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Cerebral Vasoreactivity by Transcranial Doppler in Carbon Disulfide Poisoning Cases in Korea

The abnormalities of cerebral vasoreactivity were evaluated in CS_2 poisoning cases. In 34 retired workers with CS_2 poisoning (case group) and 20 healthy individuals (control group), blood flow velocities were measured in the middle cerebral arteries (MCA) by transcranial Doppler. Compared with the control group, the case group showed lower mean values of blood flow velocities and pulsatile indices. The differences in CO_2 reactivities of both groups were remarkable (1.10-2.19% decrease/mmHg CO_2 for cases and 3.35-5.08 for controls). Multiple regression analyses were conducted to adjust the effect of age, sex, and exposure level (non-low-high exposure) to CO_2 reactivity and pulsatile index. The exposure level was statistically significant in the regression model for CO_2 reactivity of both MCA and for pulsatile index of the right MCA. Our study noted a decrease of CO_2 reactivity and pulsatile index of cerebral vessels related with CS_2 exposure. These findings suggested that CS_2 exposure could lead to a decrease of cerebral vasoreactivities by the atherosclerotic change of cerebral vessels.

Key Words: *Carbon disulfide; Ultrasonography; Transcranial sonography, Doppler; Atherosclerosis*

Eunil Lee, Myung-Hyun Kim*

Department of Preventive Medicine and Institute for Environmental Health, College of Medicine, Korea University, Seoul Korea
*Department of Neurosurgery, Ewha Woman's University, School of Medicine, Seoul Korea

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Address for correspondence
Eunil Lee, M.D.
Department of Preventive Medicine and Institute for Environmental Health, College of Medicine, Korea University, 126-1, 5-ga, Anam-dong, Sungbuk-gu, Seoul 136-705, Korea
Tel: +82.2-920-6170, Fax: +82.2-927-7220
E-mail: eunil@kuccnx.korea.ac.kr

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INTRODUCTION

Atherosclerotic changes in vessels and nerve toxicity appear to be basic mechanisms of CS_2 poisoning cases in Korea. Major clinical findings of CS_2 poisonings in Korea were peripheral neuropathy (1-4), retinopathy including microaneurysm of the fundus (4, 5), multiple brain infarcts (1, 5, 6), and glomerulosclerosis of the kidneys (7).

Diabetogenic changes of vessels caused by CS_2 were reported by Korean and Japanese studies. The occurrence of microaneurysm of the retina was reported to be higher in the CS_2 exposed group than in the control group for both Korean and Japanese studies (5, 8). Some cases of CS_2 poisoning showed intercapillary glomerulosclerosis which is one of the typical patterns of diabetic glomerulosclerosis (7, 9).

Long-term atherogenic effects of CS_2 have been suggested by Davidson and Feinleib (10). Several cohort studies in Finland have shown elevated coronary mortality in workers exposed to CS_2 (11-13). CS_2 exposure can cause atherosclerotic lesions in the cerebral vasculature (14). Vigliani et al. (15) demonstrated hyalinosis of the arterioles and precapillaries histologically, which is a finding that fits the picture of general atherosclerosis caused by carbon disulfide.

Hypertension and diabetes mellitus are related to atherosclerotic change of cerebral vessels. CO_2 reactivity as measured by Transcranial Doppler (TCD) is useful for detecting abnormalities of cerebral hemodynamics among patients with hypertension or diabetes mellitus (16). Maeda et al. (17) also reported that hypertension affected the microvascular reactivity of the brain.

However, there have been few studies which assess cerebral vasoreactivity in CS_2 poisonings using TCD. The authors assumed that CS_2 caused the abnormalities of microvasculature by atherosclerosis of the cerebral vessels and these abnormalities could be evaluated by testing the carbon dioxide (CO_2) reactivity of the brain in CS_2 poisoning cases.

In our initial case study of eleven workers with CS_2 exposure, the authors found three cases of abnormal CO_2 reactivity in the brain (18). The authors wanted to expand this study to assess the relationship between CS_2 exposure and CO_2 reactivity of the brain by including a control group and a large number of subjects who were exposed to CS_2.

