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Trans-Cranial Doppler and Peripheral Sensory Threshold Tests for Carbon Disulfide Poisoning

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Abstract: Trans-Cranial Doppler and Peripheral Sensory Threshold Tests for Carbon Disulfide Poisoning: Eunil LEE, *et al.* Department of Preventive Medicine, School of Medicine, Korea University— Trans-cranial doppler (TCD) and sensory threshold (vibration, pain and discrimination) tests, which are safe and inexpensive techniques, were applied to detect cerebral vasoreactivity or neuropathic changes between carbon disulfide (CS_2) poisoning cases and two control groups respectively. The cases were 31 male CS_2 poisoning workers, and the first control group for the TCD test consisted of eight healthy men, and the second group for the threshold test were 21 healthy male workers. In the TCD test, the blood flow velocity in both middle cerebral arteries and the CO_2 content of expired air were measured to evaluate CO_2 reactivity. The vibration and pain perception threshold were measured on both the 2nd and 5th fingers. The CS_2 poisoning cases showed higher rates of abnormal CO_2 reactivity above the cut-off value than healthy controls (80.0–81.8% vs 0%). Among the threshold tests, the proportions of abnormal pain threshold of both the 2nd and 5th fingers were higher in poisoning cases than in the controls (77.8%–88.9% vs 11.1–33.3%) among over 45 yr old subjects. CO_2 reactivity and pain threshold test showed the possibility to detect changes in cerebral vessels and the sensory threshold in CS_2 exposure cases, but there should be further study to apply these tests to workers exposed to CS_2 before the development of CS_2 poisoning, with large number of control subjects. *(J Occup Health 2001; 43: 307–313)*

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The major clinical findings in CS_2 poisoning in Korea were peripheral neuropathy, retinopathy including microaneurysms of the fundus, multiple brain infarcts, and glomerulosclerosis of the kidneys[1–5]. The basic pathogenesis of CS_2 poisoning in Korea was atherosclerotic changes in vessels and peripheral nerve toxicity. Long-term atherogenic effects of CS_2 have been reported in western studies[6–9] for coronary heart disease, and in Japanese and Korean studies[10–13] for microaneurysms of the retina and intercapillary glomerulosclerosis of the kidneys. Carbon disulfide also could be a cause of atherosclerosis of cerebral vessels and abnormalities of the microvasculature affected by atherosclerosis of the cerebral vessels can be evaluated by testing the carbon dioxide (CO_2) reactivity of the brain of Trans-cranial Doppler (TCD). Among eleven CS_2 exposed workers three cases of abnormal CO_2 reactivity in the brain by TCD were found in 1993[14], and Lee and Kim[15] reported a decrease in CO_2 reactivity and pulsatile index in CS_2 poisoning cases in 1998.

Measurement of the vibration threshold has been used successfully to quantify the sensory threshold in workers exposed to toxic substances[16] and to assess neuropathy in workers exposed to neurotoxins[17] including diabetic neuropathy[18, 19] and hand-arm vibration syndrome[20, 21]. A decreased vibration perception threshold in CS_2 workers had been reported and there was found to be a close linear correlation between the vibration threshold and carbon disulfide exposure regardless of age[22], but it was reported that light touch, pain and temperature discrimination are more reduced than the vibration sense in cases of toxic occupational neuropathies[23]. So we selected vibration, and the pain threshold test among threshold tests and discrimination sense among innervation density tests[24] to assess the effect of carbon disulfide on peripheral sense.

The aim of this study was to investigate the abnormal rates in CS_2 poisoning cases and controls for CO_2 reactivity and peripheral sense.

Table 1. Clinical findings in CS_2 poisoning subjects at the time of diagnosis for compensation (%)[a]

	Poly-neuropathy	Micro-aneurysm	Cerebral infarct	Hypertension
35–49 yr old (N=20)	6 (30.0%)	10 (50.0%)	3 (15.0%)	4 (20.0%)
50–57 yr old (N=11)	6 (54.5%)	5 (45.5%)	5 (45.5%)	8 (72.7%)
All CS_2 poisoning subjects (N=31)	12 (38.7%)	15 (48.4%)	8 (25.8%)	12 (38.7%)

a: (%) number of case/total number of subjects classified by age group.

Table 2. Age distribution of study subjects for transcranial doppler study

	35–49 yr old	50–68 yr old	Total
Carbon disulfide cases (N=31)	20 (64.5%)	11 (35.5%)	31
Healthy controls (N=8)	4 (50.0%)	4 (50.0%)	8

*All study subjects were male.

