. Measurements of IMT and IVSDD were made by ultrasound imaging using MEDISON SA 9900 PRIME system. **Results:** The mean Hg-U concentration was  $1.9 \pm 2.7 \mu\text{g/g}$  creatinine in women ( $n = 29$ ) and  $5.6 \pm 12.2 \mu\text{g/g}$  creatinine in men ( $n = 125$ ). In the group of non-smokers ( $n = 102$ ) there was a positive linear correlation between Hg-U concentration and IMT ( $r = 0.1728$ ;  $p < 0.05$ ) and a negative dependence between high density cholesterol (HDL-C) and IMT ( $r = -0.2109$ ;  $p < 0.01$ ). The negative linear correlation between serum total antioxidant status (TAS) and carotid IMT ( $r = -0.2142$ ;  $p < 0.05$ ), and the positive correlation between HDL-C and TAS ( $r = 0.1953$ ;  $p < 0.05$ ) were shown to be valid for the total studied group. Serum lipids in women were normal, but in men the mean triglyceride level was higher than normal. **Conclusions:** The occupational exposure to mercury vapour remains in a relationship with early, asymptomatic carotid atherosclerosis. The dependence between urinary mercury elimination and carotid intima-media thickness is evidenced in non-smoking workers. Defensive anti-atherosclerotic mechanisms in these workers are strongly related with HDL. In smokers, these protective mechanisms are disturbed.

## Key words:

Mercury vapour, Occupational exposure, Intima-media thickness

## INTRODUCTION

Chronic exposure to bivalent toxic metals is associated with increased frequency of cardiac and arterial disorders. It is reasonable to assume a relationship between environmental pollution and cardiovascular diseases leading to increased mortality in many countries. Some authors recommend that determinations of heavy metals (lead, cadmium and mercury) be performed in all patients with diagnosed disease of heart or blood vessels [1].

Mercury influences cardiovascular system in experimental studies [2,3]. Mechanisms of the mercury effect on arterial vessel walls include disturbances in redox system [4,5] and nitric oxide synthesis [6], increased reactivity of adrenoreceptors to catecholamines and increased muscle cells sensitivity to angiotensin II [7], also changes in intracellular signalling system [8,9]. All these changes may be responsible for mercury-induced accelerated atherosclerosis and arterial hypertension.

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Address reprint request to A. Skoczyńska, Department of Internal and Occupational Diseases, University of Medicine, Pasteura 4, 50-367 Wrocław, Poland (e-mail: annaskoc@ak.am.wroc.pl).

In a prospective study performed among 1014 middle-aged men in Finland, the high hair mercury content was associated with accelerated progression of carotid atherosclerosis [10]. The population living in the Amazon region exposed to mercury from several sources (mining, deforestation, reservoirs) displayed cardiovascular symptoms [11]. In a group of workers from Alexandria occupationally exposed to mercury, the increased blood and urinary mercury levels were associated with longer Q-T interval in electrocardiograms [12]. In another study the mortality was analysed in more than six thousand workers from mercury mines and mills in Spain, Slovenia, Italy, and Ukraine. Workers were employed between 1900 and 1990; the follow up period was from the 1950s to the 1990s. An increased mortality (in comparison to national reference rates) from hypertension and heart diseases other than ischaemic was found. Mortality from hypertension was increased with estimated cumulative exposure to mercury; mortality from ischaemic heart disease and cerebrovascular events increased with duration of employment [13]. Also an increased risk of cardiovascular mortality, especially due to hypertension or cerebrovascular pathology, was shown in a follow-up study in workers exposed to mercury in Minas de Almadény Arrayanes in Spain [14]. In spite of increasing number of publications indicating the increased cardiovascular risk resulting from mercury accumulation in human organism, there are still few studies concerning the association between markers of mercury exposure and symptoms of the cardiovascular diseases.