MATERIALS AND METHODS

Subjects

The authors examined 33 males and 6 females who were retired workers among over 500 retired Wonjin workers who had received compensation for CS_2 poisoning. The "Association for Wonjin Occupational Disease Patients" recruited the volunteers for this study. The subjects were examined from May 13 to June 29, 1996 at the Department of Neurosurgery of Ewha Womans University Mokdong Hospital. The disease status of the subjects were documented through history taking and hospital records from where they had been examined to qualify for compensation. Histories of severe head trauma and cerebrovascular accidents were not found.

The total number of case group tested by TCD was 30 males and 4 females (Table 1). Two women and three men were excluded because of their thick temporal bone or inability to detect the strongest signals by the Doppler test. The age of the subjects ranged from 35 to 68 years old. The mean duration of exposure to CS_2 was 142.1 months. Some subjects were examined on only one side of the middle cerebral artery because the strongest signal of the MCA was not detectable on the other side. Therefore, the total number of case group for CO_2 reactivity and pulsatile index of right or left MCA in Table 3 was different as shown in Table 1.

The control group consisted of 20 healthy individuals, 10 males and 10 females, who had no evidence or history of cerebral and/or cerebrovascular disease, heart disease, hypertension or abnormalities of blood chemistry. The CO_2 reactivities for this control group were measured in 1994 (19). However, all the measurements were done by the same instrument and the same examiner.

Methods

Blood flow velocities for both MCA were measured by TCD (Trans-scan, Eden Medical Electronics, US). The case and control groups were examined by an experienced neurosurgeon (co-author). The subjects were put in a supine position on the examination bed, and blood flow velocities were measured at the strongest signals through temporal bone. Exhaled CO_2 was monitored by a CO_2 monitor (SC-300 CO_2 monitor, Pryon Corporation, US). CO_2 reactivity was calculated as the change in the blood velocity over the change in the exhaled CO_2 during hyperventilation. The pulsatile index (PI) which reflects vessel elasticity was calculated as the difference of the systolic blood flow velocity and the diastolic blood flow velocity over the mean blood flow velocity.

The authors divided the subjects into two age groups (<50 and 50 or above) to reduce the effect of age in the analysis of the data. The authors compared the mean values of CO_2 reactivities, pulsatile indices and blood flow velocities between the case and control group by stratifying the age and sex.

The authors reconstructed each worker's exposure level based on work histories such as work duration and the department where the subjects had worked for. The reconstructed exposure level was expressed as cumulative CS_2 exposure indices (CI). The average CS_2 concentrations of the spinning department were about 10 ppm from 1986 to 1989, and below 5 ppm after 1990 when air supply masks were supplied to the workers (1). The authors assumed the average concentration of CS_2 in the spinning department was about 20 ppm before 1986 when the shields of the spinning machines remained open. The authors also assumed the exposure degrees of delivery and repair workers were 80% and 50% of the spinning workers respectively based on their working patterns. The other workers in the departments of raw materials, coking, washing and acid recovery were exposed to 0.2-0.5 ppm of CS_2. There had been no big changes of average concentration of CS_2 in these departments since 1986.

The average CI of all case group was 1340.5 ppm×month (Table 2). The subjects from the spinning, delivery and repair department showed average CIs of over 1,000 ppm×month, while those from the raw material, coking, acid recovery and washing department showed an average CIs of over 300 ppm×month. Depending on the exposure level, case subjects were classified into two

Table 1. Age and sex distribution of subjects

	35-49 years old			50-68 years old			Mean age (S.D.)
	Male	Female	Subtotal	Male	Female	Subtotal	
Carbon disulfide Case group (N=34)	19	3	22	11	1	12	46.1 yrs old (6.7)
Control group (N=20)	4	6	10	4	6	10	52.4 yrs old (10.5)

Work duration of cases: mean 142.1 months (S.D. 71.4) (range: 41-344)

