Cardiovascular effects of occupational exposure to carbon disulphide

K. P. Kotseva* and D. De Bacquer†
*National Centre of Occupational Diseases, University Hospital 'Sv. Ivan Rilski', Sofia, Bulgaria; and †Dept of Public Health, University Hospital, Gent, Belgium

The objective of this study was to investigate the effect of occupational exposure to carbon disulphide (CS₂) on the total cholesterol, blood pressure and prevalence of coronary heart disease (CHD). A cross-sectional study involving 252 viscose rayon workers and 252 age and sex matched controls was carried out. Depending on the job and specific work place, the CS₂ concentrations were between 10 and 64 mg/m³. A cumulative exposure index (CS₂ index) was calculated for each worker by multiplying the number of years he had held a particular job with the CS₂ concentrations in that job. CHD prevalence among the exposed was higher than among the controls; the difference reaching significance only for highly exposed workers. Cholesterol levels were significantly higher in both highly and moderately exposed groups. In conclusion, the results demonstrated that occupational exposure to CS₂ increases total cholesterol and the risk for CHD. While the risk for CHD is increased in workers exposed to high CS₂ concentration for many years (CS₂ index > 300), even the relatively modest exposure (CS₂ < 300) may increase the serum cholesterol.

Key words: Arterial hypertension; cholesterol; coronary heart disease; viscose factory; work-related cardiovascular diseases.

INTRODUCTION

There is substantial evidence from epidemiological studies that chronic exposure to high concentrations of carbon disulphide (CS₂) may increase the risk of accelerated atherosclerosis and coronary heart disease (CHD). Since the study by Tiller et al. in 1968 many investigators have found increased mortality of CHD in workers exposed to CS₂. The results of a 15-year follow-up study in Finland suggested that CS₂ increases the risk of CHD in workers with the presence of other major cardiovascular risk factors and that this increased risk is reversible and decreases with reduction or cessation of exposure. Meanwhile, the study of Swaen et al. showed that exposure to relatively low levels of CS₂ increases the risk of cardiovascular disease mortality. A significant excess of deaths from cerebrovascular disease has also been reported. Morbidity studies have given controversial results. Increased prevalence of high blood pressure, electrocardiographic (ECG) abnormalities, clinical CHD and lipid metabolism disturbances in workers exposed to CS₂ in varying degrees have been reported. However, several studies did not reveal a significant increase of the risk for CHD, especially at lower levels of exposure. A statistical analysis of the NIOSH carbon disulphide exposure database was conducted in order to establish a benchmark concentration for CS₂. None of the ischaemic heart disease risk factors had a statistically significant relationship with CS₂ exposure at levels below 15.4 ppm (47.7 mg/m³). The threshold limit value–time weighted average (TLV-TWA), proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) for CS₂ was 10 ppm (31 mg/m³).

The object of this study was to investigate the effect of occupational exposure to CS₂ on the total cholesterol, blood pressure and the prevalence of coronary heart disease among viscose rayon production workers.
SUBJECTS AND METHODS

Subjects

We studied 252 workers (111 men) aged between 20 and 60 years in a Bulgarian viscose rayon factory and 252 age- and sex-matched controls, working in the plastics industry without occupational contact with noxious chemicals. All workers were strongly recommended to participate in the study and the participation rate was 96.9% in exposed and 93.3% in non-exposed subjects. All subjects were Caucasians, Bulgarian-speaking, employed for at least 1 year with their present employer.

Methods

Medical and job histories of all subjects were taken using a standardized questionnaire, directly administered by the interviewer on the day of the screening visit, and physical examination of the heart and vessels was performed. Systolic (SBP) and diastolic (DBP) blood pressures (Korotkoff phase I and V respectively) were measured in a sitting position by one physician after 5 min rest, using a random zero aneroid sphygmomanometer. Three measurements were done at intervals of at least 5 min. Average values were used for this report. Body weight and height were measured in light indoor clothes, without shoes. The body mass index, BMI=weight/height² (where weight is in kg and height is in m) and smoking index (pack-years) were calculated. Venous blood samples were drawn from sitting, fasting subjects for serum cholesterol measurements. A 12-lead ECG at rest was recorded following WHO recommendations. All tracings were coded on the basis of the Minnesota code separately by two trained physicians with no knowledge of exposure status. The differences were discussed and a consensus reached. If a consensus could not be reached, a third trained supervisor adjudicated the differences. Codes I1-3 (abnormal Q/QS waves), IV1-3 (S-T junction and segment depression), V1-3 (abnormal T-wave) and VII1 (complete left bundle branch block) were considered as possible signs of ischaemia. The 'high cholesterol' was defined as total cholesterol levels >5.17 mmol/l. Arterial hypertension was defined as systolic blood pressure of 140 mmHg or greater, diastolic blood pressure of 90 mmHg or greater, or taking antihypertensive medication. The presence of CHD was determined by means of the Rose questionnaire and the ECG results. Possible CHD was considered to be present when either angina or infarction were recorded in the questionnaire, and/or any signs of possible ischaemia were seen on the ECG. Subjects with symptomatic hypertension and diabetes were excluded from the study.