The aim of this study was to evaluate the correlation between urinary mercury and carotid intima-media thickness (IMT) or intraventricular septum diastolic diameter (IVSDD) to find the best markers of mercury cardiovascular toxicity. Carotid IMT has been confirmed as an early atherosclerosis marker, while intraventricular septum diastolic diameter is a marker of the arterial hypertension stage. These markers could be useful for prevention of cardiovascular diseases in workers occupationally exposed to mercury and people environmentally exposed to that metal.

## MATERIAL AND METHODS

### The studied group

The previously increased mercury concentration at workplace was examined as an inclusion criterion for this study. A group of 154 workers occupationally exposed to mercury vapour, employed in a chemical factory at chlorine production was examined: 29 women and 125 men (for basal characteristics, see Table 1). They performed as maintenance staff (34 men), mechanics (19 men) master of production (17 men) and 8 workers were employed directly at chlorine production in various workplaces. The rest of them (74 workers) were employed at salvage or cleaning or tender services in conditions of temporary exposure to mercury vapour.

The workers filled-up questionnaire and then they were clinically examined. Venous blood and urine samples were collected at fasting state. Electrocardiography and ultrasonography were performed.

The mean time of employment at the factory was 25 years for women and 26 for men. There were 52 smokers (on average 16 cigarettes daily for 23 years) and 102 non-smokers. Eighteen workers were alcohol non-drinkers and the rest were alcohol-drinkers drinking once or twice a week, or occasionally.

As to the lifestyle, 47.5% workers described it as active, 49.3% as moderately active and 3.2% as non active. The physical activity included mostly gardening, biking and walking.

**Table 1.** Age, body mass index (BMI) and urinary mercury (Hg-U) concentration, serum low density cholesterol (LDL-C), high density cholesterol (HDL-C), triglyceride (TG) concentrations in studied groups

Attributes	Woman (n = 29)	Men (n = 125)
Age (years)	47.6±7.1	48.1±8.3
BMI (kg/m <sup>2</sup> )	27.6±5.7	27.7±5.7
Hg-U (µg/g creatinine)	1.9±2.7	5.6±12.2
LDL-C (mg/dL)	119.7±39.3	112.5±41.2
HDL-C (mg/dL)	58.8±16.7	52.2±12.9
TG (mg/dL)	126.8±72.8	212.8±266.8

Results are expressed as mean values ±SD.

The diet of 5.8% workers was monotonous and in 94.2% it was diversified. The diet was high-fat in 19% workers, high-fish in 33.8% workers, Mediterranean-type in 19% workers. The consumption of salt was high in 21.4% of workers.

A family history presented cardiovascular risk factor for as many as 120 workers. The most common were diseases: stroke, myocardial infarction, hypertension, followed by diabetes and osteoarthritis.

Good health condition was declared by all examined workers; however, they suffered from chronic diseases: hypertension (25 workers), caries (19), osteoarthritis (19), skin allergies (15), alimentary obesity (13), ischaemic heart disease (9), dermatomycosis or onychomycosis (8), diabetes (6), post-trauma skeletal changes (3), glaucoma (1 worker). The total number of amalgam tooth fillings in the studied group was 227, the average was nearly 3, maximum 13.

## Methods

Urinary mercury was determined by atomic absorption spectrometry (spectrophotometer Solaar M6, Thermoelemental). Serum lipids were assessed with the use of routine methods by enzymatic assay (SPINREACT, S.A. Ctra. Santa Coloma, 7 E-17176 SANT ESTEVE DE BAS (GI) SPAIN). RANDOX LABORATORIES test was applied for the quantitative determination of serum total antioxidant status (TAS). Colorimetric measurements were done using a HITACHI U-2810 spectrophotometer.

Blood pressure (BP) was measured by standard mercury sphyngomanometry according to ESH/ESC guidelines. Twelve-lead electrocardiograms (ECG) were recorded using an ASCARD MYSTER BLUE (ASPEL, Poland) apparatus and hypertrophy of left ventricle was diagnosed using the widely accepted voltage criteria.

