

Vascular Changes in Workers Exposed to Carbon Disulfide

L Braeckman,^{*MD, PhD}, K Kotseva,^{**MD, PhD}, D Duprez,^{***MD, PhD}, D De Bacquer,^{****MSc, PhD}, M De Buyzere,^{+MSc},
N Van De Veire,^{++MD}, M Vanhoorne,^{+++MD, PhD}

Abstract

Aim: To assess the effects of occupational exposure to carbon disulfide (CS₂) concentrations below the threshold limit value (31 mg/m³) on the structural and the functional properties of the arteries, heart rate, blood pressure and lipids. **Methods:** Study subjects were 85 male workers in the viscose industry and 35 men without such exposure. The CS₂ concentration was determined by personal active sampling. From the common carotid artery diameter, the change in diameter (echography) during the heart cycle and the pulse pressure, local arterial distensibility and compliance were calculated. Global large and small artery elasticity were calculated from registrations of radial artery waveforms. Simultaneously, heart rate and blood pressure were recorded and blood samples were collected for lipid measurements. **Results:** CS₂ concentrations ranged from 2.34 to 32.4 mg/m³. No significant effect of CS₂ on blood pressure, total cholesterol, HDL and LDL cholesterol or triglycerides was found. Among the vascular parameters under study, common carotid artery distensibility was significantly lower, and heart rate significantly higher in exposed workers compared to controls. The differences remained significant after adjustment for age, body mass index, smoking habits, alcohol consumption, heart rate and systolic blood pressure. Common carotid artery intima media thickness and global arterial indices did not differ significantly between the two groups. **Conclusions:** Exposure to CS₂ under the current level may already cause alterations in common carotid artery elastic properties in apparently healthy individuals. Even before biochemical and clinical findings occur, important functional changes in the vessel wall were observed, at least in some vascular territories.

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Introduction

Carbon disulfide (CS₂) is an organic solvent which is used all over the world in the production of viscose rayon fibres. A large number of animal, clinical and epidemiological studies have shown that CS₂ toxicity may harm many organ systems including the neurological and cardiovascular systems.^{1,2} The vascular effects of CS₂ have been studied particularly on coronary artery disease, cerebral vascular disease and retinopathy. Regarding the latter, a consistent association has been seen between high CS₂ exposure, retinal microaneurysms and haemorrhages.^{3,4} An increased mortality from coronary heart disease, first demonstrated among workers exposed to CS₂ in the United Kingdom, has been confirmed in several other surveys.⁵⁻¹⁰

Finnish studies suggested that the increased risk is reversible and normalises with the reduction or cessation of exposure.^{7,8} A significant excess of death from cerebrovascular diseases has also been reported.^{11,12}

In contrast to the consistent results from mortality studies, the data of morbidity studies do not agree completely. Several studies indicate that workers exposed to high concentrations of CS₂ (>60 mg/m³) are at an elevated risk for cardiovascular morbidity. Increases in prevalence of arterial hypertension, hypercholesterolaemia, electrocardiographic abnormalities and clinical ischaemic heart disease have been reported in varying degrees.¹³⁻¹⁶ At lower levels of exposure, however, no significant increases in cardiovascular risk factors were observed.¹⁷⁻²⁰

* Doctor-assistant

** Postdoctoral Fellow

**** Statistician

+++ Professor, Head of the Section of Occupational Health
Department of Public Health
Ghent University, Belgium

*** Professor, Head of the Vascular Laboratory

+ Research Fellow

++ Research Assistant

Department of Cardiology and Angiology
Ghent University Hospital, Belgium

Address for Reprints: Dr Lutgart Braeckman, Department of Public Health, Block A, 2nd Floor, De Pintelaan 185, B-9000 Gent, Belgium.

E-mail: Lutgart.Braeckman@rug.ac.be

The current threshold limit value for the 8-hour time-weighted average concentration (TLV-TWA) proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) is 31 mg/m³.²¹ More differentiating and subtle techniques may enable the early detection of CS₂ effects at concentrations below TLV-TWA. A Doppler ultrasound study has been reported by Aaserud et al²² which showed slight stenosis in 1 out of 15 workers. In another limited group of 10 persons who had polyneuropathy after long-term high CS₂ exposure, carotid duplex sonography revealed mild atherosclerosis with plaques in 6 of them.²³ Studies of larger groups of Japanese and German rayon workers failed to demonstrate any effect of CS₂ on stiffness and blood flow or changes of the carotid artery.^{20,24}

The objective of this study was to assess the effects of occupational CS₂ exposure below the current limit value of 31 mg/m³ on structural and functional properties of common carotid artery, heart rate, blood pressure and lipids. Early changes of the vessel wall morphology and function were studied by examining the intima media thickness of the vessel wall, the global arterial compliance and the arterial distensibility and compliance of the common carotid artery.