In our study, CS₂ was the only chemical in the working environment that was considered to be important for the investigated cardiovascular parameters. Concentrations of CS₂ were assessed using stationary measurements and personal sampling methods. A preliminary estimate of CS₂ concentrations in the manufacturing area was made by short-term sampling using activated charcoal (Hygitest 100 mg/50 mg) through which air was passed at rate of 50 ml/min using a calibrated pump (Gillian). Area samples of CS₂ were collected at a height of 100–150 cm from 22 different locations. To estimate the current CS₂ exposure at the time of the study 8-hour weighted average (TLW) personal breathing zone samples were collected from some workers in each job category. Samples were collected with NIOSH type 100/50 mg charcoal absorption tubes at a flow rate up to 50 ml/min using calibrated Gillian low flow sampling pumps. Charcoal samples were desorbed with toluene and analysed by gas chromatography according to NIOSH method 1600. Desorption efficiency of the charcoal tube was determined by the spiked tube method at 0.5, 1 and 2 times the threshold limit value (TLV). The average desorption efficiency was 91.8%. To test the validity, reliability and uncertainty, standard procedures described in the NIOSH methodology were used. The personal CS₂ exposure was considered in three ways.

1. Binary (exposed persons vs. 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 concentrations for that job.
3. According to the degree of personal exposure, the study population was allocated to three groups: highly exposed (CS₂ index ≥300), moderately exposed (CS₂ index <300) and non-exposed.

Statistical analysis

The equality of distributions of baseline characteristics and cardiovascular outcomes between the exposed and the reference group were evaluated using the nonparametric Kruskal-Wallis and Mann-Whitney tests for continuous variables and χ² analysis or Fisher's exact tests for proportions. To eliminate possible confounding factors, multiple linear regression or multiple logistic regression were carried out. The variables considered as potential confounders in the analyses of the investigated cardiovascular parameters were age, smoking status (pack-years), sex and BMI. Multiple linear regression models were applied to assess the effect of the CS₂ index (representing the CS₂ exposure and the length of service as a continuous variable) on the quantitative cardiovascular parameters (SBP, DBP and cholesterol), adjusted for the other risk factors. Logistic regression was used to evaluate the relationship between the risk of CHD, hypertension and hypercholesterolaemia (dependent variables), and CS₂ exposure (independent variable). The level of statistical significance was accepted to be α=0.05. All calculations were carried out by SPSS 7.5 for Windows statistical software.

RESULTS

The results about mean exposure values for the different job categories showed that personal exposure for some
jobs exceeded TLV-TWA. Depending on the job category, the personal CS$_2$ exposure ranged from 10 to 64 mg/m$^3$. A total of 134 subjects were moderately exposed (CS$_2$ index < 300), while 118 subjects were highly exposed (CS$_2$ index ≥ 300). Detailed assessment of exposure will be published elsewhere (in preparation).

Personal characteristics listed in Table 1 reflect the fact that 44.0% of the exposed and 44.4% of the controls were males. The mean age was 42.4 (±8.51) years in the exposed and 42.5 (±8.57) years in the controls. No significant differences were found between the two exposed groups and the controls in relation to their BMI and smoking habits. A total of 46.8% of the exposed and 48.8% of the controls were smokers. The cardiovascular outcomes according to the degree of exposure are presented in Table 2. There was a significant dose–response relationship between the degree of exposure (assessed in three groups depending on CS$_2$ index), the total cholesterol, and CHD. The cholesterol levels and the CHD prevalence were the highest in the highly exposed group and decreased significantly in the moderately exposed group and the controls. The same association was found concerning the prevalence rates of the possible ischaemic ECG and the history of angina or myocardial infarction. The results of multiple linear regression analysis, in which personal exposure was examined as a continuous variable, are presented in Table 3. After adjustment for age, BMI, smoking and sex, we found a significant positive linear trend between the CS$_2$ index and total cholesterol ($R^2=0.33; P<0.001$) and SBP ($R^2=0.35; P=0.02$). The age and BMI were significantly associated with SBP, DBP and total cholesterol. A significant association was also found between smoking (in pack-years) and total cholesterol.

The prevalence of CHD in the exposed (9.1%) was significantly higher than in the controls (4.4%, $P<0.05$). Elevated blood cholesterol was present in 46.8% of the exposed and 26.6% of the controls ($P<0.001$). No significant difference between the prevalence of hypertension in exposed (19.0%) and controls (15.5%) was established.