High-resolution B-mode ultrasound images obtained on the MEDISON SA 9900 PRIME system were used to determine intima-media thickness (IMT), while both carotid arteries were measured with a 7.5-MHz linear-array transducer. Measurements of IMT were taken on the distal 10 mm of both right and left common carotid artery in the far wall. Five determinations were done on

each side and the average measurement was used as the IMT. IVSDD was assessed by echocardiography using the MEDISON SA 9900 PRIME system.

Results of cardiovascular examination were analysed in subgroups of the workers selected depending on urinary Hg elimination. The arterial blood pressure, heart rate, and intima-media thickness were compared with values regarded as normal, since control group was not selected.

## Statistical analysis

Statistical analysis was performed with the „STATISTICA PL 6.0” package (StatSoft Poland). The data were expressed as mean values and standard deviations. The Shapiro-Wilk test for normality was employed. For cases when distribution of variables was not normal, further analysis was performed using non-parametric Kruskal-Wallis analysis of variance (ANOVA) followed by the post hoc Sheffe or Tukey test. The linear correlation analysis using Spearman's rank correlation coefficients was performed. A p-value < 0.05 was assumed to be statistically significant.

## RESULTS

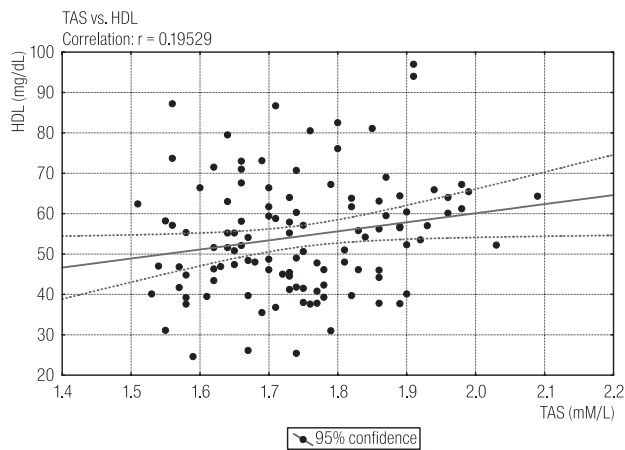
### Urinary mercury (Hg-U) concentration

The mean Hg-U concentration was  $4.9 \pm 11.2$   $\mu\text{g/g}$  creatinine. In the group of workers with stipulated high mercury elimination (above 10  $\mu\text{g/g}$  creatinine; 21 men) a negative linear correlation between the age and Hg-U ( $r = -0.5251$ ;  $p < 0.01$ ) was noted. Moreover, the mean Hg-U concentration was higher ( $p < 0.001$ ) in smokers than in non-smokers ( $39.9 \pm 23.8$   $\mu\text{g/g}$  creat.;  $n = 6$  vs.  $21.1 \pm 13.7$   $\mu\text{g/g}$  creat.;  $n = 15$ , respectively).

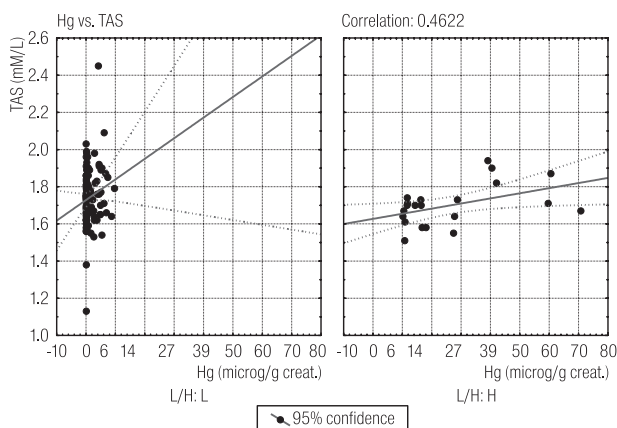
### Serum lipids and total antioxidant status (TAS)

The serum lipids in women were normal, but in men the mean TG level was higher than the normal value of 150 mg/dL, Table 1. The mean serum total antioxidant status was similar in both groups ( $1.72 \pm 0.15$  mM/L in men and  $1.8 \pm 0.14$  mM/L in women).