Materials and Methods

Study Population

The study subjects comprised 91 men exposed to CS₂ in a Belgian viscose rayon factory. The controls were 37 males working in a metal, a plastic, a textile and a starch processing factory without occupational exposure to chemicals known to be noxious for the cardiovascular system. Subjects with diabetes and intake of drugs with vascular effects were excluded, leaving a total of 85 subjects in the exposed group.

The participation was on a voluntary basis and the response rate was 58% in the exposed and 48% in the control population. All subjects included in this study gave written informed consent and the protocol of the study has been approved by the local medical ethics committee.

Assessment of Exposure

The only chemical in the working environment that was considered to be important for the investigated vascular and lipid parameters in our study was CS₂. Workers exposed to CS₂ consisted of all workers from three departments (viscose preparation, spinning and bleaching departments). When working in and around spinning machines and in the churns, protective respirators had to be worn. Exposure to CS₂ was assessed using personal monitoring pumps (Dupont P125A, Gilair-3 and -5, Ametek MG4) and charcoal tubes (SKC nr 226-01, 400 mg/200 mg). These tubes were fixed on the collar of the worker in order to measure the CS₂

concentration outside the respirators or were fixed on the face of the worker in order to measure the CS₂ inside the respirators. Charcoal samples were desorbed with toluene and analysed by gas chromatography according to the NIOSH method 1600.²⁵

The CS₂ exposure was considered in two ways:

- 1) binary (exposed persons versus non-exposed persons);
- 2) in order to model exposure as a continuous variable, a cumulative exposure index (CS₂ index) was calculated for each worker by multiplying the number of years he had held a particular job in the viscose factory with the CS₂ exposure (in mg/m³) in that job.

Medical Examinations

Self-administered questionnaires were used to collect data on job history, personal and family medical history, drinking and smoking habits and use of medication. The completed forms were checked by interview at the time of medical examinations at the University Hospital.

Venous blood was collected from sitting, fasting subjects and analysed for total cholesterol (Chol), HDL cholesterol (HDL) and triglycerides (TG). Total cholesterol and triglycerides were measured with an enzymatic assay. HDL cholesterol was assayed automatically without sample pre-treatment. The coefficients of variation ranged between 1.3% and 6.7%. LDL cholesterol (LDL) was calculated according to the classical formula of Friedewald.

Standing height and body weight were measured in light indoor clothes, without shoes. The body mass index (BMI, kg/m²) and smoking index (pack-years) were calculated.

Systolic (SBP) and diastolic (DBP) blood pressure (Korotkoff phase I and V respectively) readings were registered in supine position after 5 min rest with a mercury manometer. To minimise observer error, all readings were done by one physician.

To assess global arterial compliance, defined as the change in volume for a given change in pressure, a non-invasive arterial pulse pressure sensor system was used to obtain waveforms at the radial artery.²⁶ Elasticity indices of the large arteries (C₁, capacitive arterial compliance, units in mL/mmHg, representative of the aorta and major branches) and of the small arteries (C₂, reflective arterial compliance, units in mL/mmHg, representative of the distal part of the circulation) were derived from a third order, four-element model of the arterial circulation.²⁶

The measurements of the common carotid artery were performed with a non-invasive ultrasound wall movement detector system. It consists of a conventional ultrasound imager (Sonotron/Diasonics, model PRISMA, Les Ulis, France) with a 7.5 MHz transducer, a data acquisition system and a personal computer. The transducer was

positioned on the surface of the skin directly above the artery being studied. The arterial diastolic diameter (Dd) and the arterial wall distension (ΔD) were recorded for 5 s. Simultaneously, blood pressure (BP) was measured with an automated device to calculate pulse pressure (ΔP = systolic minus diastolic BP). From the arterial diameter, the change in diameter during heart cycle (distension) and the pulse pressure, arterial distensibility [$DC = (2\Delta D/Dd)/\Delta P$, units in ($10^{-3}/\text{kPa}$)] and compliance [$CC = (\pi Dd \times \Delta D)/2\Delta P$, units in (mm^2/kPa)] were calculated.²⁷

On the ultrasound images of the carotid artery, the thickness of the intima media layers (IMT, units in mm) was determined by a leading-edge technique.²⁸ The same experienced investigator with no knowledge on exposure status performed all measurements. The technical reproducibility of the vessel wall movement detector system was evaluated regularly and was found to be acceptable.²⁷