Table 1. Characteristics of the population exposed to carbon disulphide, compared to the controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=252)</th>
<th>Moderately exposed subjects (n=134)</th>
<th>Highly exposed subjects (n=118)</th>
<th>Significance*</th>
<th>All exposed</th>
<th>Significance†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%) (n)</td>
<td>44.4 (112)</td>
<td>44.8 (60)</td>
<td>43.2 (51)</td>
<td>0.97</td>
<td>44.0 (111)</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean age (years) (SD)</td>
<td>42.5 (8.57)</td>
<td>42.8 (8.40)</td>
<td>42.0 (8.65)</td>
<td>0.76</td>
<td>42.4 (8.51)</td>
<td>0.91</td>
</tr>
<tr>
<td>Mean BMI (kg/m$^2$) (SD)</td>
<td>24.2 (2.92)</td>
<td>24.1 (3.47)</td>
<td>24.4 (3.32)</td>
<td>0.54</td>
<td>24.2 (3.40)</td>
<td>0.58</td>
</tr>
<tr>
<td>Mean pack-years* (SD)</td>
<td>48.8 (123)</td>
<td>47.0 (63)</td>
<td>46.6 (55)</td>
<td>0.90</td>
<td>46.8 (118)</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean BMI (kg/m$^2$) (SD)</td>
<td>15.8 (10.64)</td>
<td>14.6 (11.68)</td>
<td>14.0 (9.18)</td>
<td>0.40</td>
<td>14.3 (10.55)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Testing equality of distributions of CHD risk factors between the two exposed groups and the controls according to the Kruskal–Wallis test (continuous variables) and $\chi^2$ test (for proportions).
†Testing equality of distributions of CHD risk factors between all exposed and controls according to the Mann–Whitney test (continuous variables) and Fisher's exact test (for proportions).

Table 2. Cardiovascular outcomes according to the degree of exposure

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Controls (n=252)</th>
<th>Moderately exposed subjects (n=134)</th>
<th>Highly exposed subjects (n=118)</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean SBP (mmHg) (SD)</strong></td>
<td>127.6 (18.7)</td>
<td>129.0 (20.0)</td>
<td>131.6 (22.1)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Mean DBP (mmHg) (SD)</strong></td>
<td>83.7 (10.4)</td>
<td>83.8 (11.8)</td>
<td>85.3 (11.3)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Mean cholesterol (mmol/l) (SD)</strong></td>
<td>4.64 (0.70)</td>
<td>4.89 (0.69)</td>
<td>5.18 (1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina (%) (n)</td>
<td>2.0 (5)</td>
<td>3.7 (5)</td>
<td>7.6 (8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ischaemic ECG (%) (n)</td>
<td>3.6 (9)</td>
<td>2.2 (3)</td>
<td>10.2 (12)</td>
<td>0.01</td>
</tr>
<tr>
<td>CHD (%) (n)</td>
<td>4.4 (11)</td>
<td>5.2 (7)</td>
<td>13.6 (16)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*According to the Kruskal–Wallis test (continuous variables) or $\chi^2$ exact test (for proportions).

Table 3. Multiple linear regression analysis (regression coefficients and significance)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Intercept</th>
<th>CS$_2$ index</th>
<th>Age</th>
<th>BMI</th>
<th>Pack-years</th>
<th>Sex</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>43.72</td>
<td>0.007*</td>
<td>0.562***</td>
<td>2.419***</td>
<td>0.199</td>
<td>0.258</td>
<td>0.35</td>
</tr>
<tr>
<td>DBP</td>
<td>36.23</td>
<td>0.003</td>
<td>0.275**</td>
<td>1.436***</td>
<td>0.137</td>
<td>-0.065</td>
<td>0.35</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>2.68</td>
<td>0.001***</td>
<td>0.031***</td>
<td>0.024*</td>
<td>0.002*</td>
<td>0.028</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01; ***P<0.001
Table 4. Prevalence odds ratios (95% confidence intervals) of qualitative cardiovascular outcomes versus the degree of exposure to CS₂

<table>
<thead>
<tr>
<th></th>
<th>Moderately exposed (n = 134)</th>
<th>Highly exposed (n = 118)</th>
<th>All exposed (n = 252)</th>
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<tr>
<td></td>
<td>vs controls (n = 252)</td>
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</tr>
<tr>
<td></td>
<td>OR* (95% CI)</td>
<td>OR* (95% CI)</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.17 (0.64–2.14)</td>
<td>1.35 (0.74–2.48)</td>
<td>1.25 (0.76–2.07)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>2.19 (1.79–4.75)</td>
<td>3.05 (1.84–5.09)</td>
<td>2.98 (1.97–4.82)</td>
</tr>
<tr>
<td>CHD</td>
<td>1.29 (0.47–3.51)</td>
<td>4.32 (1.84–10.11)</td>
<td>2.52 (1.16–5.44)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, BMI and smoking (pack–years).