Table 2. Cumulative CS_2 exposure indices of each department in case group

Department	Exposure levels (ppm)			Number of subjects	Mean (S.D)*	Minimum*	Maximum*	Total*
	1962-1985	1986-1990	1986-1993					
Spinning	20	10	5	13	1699.9 (1059.7)	523.0	3575.0	
Delivery	16	8	4	8	1169.5 (712.1)	244.0	2115.0	Mean=1340.5
Repair	10	5	2.5	8	1542.2 (830.5)	756.0	3020.0	S.D.=942.7
Raw material, coking, acid recovery		0.5		3	338.7 (261.5)	52.0	564.0	Median=1188.8
Washing		0.2		2	384.3 (506.1)	26.4	742.2	

* unit: ppm×month

groups as high and low based on the median of CI, 1188.8 (CS_2 ppm×work-month). So all exposure groups were three, i.e., no exposure group (control), low group and high exposure group.

The authors used t-tests to compare the mean values of the case and control group, and also used analysis of variance (ANOVA) to compare the mean values of the three exposure groups. Multivariate analysis was done by multiple stepwise regression analysis to control the effects of several explanatory variables such as age, sex, and exposure level. All the statistical analysis was performed by PC/SAS 6.11.

RESULTS

All the mean values of CO_2 reactivity between the case group and control group were stratified by both gender and age group as shown in Table 3. They showed statistically significant differences in 35-49 year-old groups of both genders (Table 3). In 50-68 year-old group, the average values of controls were higher than those of cases. The mean values of the case group were 1.10-2.19 %/mmHg of CO_2, and those of the control group were 3.35-5.08%/mmHg of CO_2.

The average values of CO_2 reactivity were also statistically significant differences among three exposure groups in 35-49 year-old male subjects. However, these values did not show a dose-response pattern (Table 4). The mean values in 50-68 year-old male subjects showed a decreasing trend according to exposure levels, but the differences of these values were not statistically significant.

Most of the average values of pulsatile indices (PI) of the case group were lower than those of the control group (Table 3). However, there were no statistically significant differences in stratified tables. The difference between total mean values of PI for the case and control group were statistically significant in the right MCA. The total mean values of cerebral blood flow velocity were higher in the control group than in the case group. But there were no statistically significant differences (Table 3).

Only in the male subjects, there were segmental blood flow changes in cerebral vessels (Table 5). Frequencies of these changes showed dose-response patterns in the 35-49 year-old male group, such as 27.3% in the high exposure group, 12.5% in the low exposure group and 0% in no exposure group. In 50-68 year-old male group, only the high exposure group showed a segmental blood flow change in cerebral vessels.

In simple correlation analysis, exposure group was correlated better with CO_2 reactivity than CI in 35-49 year-old-groups of both genders (Table 6). The correlation coefficients between exposure group and CO_2 reactivity were -0.73 to -0.77. CIs were significantly correlated with CO_2 reactivity, pulsatile index and cerebral blood flow velocity in 50-68 year-old male subjects.

The variable "exposure groups (EXP)" was statistically significant in the regression of CO_2 reactivity of both MCA (Table 7). In terms of pulsatile index (PI), the EXP variable was statistically significant only in the model for the right MCA. The regression model for mean cerebral blood flow velocity did not show any significant exposure variable.

DISCUSSION

The perfusion pressure of the human brain cannot be measured directly. The CO_2-stimulation technique by Transcranial Doppler (TCD) sonography, however, is one of the safest and most inexpensive as well as most reliable techniques to evaluate cerebral arterial reserve (20). The changing effect of CO_2 is restricted mainly to the peripheral vascular bed (21, 22), leaving proximal arterial diameters constant (23). TCD sonography delivers flow velocity data to assess the cerebral vasomotor reactivity (20) and detects reduced cerebral perfusion states (15).