Statistical Analysis

The equality of distributions of baseline characteristics and cardiovascular outcomes between the exposed and the non-exposed group was evaluated using the non-parametric Mann-Whitney U test for continuous variables and Fisher's exact test for proportions. Data are presented as mean and standard deviation (SD). Multiple linear regression was applied to assess the effect of exposure and to describe the relationship between CS₂ index (representing the CS₂ exposure as a continuous variable) and the quantitative vascular and lipid variables, adjusted for other risk factors. The confounding variables concerned were age, BMI, smoking (in pack-years), alcohol consumption, ethnic descent, heart rate and blood pressure. The normality of arterial distensibility, intima media thickness, C₁ and triglycerides was improved by natural logarithmic transformation and transformed values were used in the analyses. The global level of statistical significance for testing was set at $\alpha = 0.05$. All calculations were performed using SPSS statistical software.

Results

Exposure Data

The CS₂ exposure remained in the different departments below the TLV-TWA of 31 mg/m³. The CS₂ concentrations (geometric means) inside the respirators ranged from 6 to 10.09 mg/m³ in the viscose preparation department and from 2.2 to 13.02 mg/m³ in the spinning department. The CS₂ concentrations outside the respirators ranged from 1.3 to 20.8 mg/m³ in the viscose preparation department and from 3.9 to 32.4 mg/m³ in the spinning department. The CS₂ exposure in the bleaching department was very low (up to 3.2 mg/m³).

Population

Baseline characteristics of the study subjects are presented in Table I. The mean age was 37.1 (± 8.0) years in the exposed subjects and 40.5 (± 8.73) years in the controls. No significant differences between the study populations were found for BMI, alcohol intake (g/day) and smoking habits (pack-years). The percentages of low educated workers, shift workers and foreign persons (Turkish and North-Africans) in the control group were comparable to those in the exposed group.

Medical Findings

Table II summarises mean lipid and blood pressure values. No significant differences were found between all exposed and non-exposed concerning total cholesterol, HDL, LDL, triglycerides, systolic and diastolic blood pressure. The heart rate in the exposed group was significantly higher compared to the controls.

The arterial wall properties of the common carotid are shown in Table III. The distensibility coefficient was significantly lower in the exposed workers than in the controls. This difference remained statistically significant after adjustment for age, smoking (pack-years), alcohol consumption (g/day), ethnic descent, BMI, heart rate and systolic blood pressure. There were no significant differences between exposed and non-exposed subjects with regard to the elasticity indices C₁ and C₂, the compliance coefficient or intima media thickness. The results of the multiple linear regression analysis are presented in Table IV. CS₂ exposure was significantly associated with heart rate and the distensibility coefficient but not with any of the lipid parameters. As might be expected, age and BMI were determinants of several of the outcomes, including triglycerides and the distensibility coefficient. Smoking was significantly associated with HDL and C₁. Significant associations have also been found between alcohol consumption and diastolic blood pressure, LDL and C₂; ethnic descent and total cholesterol, LDL and the

TABLE I: CHARACTERISTICS OF THE STUDY POPULATIONS

	Exposed n = 85	Non-exposed n = 37	P ^a
Age (y)	37.1 (8.0)	40.5 (8.73)	0.13
BMI (kg/m ²)	24.9 (3.4)	25.3 (3.2)	0.77
Alcohol (g/day)	7.7 (12.3)	11.4 (14.8)	0.15
Pack-years	9.1 (10.3)	8.0 (11.9)	0.20
Low educational level (%)	26.2	27.0	0.99
Rotating shift work (%)	75.0	87.9	0.14
Turkish and North-African descent (%)	39.3	35.1	0.69

BMI: body mass index

^a According to Mann-Whitney U test for comparing distributions of continuous variables and Fisher's exact test for comparing proportions

TABLE II: AVERAGE VALUES (SD) OF BLOOD PRESSURE, HEART RATE AND LIPID PARAMETERS IN RELATION TO CS₂ EXPOSURE

	Exposed n = 85	Non-exposed n = 37	Significance ^b	Significance ^c
SBP (mmHg)	127.01 (13.48)	127.22 (14.81)	0.85	0.97
DBP (mmHg)	84.17 (10.02)	82.13 (9.58)	0.53	0.23
HR (beats/min ⁻¹)	65.48 (10.23)	60.87 (10.16)	0.04	0.04
Chol (mg/dL)	203.16 (47.82)	214.89 (39.70)	0.09	0.21
HDL (mg/dL)	58.25 (11.54)	61.77 (10.66)	0.25	0.27
LDL (mg/dL)	117.89 (43.44)	129.10 (37.88)	0.10	0.14
TG ^a (mg/dL)	138.18 (100.23)	125.19 (70.29)	0.68	0.53