The prevalence odds ratios of qualitative cardiovascular outcomes were computed by logistic regression analysis (Table 4). After adjustment for age, BMI, sex and smoking both groups of moderately and highly exposed appeared to have a significantly increased risk for elevated cholesterol. The odds ratio for CHD was significant only for highly exposed. No increased risk of hypertension was found. Furthermore, stepwise logistic regression analysis for CHD including CS₂ index, smoking, hypertension and increased total cholesterol as independent variables demonstrated that CS₂ index entered as a significant determinant for CHD at the third step after hypertension and elevated cholesterol (regression equation: CHD = 3.27 + (2.42 x hypertension) + (2.18 x increased cholesterol) + (0.002 x CS₂ index) + (1.13 x smoking)). This could mean that CS₂ exposure along with the major cardiovascular risk factors is a significant determinant for CHD.

DISCUSSION

There are several limitations that should be considered in this study. Firstly, due to the nature of a cross-sectional study, a causal association cannot be confirmed or denied. Secondly, it is well known that investigated outcomes (arterial hypertension, hypercholesterolaemia and CHD) can be influenced by many major and additional cardiovascular risk factors. To avoid confounding by age and sex, a matched design was applied in our study. No significant differences have been found between exposed persons and controls in relation to their BMI and smoking habits. In addition, the analyses of the effect of exposure on blood pressure, total cholesterol and CHD have been performed after adjustment for age, sex, BMI and smoking habits. Increased blood pressure and total cholesterol are known risk factors for CHD, but were not considered as determinants in this study, as they may reflect mechanisms through which CHD is caused.

The present cross-sectional study showed a significantly higher prevalence of possible myocardial ischaemia in workers exposed to CS₂. These findings are consistent with those reported by Oliver and Weber and Kuo et al. In our study, CHD as defined by the presence of angina or history of myocardial infarction, or coronary ECG, or a combination of these is also significantly correlated with exposure. The cumulative exposure index was used to assess not only the current exposure, but also the duration of exposure. The results indicated that workers with a CS₂ index > 300 had an increased risk for elevated cholesterol and CHD. In the presence of a cumulative index < 300, the odds ratio was significant only for having high cholesterol. Should the cumulative exposure model hold, this would mean that exposure to the present TLV-TWA values of 31 mg/m³ over 10 years could increase the risk for CHD. Our data are in accord with other studies, showing disturbances of the lipid metabolism in workers exposed to CS₂. In contrast to CHD, cholesterol levels were significantly higher in both highly and moderately exposed groups, which indicated that relatively modest exposure may raise the total cholesterol level. It may be speculated that prolonged exposures may give way to morbid changes even at lower CS₂ concentrations.

There is conflicting evidence for the effect of CS₂ on blood pressure. A significant effect of CS₂ on blood pressure has also been reported by Vanhoorne et al. and Egeland et al. In our study, comparing the two exposed groups and the controls (according to the Kruskal–Wallis test) we did not find a significant difference between systolic and diastolic blood pressure values or the prevalence of hypertension (χ² test). A significant association (P=0.02) between CS₂ index and systolic blood pressure has been found only by multiple linear regression analysis.

Data gathered so far do not allow a straightforward picture of the pathogenic mechanism of the cardiovascular effects of CS₂. The possibility of accelerated atherogenesis due to CS₂ has not been proven. One of the hypotheses implies that CS₂ causes metabolic abnormalities such as disturbances of lipid metabolism, which are risk factors for atherosclerosis. Other possible mechanisms are an increase in blood pressure, disturbances in thyroid function (hypothyroidism) and catecholamine metabolism, depressed fibrinolytic activity, impaired neurovegetative regulation, and a direct toxic effect on the cardiovascular system. Our results may be explained through a hypothetical pathogenic mechanism involving a CS₂ effect on the lipid
metabolism leading to enhanced atherogenesis, resulting in an increased risk for CHD.

Conclusions

The results of our study show that occupational exposure to CS₂ may increase total cholesterol and the risk of CHD. There is a dose–response relationship between the level and duration of exposure and the prevalence of CHD. While the risk for CHD is increased in workers exposed to high CS₂ concentration for many years (CS₂ index ≥300), even a relatively modest exposure (CS₂ index <300) may increase serum cholesterol. The results imply that CS₂ may act by inducing disturbances in the lipid metabolism and acceleration of the atherosclerosis. There is no conclusive evidence of increased blood pressure associated with occupational exposure to CS₂.

REFERENCES