A positive linear correlation was shown to occur between HDL cholesterol and TAS ( $r = 0.1953$ ;  $p < 0.05$ ;  $n = 154$ ) (Fig. 1).



**Fig. 1.** Dependence between serum HDL cholesterol and TAS ( $p < 0.05$ ) in the studied group ( $n = 154$ ).



**Fig. 2.** Dependence between Hg-U and TAS ( $p < 0.05$ ) in the group of workers with high urinary mercury elimination (H:  $n = 21$ ) and no such correlation in the group of workers with low Hg-U (L:  $n = 133$ ).

In the group of workers with low mercury elimination ( $\leq 10 \mu\text{g/g creatinine}$ ; 133 workers) the mean TAS was similar to that in the group of workers with high Hg-U ( $> 10 \mu\text{g/g creatinine}$ ;  $n = 21$ ):  $1.74 \pm 0.16 \text{ mM/L}$  vs.  $1.70 \pm 0.11 \text{ mM/L}$ , respectively. The positive linear correlation between Hg-U and TAS was demonstrated only in the second group ( $r = 0.4622$ ;  $p < 0.05$ ) (Fig. 2).

**Table 2.** Serum lipids and total antioxidant capacity in groups of smoker and non smoker workers

Groups	TG (mg/dL)	CHOL-C (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	TAS (mM/L)
Smokers ( $n = 52$ )	$185.3 \pm 140.8$	$202.9 \pm 49.0$	$52.5 \pm 13.8$	$116.1 \pm 48.3$	$1.7 \pm 0.11$
Non-smokers ( $n = 102$ )	$202.4 \pm 283.7$	$204.7 \pm 53.4$	$53.8 \pm 13.9$	$112.6 \pm 36.3$	$1.7 \pm 0.16$

Results are presented as mean values  $\pm$ SD.  
 $n$  = number of studied workers.

There were no significant differences between smokers and non-smokers in serum lipids or total antioxidant capacity (Tab. 2).

### Cardiovascular examination

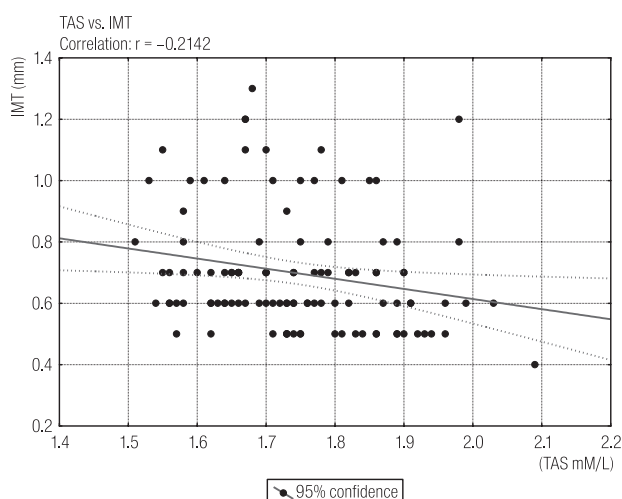
The mean values of systolic and diastolic arterial pressure were  $124/79 \text{ mm Hg}$  in women ( $n = 29$ ) and  $133/83 \text{ mm Hg}$  in men ( $n = 125$ ). There were 25 workers with arterial hypertension diagnosed earlier and 25 men with increased arterial blood pressure values measured during this study. The mean blood pressure pattern depending on the mercury elimination (low or high) and smoking (yes or no) is presented in Table 3.