Chol: total cholesterol; DBP: diastolic blood pressure; HDL: HDL cholesterol; HR: heart rate; LDL: LDL cholesterol; SBP: systolic blood pressure; TG: triglycerides

^a Natural logarithmic transformation used for statistical analysis

^b Significance of difference with reference group according to the Mann-Whitney U test

^c Adjusted for age, pack-years, alcohol (g/day) and ethnic descent

TABLE III: AVERAGE VALUES (SD) OF VESSEL PARAMETERS IN RELATION TO CS₂ EXPOSURE

	Exposed n = 85	Non-exposed n = 37	Significance ^b	Significance ^c
C ₁ ^a (mL/mmHg)	1.91 (0.49)	1.87 (0.44)	0.77	0.27
C ₂ (mL/mmHg)	0.08 (0.03)	0.08 (0.03)	0.98	0.87
CC (mm ² /kPa)	0.92 (0.22)	0.91 (0.26)	0.34	0.39
DC ^a (10 ⁻³ /kPa)	18.52 (4.95)	21.61 (10.67)	0.03	0.02
IMT ^a (mm)	0.53 (0.13)	0.55 (0.15)	0.88	0.86

C₁: capacitative arterial compliance; C₂: reflective arterial compliance; CC: cross-sectional compliance coefficient; DC: distensibility coefficient; IMT: intima media thickness

^a Natural logarithmic transformation used for statistical analysis

^b Significance of difference with reference group according to the Mann-Whitney U test

^c Adjusted for age, pack-years, alcohol (g/day), ethnic descent, BMI, heart rate and systolic blood pressure

TABLE IV: MULTIPLE LINEAR REGRESSION ANALYSIS (REGRESSION COEFFICIENTS AND SIGNIFICANCE)

	Intercept	Exposure	Age	BMI	Pack-years	Alcohol	Descent	HR	SBP	R ²
SBP	81.348	-2.215	0.102	0.654	-0.029	0.114	-2.966	0.462***		0.230
DBP	42.635	1.079	0.147	0.393	0.014	0.151*	0.852	0.339		0.231
HR	14.054	4.367*	0.101	0.106	0.041	-0.089	2.366		0.295***	0.242
Chol	150.758	-9.972	1.424**	1.474	0.433	-0.616	-20.204*			0.190
HDL	74.431	-2.067	0.172	-0.567*	-0.197*	0.142	-3.906			0.147
LDL	100.232	-11.956	0.910	0.968	0.481	-0.737*	-20.721*			0.162
TG ^a	2.820	0.081	0.016*	0.038**	0.007	3.8E-04	0.163			0.165
C ₁ ^a	1.4	0.06	-0.003	0.009	0.005**	-8.3E-04	-0.03	-0.15**	-0.03**	0.349
C ₂	0.22	0.002	-0.002***	7.18E-04	-3.7E-04	-9.3E-05*	-0.012	-9.5E-04***	-0.17	0.197
CC	1.903	0.039	-0.004	-0.002	-0.001	4.3E-04	-0.035	-0.009***	-0.002	0.206
DC ^a	5.009	-0.130*	-0.013***	-0.027***	-0.001	6.5E-04	0.120*	-0.007*	-0.005*	0.465
IMT ^a	-1.138	0.008	0.009**	0.007	0.001	0.002	-0.034	-0.002	6.1E-04	0.210

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

^a Natural logarithmic transformation used for statistical analysis

See previous Tables for explanation about abbreviations

distensibility coefficient. There was a significant interaction between heart rate and systolic blood pressure, compliance and distensibility coefficients; and between systolic blood pressure and heart rate and the distensibility coefficient.

The multiple regression analysis has also been used in order to describe the relationship between cumulated CS₂ exposure and cardiovascular outcomes. However, no significant associations between the CS₂ index and the investigated parameters were observed (data not shown).