However, age and sex have to be taken into account for a correct interpretation when examining the blood velocity in cerebral artery (24). The cerebral blood veloci-

Table 3. Differences of CO_2 reactivity, pulsatile index, and mean cerebral blood velocity in male and female subjects between carbon disulfide poisoning case group and control group

			Male subjects		Female subjects		Total
			35-49 year-old-group	50-68 year-old-group	35-49 year-old-group	50-68 year-old-group	
CO_2 rex.	Rt	Case	1.93 (1.15) N=18	2.19 (1.33) N=10	1.25 (1.03) N=3	1.10 (.) N=1	1.92 (1.18) N=32
		Control	5.05 (1.47) N=4 (p=0.0001)	3.42 (0.21) N=4 (p=0.017)	4.43 (1.53) N=6 (p=0.015)	4.83 (3.14) N=6 (p=0.32)	4.48 (1.98) N=20 (p=0.0001)
	Lf	Case	2.06 (1.07) N=19	2.18 (1.28) N=11	1.34 (0.66) N=3	1.63 (.) N=1	2.02 (1.10) N=34
		Control	5.08 (1.38) N=4 (p=0.0001)	3.35 (0.59) N=4 (p=0.11)	4.13 (1.45) N=6 (p=0.018)	3.70 (1.44) N=6 (p=0.24)	4.04 (1.35) N=20 (p=0.0000)
PI	Rt	Case	0.75 (0.13) N=18	0.72 (0.10) N=9	0.67 (0.04) N=3	0.84 (.) N=1	0.73 (0.11) N=31
		Control	0.75 (0.15) N=4 (p=0.97)	0.86 (0.23) N=4 (p=0.15)	0.89 (0.22) N=6 (p=0.14)	1.05 (0.20) N=6 (p=0.37)	0.90 (0.22) N=20 (p=0.004)
	Lf	Case	0.78 (0.30) N=19	0.70 (0.14) N=10	0.64 (0.07) N=3	0.78 (.) N=1	0.74 (0.24) N=33
		Control	0.76 (0.20) N=4 (p=0.89)	0.85 (0.16) N=4 (p=0.13)	0.69 (0.10) N=6 (p=0.50)	0.95 (0.11) N=6 (p=0.24)	0.81 (0.16) N=20 (p=0.27)
BV	Rt	Case	49.3 (12.9) N=18	49.6 (9.9) N= 9	62.0 (11.4) N=3	55.0 (.) N=1	50.8 (12.0) N=31
		Control	55.5 (15.0) N=4 (p=0.40)	45.8 (11.4) N=4 (p=0.55)	75.3 (28.0) N=6 (p=0.47)	58.3 (25.6) N=6 (p=0.91)	60.4 (23.6) N=20 (p=0.11)
	Lf	Case	48.3 (18.2) N=19	63.9 (40.5) N=10	58.3 (12.5) N=3	54.2 (24.7) N=6	54.0 (26.6) N=33
		Control	70.0 (43.3) N=4 (p=0.39)	39.5 (11.5) N=4 (p=0.26)	76.5 (22.4) N=6 (p=0.24)	49.0 (.) N=1 (p=0.85)	61.1 (28.5) N=20 (p=0.36)

Rt, right middle cerebral artery; Lf, left middle cerebral artery; CO_2 rex., CO_2 reactivity (% per mmHg of CO_2); PI, Pulsatile index; BV, mean cerebral blood flow velocity (cm/sec)

Table 4. Differences of CO_2 reactivity according to the CS_2 exposure groups stratified by age-group and sex

		Male subjects				Female subjects			
		35-49 year-old-group		50-68 year-old-group		35-49 year-old-group		50-68 year-old-group	
Rt	No exposure group	5.05 (1.47) N=4	p=0.0008	3.43 (0.21) N=4	p=0.10	4.43 (1.53) N=6	p=0.05	4.83 (3.14) N=6	p=0.32
	Low exposure group	1.86 (1.51) N=8		2.70 (1.40) N=6		0.79 (0.91) N=4		- -	
	High exposure group	1.99 (0.85) N=10		1.69 (1.17) N=7		2.18 N=1		1.10 N=1	
Lf	No exposure group	5.08 (1.38) N=4	p=0.0001	3.35 (0.59) N=4	p=0.28	4.13 (1.45) N=6	p=0.075	3.7 (1.44) N=6	p=0.24
	Low exposure group	1.54 (0.60) N=9		2.27 (1.56) N=6		1.28 (0.92) N=2		- -	
	High exposure group	2.53 (1.21) N=10		2.07 (1.01) N=5		1.45 N=1		1.63 N=1	