Mean heart rate (HR) calculated from electrocardiogram was  $73 \pm 12.7 \text{ min}^{-1}$  in the group of men and  $71 \pm 8.8 \text{ min}^{-1}$  in women. In the group of 21 workers with high mercury elimination ( $> 10 \mu\text{g/g creat.}$ ) the mean HR ( $78.9 \pm 15.7$ ) was higher ( $p < 0.05$ ) than in the group of studied workers with low Hg-U removal ( $71.5 \pm 11.2$ ). There were no linear dependences between Hg-U concentration and arterial pressure or heart rate values.

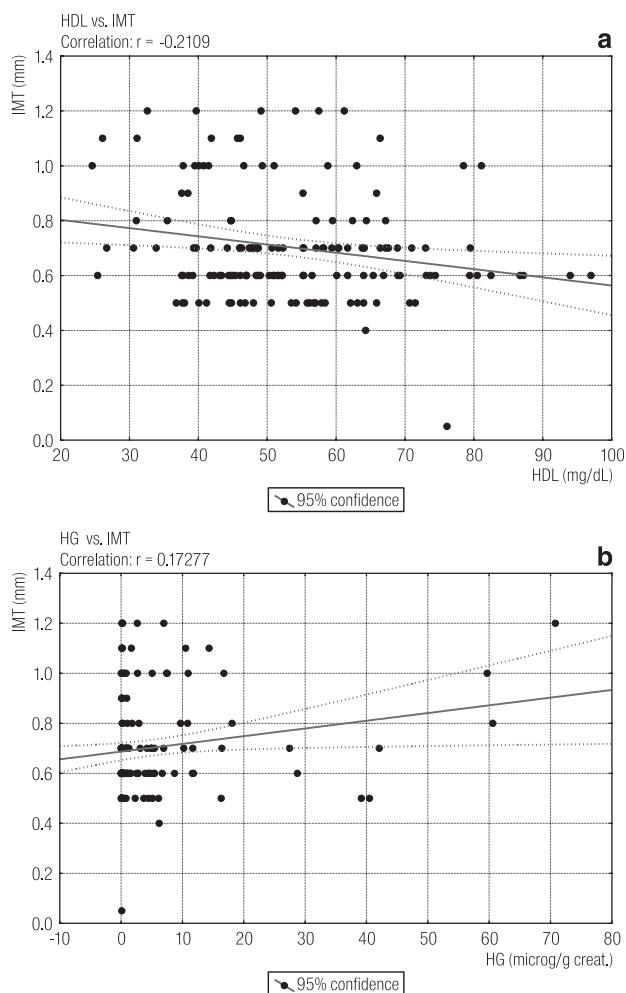
**Table 3.** Mean blood pressure pattern (systolic, RRS and diastolic, RRD) depending on the mercury elimination (high or low) and smoking (yes or no)

L/H	Smoking	N	RRS (mm Hg)	RRD (mm Hg)
L	Yes	46	$130.3 \pm 19.9$	$81.7 \pm 10.5$
L	No	86	$130.0 \pm 23.8$	$83.7 \pm 11.3$
H	Yes	6	$131.6 \pm 12.9$	$83.3 \pm 10.8$
H	No	15	$133.3 \pm 23.1$	$78.6 \pm 12.0$

Results are presented as mean values  $\pm$ SD.  
 $N$  — number of group.  
 L — mercury elimination  $\leq 10 \mu\text{g/g creat.}$   
 H — mercury elimination  $> 10 \mu\text{g/g creat.}$



**Fig. 3.** Linear dependence ( $p < 0.05$ ) between total antioxidant capacity and intima-media thickness in workers occupationally exposed to mercury ( $n = 154$ ).