Discussion

During recent years, the clinical pictures of CS₂ intoxication have changed a lot from increased coronary and cerebrovascular mortality, through hyperlipidaemia and hypertension to subclinical effects because of improvement of occupational hygienic standards and measures. In agreement with the latest reliable studies, we did not observe any effect of chronic CS₂ exposure at the current level of 31 mg/m³ on blood pressure or lipid

levels.¹⁷⁻²⁰ But in accordance with the findings reported by Kuo et al¹⁵ and Bortkiewicz et al,²⁹ the average heart rate was higher for the exposed subjects. An increased heart rate at rest has been recognised as an independent risk factor of overall mortality and cardiovascular mortality.³⁰ The main factor for high heart rates among exposed workers has been speculated to be due to the stimulation of the sympathetic nervous system.^{15,29} The mechanisms by which CS₂ may contribute to cardiovascular disease are not well defined. Besides this impaired neurovegetative regulation of the cardiovascular function, several other possibilities have been proposed:

- 1) changes in lipid metabolism such as increased level of cholesterol and beta-lipoprotein;
- 2) elevation of blood pressure;
- 3) increased tendency to thrombosis or decreased fibrinolytic activity;
- 4) disturbance of the catecholamine metabolism; and
- 5) direct cardiotoxic effect.^{1,2,13,14}

Observation of workers exposed to CS₂, using newer and specific techniques, may enable the early detection of functional and structural arterial abnormalities. There are a few recently published studies of the vascular effects of CS₂ evaluated by ultrasound measurements of the stiffness of the carotid artery and the aortic wall and their results are not convincing.^{20,22-24} The only exposure-related effect in our series was a decreased distensibility of the common carotid artery. Distensibility reflects the elasticity of the artery and is a determinant of the vessel wall, while compliance reflects the buffering capacity of the large arteries and is an important determinant of the afterload of the heart. Age, hypertension, hypercholesterolaemia and higher heart rate are known to decrease arterial distensibility and systematic compliance.^{27,31-34} In our study, the effect of exposure on the distensibility coefficient remained statistically significant after adjustment for age, BMI, smoking, alcohol consumption, ethnic descent, heart rate and systolic blood pressure. In linear regression analysis, the distensibility coefficient was negatively associated with exposure, age, BMI, heart rate and systolic blood pressure. No effect of CS₂ exposure on arterial compliance, C₁, C₂ and IMT was found. While arterial distensibility is suggested to be an early indicator of coronary heart disease, arterial compliance was significantly altered only in extensive atherosclerosis.³¹ The results of our study show that occupational exposure to CS₂ may cause alterations in arterial elastic properties in young individuals and even before anatomical lesions had occurred, important functional changes in the vessel wall can be present, at least in some vascular territories. It may be hypothesised that CS₂ induces endothelial dysfunction, leading to increased vascular tone and as a consequence to decreased arterial

distensibility.³⁵

Although we observed a significant effect of exposure on heart rate and on the distensibility coefficient, we could not assess a dose-response relationship. In linear regression, the CS₂ index was not associated with any of the investigated parameters. The problem of how to best integrate information on exposure to reflect adequately the acquired risk of disease, is a general and unsolved problem in occupational epidemiology. The most widely used measure of exposure is the so-called cumulative exposure index. However, the calculation of this cumulative exposure is an averaging procedure insensitive to patterns of concentrations over time. Therefore, the approach of using the cumulative index may be responsible, at least partially, for the lack of a dose-response relationship in the present study.

Other possible limitations should also be considered. Evaluating pathological findings in a cross-sectional occupation-based study is difficult. A causal relationship cannot be established and a major bias problem may arise because of the healthy worker effect. A large number of workers may have left the industry because of the very type of health effect that is under study. We contacted the persons who had left the factory during the last 10 years: 31% of the viscose workers versus 13% of the controls mentioned health complaints as reasons for leaving the industry but cardiovascular complaints were rarely mentioned.

Another danger of selection bias may be caused by the way the subjects were enrolled in the study. Participation was voluntary and workers self-selected themselves into this study. Since persons with health complaints may be more motivated to participate to obtain a social or economic gain (indemnification for an occupational disease), this could lead to an overestimation of disease. We believe, however, that there is no reason to believe that such mechanism would operate differently in the exposed and non-exposed workers.

Confounding bias occurs when the observed effect of an exposure on risk is distorted because of the association of exposure with other factors that influence the outcome under study. Possible confounders in our study included age, BMI, smoking, alcohol, ethnic descent, heart rate and blood pressure. In our analyses, we have adjusted for these confounders and, therefore, confounding will probably not have affected our study results.

In conclusion, in CS₂ exposed workers up to the current level of 31 mg/m³ there are already functional changes in the vessel wall (decreased common carotid distensibility), even before the appearance of known clinical and biochemical abnormalities. Follow-up of these viscose rayon workers is recommended to verify if this direct toxic effect of CS₂ on the vessel wall does not lead to clinical

manifestations of coronary heart disease within the coming years. Further studies are also warranted to assess whether non-invasive measurement of arterial distensibility and compliance can be considered as a screening tool to detect early vascular alterations in occupational health settings.

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