Materials and Methods

We examined 31 male workers who retired from Wonjin Rayon Company and had been diagnosed with CS_2 poisoning. They suffered from several diseases including polyneuropathy, microaneurysm, cerebral infarct and hypertension (Table 1). They were exposed to various level of CS_2 according to their working department when they worked in Wonjin rayon company (0.2–20 ppm). To evaluate the exposure level of poisoning cases, we reconstructed each worker's cumulative exposure index (CEI) based on work histories including work duration and the department where the subjects had worked[15]. All subjects voluntarily joined this study, and they were examined between May 13 and June 29, 1996 at the department of neurosurgery of Ewha Women's University Mokdong Hospital. Their disease status was investigated by examining the records of hospitals where they had been examined. We also took down their history. There were 12 hypertensive patients among 31 subjects (Table 1).

The control group for TCD test was eight healthy males who had no evidence or history of cerebral and/or cerebrovascular disease, hypertension, heart disease or abnormalities of blood chemistry. We recruited and examined these subjects in a health examination study in 1993 to establish reference values for TCD tests[25]. They were all white-collar people with diverse occupations, and they were not occupationally exposed to toxic materials. We stratified the subjects for TCD tests into two age groups, more and less than 50 years old, to reduce the aging effect (Table 2).

All study subjects were examined by the same experienced neurosurgeon, who measured the blood flow velocity in each middle cerebral artery (MCA) by TCD (Trans-scan, Eden Medical Electronics, US) through the temporal bone. They were asked to lie supine on a bed in the out-patient room. Blood flow velocity was taken as the strongest signal. Exhaled CO_2 was monitored by means of a CO_2 monitor (SC-300 CO_2 monitor, Pryon Corporation, US). CO_2 reactivity was taken as the change in blood velocity over the change in CO_2 during hyperventilation. The pulsatile index (PI), which reflected vessel distensibility, was calculated as the sum of systolic blood flow velocity and diastolic blood flow velocity over the mean blood flow velocity. Suspected stenotic change in vessels could be found as abrupt high segmental blood flow change during the TCD test. Normal remote arteries showed vascular reactivity of 2.3 to 4.0% per mmHg of CO_2[26], and the cut off value of CO_2 reactivity for this study was below 2.0% per mm Hg of CO_2[25]. The cut-off value of the pulsatile index in this study was below 1.1[27].

The quantitative sensory tests for cases were examined by two physicians after the TCD test in the same room. The vibration and pain thresholds were measured on both the index and 5th fingertips. Eye covers kept them from seeing. The fingertip examined was placed lightly on the button of a Vibrometer (Rion) to examine the vibration threshold. The perception threshold of vibration sense was measured at 125 Hz. The pain threshold was measured by an Algometer (TKK 1335) at the tip of the fingers, and when the subject did not respond at above 14 g, the pain threshold was recorded as 14 g because we could not measure above that. The discrimination sense was measured by means of a Spearman-type aesthesiometer on both 2nd fingers.

The control group for the quantitative sensory tests consisted of 21 healthy male automobile manufacturing workers who had no neurologic symptoms and no evidence of high blood pressure, blood sugar or abnormal blood chemistry. They might be exposed to a low level of hand-arm vibration because they used vibratory tools such as grinders. We collected the data of the workers

Table 3. Age distribution of study subjects for quantitative sensory tests study

	35–44 yr old	45–59 yr old	Total
Carbon disulfide cases (N=31)	13 (41.9%)	18 (58.1%)	31
Healthy workers (N=21)	12 (57.1%)	9 (42.9%)	21

*All study subjects were male.

Table 4. Distribution of subjects who showed CO_2 reactivity above the cut-off value in carbon disulfide poisoning cases (Case) and healthy controls (Non case)

	Right		Left		Total[a]	
	Case	Non case	Case	Non case	Case	Non case
35–49 yr old	14 (70.0%)[b]	0 (0.0%)	14 (70.0%)[b]	0 (0.0%)	16 (80.0)[b]	0 (0.0%)
	N=20	N=4	N=20	N=4	N=20	N=4
50–68 yr old	6 (55.6%)	0 (0.0%)	7 (63.6%)	0 (0.0%)	9 (81.8)[b]	0 (0.0%)
	N=11	N=4	N=11	N=4	N=11	N=4

a: Number of cases who had above cut-off value in either right or left side. b: $p<0.05$ by Fisher's exact test.

Table 5. Distribution of subjects who showed above cut-off values for the pulsatile index in carbon disulfide poisoning cases (Case) and healthy controls (Non case)

	Right		Left		Total[a]	
	Case	Non case	Case	Non case	Case	Non case
35–49 yr old	2 (10.0%)	0 (0.0%)	3 (15.0%)	0 (0.0%)	4 (20.0%)	0 (0.0%)
	N=20	N=4	N=20	N=4	N=20	N=4
50–68 yr old	2 (18.2%)	0 (0.0%)	2 (18.2%)	0 (0.0%)	3 (27.3%)	0 (0.0%)
	N=11	N=4	N=11	N=4	N=11	N=4

a: Number of cases who had above cut-off values in either right or left side.

without symptoms and disease whose age ranged from 35 to 55 years among 103 male healthy workers who received quantitative sensory tests and an annual medical examination in October, 1995[28]. All control subjects were examined after at least 20 min rest after work by the same two physicians who examined the cases.