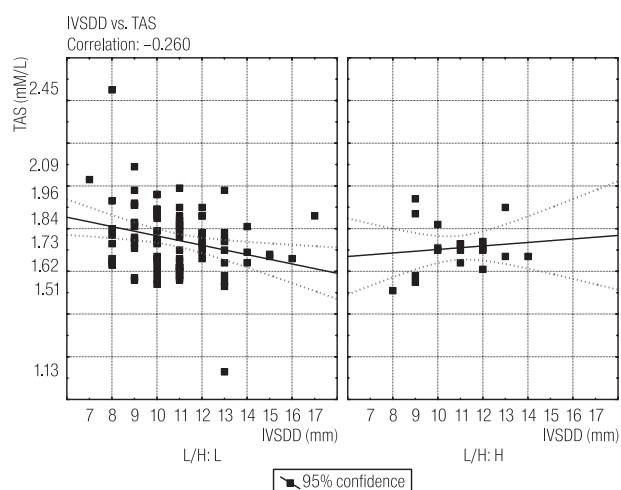
**Fig. 4.** Linear dependences ( $p < 0.05$ ) between HDL cholesterol (a) or Hg-U (b) concentration and intima-media thickness in non-smokers occupationally exposed to mercury vapour ( $n = 102$ ).

ECC abnormalities were observed in 16 workers as arrhythmia (in 5 men), conductance disturbances (in 11 persons) and ischaemia (in 25 workers).

The presence of atherosclerotic plaque in common carotid artery was detected by ultrasonography in 24 (15%) of workers: 22 men and 2 women (mean age  $52 \pm 5.2$  years). The carotid artery intima-media thickness measured by Doppler duplex method averaged  $0.71 \pm 0.2$  mm in all 154 workers. The mean IMT in men was  $0.72 \pm 0.20$  mm, but in women it was  $0.60 \pm 0.14$  mm. In the group of men, IMT value greater than 1 mm was found in 23 workers. In the absence of clinical symptoms, the carotid IMT  $> 1$  mm may serve as an indicator of asymptomatic atherosclerosis. In the group of workers with Hg-U  $> 10$   $\mu\text{g/g}$  creatinine ( $n = 21$ ) the mean IMT was greater than in workers with Hg-U  $\leq 10$   $\mu\text{g/g}$  creatinine ( $n = 133$ ):  $0.78 \pm 0.21$  mm vs.  $0.68 \pm 0.19$  mm ( $p = 0.057$ ).

The existence of the negative linear correlation between TAS and carotid IMT was shown in the total studied group ( $r = -0.2142$ ;  $p < 0.05$ ;  $n = 154$ ) (Fig. 3).

In the group of non-smokers ( $n = 102$ ) there was also a negative linear correlation between HDL cholesterol and IMT ( $r = -0.2109$ ;  $p < 0.01$ ) and the positive dependence between Hg-U concentration and IMT ( $r = 0.1728$ ;  $p < 0.05$ ) (Fig. 4 a-b).



**Fig. 5.** Dependence between TAS and IVSDD ( $p < 0.05$ ) in the group of workers with low urinary mercury elimination (L:  $n = 133$ ) and no such correlation in the group of workers with high Hg-U concentration (H:  $n = 21$ ).



The intraventricular septum thickness measured by Doppler duplex method in all examined workers was  $10.85 \pm 1.77$  mm ( $11.0 \pm 1.7$  in men and  $10.0 \pm 1.9$  mm in women). The IVSDD value greater than 11 mm was found in 46 workers within the group of men. In the absence of clinical symptoms, the IVSDD  $> 11$  mm may serve as an indicator of an early cardiac complication of arterial hypertension. However, in the group of workers with Hg-U  $> 10$   $\mu\text{g/g}$  creatinine, the mean IVSDD was the same as in workers with Hg-U  $\leq 10$   $\mu\text{g/g}$  creatinine ( $10.8 \pm 1.6$  vs.  $10.8 \pm 1.6$  mm). On the other hand, only in the group of workers with low Hg-U, the negative correlation between TAS and IVSDD ( $r = -0.2601$ ;  $p < 0.05$ ) was noted (Fig. 5).