unit: % per mmHg of CO_2

Table 5. Segmental blood flow changes in cerebral vessels

	Male subjects		Female subjects	
	35-49 year-old-group	50-68 year-old-group	35-49 year-old-group	50-68 year-old-group
No exposure group	0 of 4 (0%)	0 of 4 (0%)	0 of 6 (0%)	0 of 6 (0%)
Low exposure group	1 of 8 (12.5%)	0 of 4 (0%)	0 of 2 (0%)	-
High exposure group	3 of 11 (27.3%)	2 of 7 (28.6%)	0 of 1 (0%)	0 of 1 (0%)

Table 6. Correlation analysis between exposure and response variables stratified by sex and age group

			CI	EXP	CO_2 (Rt)	CO_2 (Lf)	PI (Rt)	PI (Lf)	BV (Rt)	BV (Lf)
35-49	Male (N=22)	CI	1.0	0.52*	-0.22	-0.11	0.02	0.03	0.02	0.06
		EXP		1.0	-0.73*	-0.73*	-0.007	0.03	-0.19	-0.34
	Female (N=9)	CI	1.0	0.57	-0.30	-0.43	-0.24	-0.30	0.03	-0.28
		EXP		1.0	-0.77*	-0.76*	-0.53	-0.26	-0.28	-0.44
50-68	Male (N=14)	CI	1.0	0.66*	-0.52*	-0.18	-0.26	-0.65*	-0.02	0.61*
		EXP		1.0	-0.46	-0.43	-0.42	-0.43	0.18	0.32
	Female (N=7)	CI	1.0	1.0*	-0.44	-0.51	-0.40	-0.52	-0.05	-0.09
		EXP		1.0	-0.44	-0.51	-0.40	-0.52	-0.05	-0.09

CI, cumulative CS_2 exposure index; EXP, exposure group; CO_2, CO_2 reactivity; 35-49, 35-49 year-old-group; 50-68, 50-68 year-old-group.
*$p<0.05$

Table 7. Multiple stepwise regression analysis of age, sex, exposure groups (EXP) to CO_2 reactivity, pulsatile index, and mean cerebral blood flow velocity

		R^2 (p value)	Variables (parameter estimate, p value)
CO_2 reactivity	Rt	0.33 (0.0001)	EXP (-1.29, p=0.0001)
	Lf	0.23 (0.0002)	EXP (-0.86, p=0.0002)
Pulsatile index	Rt	0.23 (0.0018)	EXP (-0.065, p=0.033), Sex (0.096, p=0.09)
	Lf	0.04 (0.13)	EXP (-0.052, p=0.13)
Mean cerebral blood flow velocity	Rt	0.17 (0.0031)	SEX (15.5, 0.0031)
	Lf	No significant model	

ty at rest decreased significantly with age increase. Females up to 50 years of age had significantly higher blood velocity values than males. To adjust the effects of age and sex, the authors stratified the data according to sex and age-groups.

Smoking and drinking were not considered in stratified analysis and multiple regression analysis of CO_2 reactivity because the authors did not have any history of smoking and drinking habits for the control group. Some intracranial circulatory changes, predominantly in the vertebral arteries, and some pathologic intimal changes in the carotid arteries have been found in smokers (25). Smoking also can cause significant intracranial blood flow disturbances. However, there have been few reports indicating any relationship between the decrease of CO_2 reactivity and drinking.

In this study, CO_2 reactivities of the case group were much lower than those of the control group in the same sex and age-groups (Table 3). In spite of no adjustment for smoking and drinking, it is unlikely that these large differences could be explained entirely by behavioral or other factors which were not considered in this study.

TCD study is applied to various clinical conditions such as occlusion and stenosis of the carotid artery (20), and stroke or intracranial hemorrhages (26, 27). TCD study is also applied to diseases such as hypertension and diabetes mellitus to detect reduced vasoreactivity of the brain (15, 16). Hypertension is one of the major risk factors for arteriosclerosis, and cerebral vessels are often affected (28, 29). Hypertensive patients showed decreased CO_2 reactivities measured by TCD (16).

Atherosclerosis of cerebral vessels may be a common change in CS_2 poisoning. Vascular changes due to carbon disulfide exposure are similar to those produced by atherosclerosis due to aging, and these changes are particularly prominent in the central nervous system and

kidneys (30). These changes can be detected by TCD like hypertension. The atherosclerotic change of cerebral vessels may be the basic mechanism which can explain the abnormal findings of CS_2 poisoning cases in this study. CO_2 reactivities of the case group were statistically lower than those of the control group (Table 3). Pulsatile indices and mean blood flow velocities of the case group were lower than those of the control group. Decreased cerebral vasoreactivity was also related with CS_2 exposure. Exposure indices were statistically significant in the multiple regression analysis for CO_2 reactivity and pulsatile index with age and sex adjusted (Table 7). All these findings suggest atherosclerotic changes of cerebral vessels.

Another possible explanation for the decrease in cerebral vasoreactivity may be a direct toxic effect of CS_2. Aaserud et al. (31) reported both brain atrophy and vascular encephalopathy. Brain atrophy was found in approximately 81% (13/16) of the workers exposed to 30-60 mg/m^3 CS_2 for at least 10 years. The subjects in that study also showed vascular encephalopathy in the examination of regional cerebral blood flow. They reported that CS_2 induced encephalopathy is not exclusively a result of vasculopathy at the acute exposure level.

However, there were no brain atrophy cases reported in the Korean Wonjin workers exposed to CS_2. Some of them were exposed to similar level of CS_2. Brain infarcts were among the major findings in these workers (1). Other major clinical findings were microaneurysm of the fundus (4, 5) and glomerulosclerosis of the kidneys (7). These findings suggest that atherosclerotic changes of cerebral vessels were more important in reducing cerebral vasoreactivity in Korean CS_2 workers than direct toxic vasculopathy.

This study was a cross-sectional study, the number of subjects was small, and age difference remained between case and control group after stratification of age. In spite of these limitations, the authors concluded that the decrease in CO_2 reactivity, and pulsatile index, and the stenotic change of the MCA in CS_2 exposed workers may be caused by the atherosclerotic effects of long term exposure to CS_2.

TCD test can detect the arterial reserve before the development of brain infarcts which is one of the most common clinical findings in workers with CS_2 poisoning. This study showed the possibility of TCD test to detect abnormal vasoreactivity in CS_2 poisoning workers. However, further study is needed to evaluate the usefulness of the TCD test as a screening or detection tool to assess the decreased arterial reserve in workers with CS_2 exposure who do not manifest clinical abnormalities of CS_2 poisoning.

In conclusion, the authors examined whether CO_2 reactivity of cerebral vessels measured by TCD was related to CS_2 exposure. Cerebral atherosclerosis is a basic toxic effect caused by in CS_2 poisoning. Recognizing that TCD test is one of the safest, most inexpensive and reliable techniques available to evaluate arterial cerebral vasoreactivity, the authors decided to use this method in this study. Workers with CS_2 poisoning showed decreased vasoreactivities of cerebral vessels. There were statistically significant differences in CO_2 reactivity and pulsatile index between the case group and the control group. The variable "CS_2 exposure group" was significant in multiple regression analyses for CO_2 reactivity and pulsatile index. These findings suggested that deceased vasoreactivities of cerebral vessels in the case group were caused by atherosclerotic effects of CS_2 exposure. Further study is needed to evaluate the usefulness of the TCD test as a screening or detection tool to assess the decreased arterial reserve in workers with CS_2 exposure who do not manifest clinical abnormalities of CS_2 poisoning.

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