### Discussion

In most population studies, hair mercury content is measured as a marker for accumulation of methyl mercury resulting from dietary sources, mainly from contaminated fish. Salonen et al. observed that high hair mercury content was one of the strongest predictors of the 4-year increase in the mean carotid intima-media thickness [10]. Our study was performed in workers occupationally exposed to mercury vapour, and mercury in urine was measured as a marker for metallic Hg body burden. The existence of the positive linear correlation between urinary mercury and carotid intima-media thickness indicates the role of inorganic mercury in development of atherosclerosis. This correlation existed in the group of non-smoking workers where the impact of smoking as a confounding factor was absent.

Moreover, the negative linear correlation between HDL cholesterol and IMT in this group was shown. This dependence confirmed the known protective anti-sclerotic activity of high-density lipoproteins [15–17].

The presence of the negative linear correlation between TAS and carotid IMT in the group of all studied workers is consistent with hypothesis about protective role of antioxidant mechanisms inhibiting early atherosclerosis. The existence of positive linear correlation between HDL-C and TAS in group of workers exposed to mercury vapour confirms strong antioxidant properties of HDL. These properties can be related to inhibition of LDL oxidation

and adhesion molecule expression in vessel walls [17], antioxidant activity of apolipoprotein AI [18]. Antioxidant effect of HDL can be also coupled with HDL paraoxonase (thiolactonase) [19,20].

Furthermore, the increased carotid IMT index in workers with high (above 10  $\mu\text{g/g}$  creatinine) urinary mercury elimination was associated with tendency to increased total antioxidant capacity. Similar changes in redox system were observed in other workers occupationally exposed to organic mercury compounds [21] as well as in experimental animals poisoned with metallic mercury [7]. Increased antioxidant capacity is considered to represent compensatory or adaptive/defence response to pro-oxidative effect of various toxic metals [22,23]. However, the inhibitory effect of mercury on antioxidative system is described more frequently [4,24]. This effect has been usually mediated by mercury-induced inhibition of antioxidant enzymes and decrease of glutathione [6,9,25,26] or vitamins such as tocopherol [27] and ascorbic acid [28].

In this study, anti-atherosclerotic mechanisms coupled with HDL (indicated by negative linear correlation between HDL-C and IMT) appeared only in non-smokers exposed to mercury vapour. Analysis of the diet and physical effort suggested the relatively healthy life style in the majority of the workers. Thus, smoking interfered with HDL-mediated defence mechanisms, although it did not decrease serum HDL-C level. Simultaneously, smoking significantly ( $p < 0.001$ ) increased urinary mercury elimination, although in workers with high Hg-U, mercury elimination decreased with age.

The increase of carotid intima-media thickness precedes the development of clinical symptoms of atherosclerosis. It has been often associated with arterial hypertension and hypotensive therapy connected with oxidative stress inhibition leading to IMT regression [29]. Chronic mercury intoxication seems to be associated with arterial hypertension [1,4,7]. It can be either caused by mercury's direct impact on vessel walls or mercury-induced nephrotoxicity. Compared to general population, the percent of mercury vapour-exposed hypertensive persons was similar (16.2% vs. 20%, respectively). However, the number of workers with increased blood pressure values during this

study (non-diagnosed arterial hypertension) increased this percent to 32.4%. Similarly, the increased IVSDD thickness, indicating the first cardiac complication of hypertension, was found in 29.8% of workers. It suggests the role of mercury in development of arterial hypertension. No negative TAS-IVSDD correlation in the group of workers with high Hg-U concentration, the existence of correlation in the group of workers with low Hg-U, as well as significantly increased heart rate in the group of workers with high Hg-U in comparison to workers with low Hg-U pointed out mercury-induced significant disturbances in cardiovascular homeostasis.

Summarising, occupational exposure to mercury vapour is related to early, asymptomatic carotid atherosclerosis. The dependence between urinary mercury concentration and carotid intima-media thickness is evidenced in non-smoking workers. Defense anti-atherosclerotic mechanisms in these workers are intensely connected with HDL. In smokers, these protective mechanisms are disturbed.

The authors declare that there are no conflicts of interest.

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