In the analysis of data, the subjects were stratified into two age groups divided at age 45 rather than 50 to reduce the effect of age because the control subjects for quantitative sensory tests were younger than those for TCD tests (Table 3). The cut-off value for a normal vibration perception threshold was over 7.5 dB[22, 29], that for pain threshold was over 10 g[29], and that for discrimination sense was over 6 mm[24]. We used the Chi-square test, Fisher's exact test, and multiple regression for statistical analysis by SAS software.

Results

The poisoning cases had higher rates of abnormal CO_2 reactivity and PI than controls in both age groups (Table 4, 5), but there was no statistically significant difference between cases and controls in PI (Table 5). Compared with the controls, the proportion of abnormal CO_2 reactivity in cases was statistically much higher than in the controls in the 35–49 yr age group (70.0% vs. 0% in both sides) (Table 4). When an abnormal case was defined as one who had above the cut-off value in either the right or left MCA, the differences between cases and controls were statistically significant both in 35–49 and 50–68 yr age groups (80.0%–81.8% vs 0%).

Only 6 cases showed suspected stenotic change in MCA among 30 poisoning cases (Table 6). These stenotic change cases had higher cummulative exposure indices (CEI) of CS_2 than those who did not have stenotic change. The difference in CEI was statistically significant among all cases.

The proportion of abnormal vibration thresholds was higher in case subjects than in control workers in the 45–59 yr-old age group, but it did not show any statistically significant difference (Table 7). In the 35–44 yr-old age group, the proportion over the cut-off value was higher than in the control workers in the left 2nd fingers. The pain threshold of fingers showed a consistent result. The abnormal rates in cases were higher than those in control workers in both age groups. There were statistically significant differences in abnormal rates between cases (77.8%–88.9%) and control workers (11.1–33.3%) in the 45–59 yr age group. In terms of the discrimination threshold, there were one or two abnormal cases in CS_2 poisoning cases in each age group, and no statistically significant difference between cases and control workers.

Discussion

Atherosclerotic change in cerebral arterioles may cause a decrease in CO_2 reactivity due to stiffening of small arterioles in the brain and decreasing blood flow velocity caused by increasing peripheral vascular resistance. CS_2 exposure can cause atherosclerotic lesions in the cerebral vasculature[30)] and the CO_2-stimulation technique by means of TCD sonography is one of the safest and most inexpensive as well as the most reliable techniques to evaluate cerebral arterial reserve[31)]. In our previous studies[14, 15)], decreased CO_2 reactivity of CS_2 poisoning cases was found by TCD test, and it was related to CS_2 exposure[15)]. These findings suggested that decreased vasoreactivity of cerebral vessels was related to atherosclerotic change in vessels caused by CS_2. The TCD test had already been applied to other diseases, such as hypertension which showed arterosclerosis of the brain[32–35)].

In this study, about 80% of poisoning subjects showed abnormal CO_2 reactivity in either the right or left MCA in both age groups (Table 4). The mean values for the case group were 1.10–2.19%/mmHg of CO_2, and those for the non-case group were 3.35–5.08%/mmHg of CO_2. The differences between cases and non-cases in means were statistically significant. The sensitivity and specificity of CO_2 reactivity for CS_2 poisoning could be calculated from Table 4. The sensitivity and specificity were 80.6% and 100% respectively, but a total of 12 subjects among 31 cases had hypertension. Hypertension of poisoning cases developed after they worked at the Rayon factory, and hypertension could be regarded as one of the manifestations of CS_2 poisoning[36)], but CS_2 could not be the only possible cause of hypertension, which also related to aging. There were no statistically significant differences between hypertension cases and normotensive cases in mean CO_2 reactivity (1.39–2.64 vs 1.91–2.76 %/mmHg of CO_2). This showed that hypertension might not seriously affect CO_2 reactivity in poisoning cases.

Atherosclerotic changes in vessels could induce stenotic changes in vessels. In the TCD test, the blood flow velocity can be detected, and some vessels showed abrupt high blood flow velocity. Those vessels should narrow at that point for several possible reasons, such as congenital anomaly and atherosclerotic change in the vessels. The subjects who had suspected stenotic change in the vessels had higher CS_2 exposure indices than those who had not (Table 6). These finding suggested that these stenotic changes were caused by atherosclerotic change in cerebral vessels after CS_2 exposure.

The cases were compared to controls in a similar age group without adjusting for smoking or drinking habit because of a lack of information about smoking and drinking for the controls. The smoking rate for cases was 61%, which was lower than the Korean adult smoking rate of 70%. And there have been few reports indicating any relationship between a decrease in CO_2 reactivity and drinking. Smoking and drinking factors did not seem to be serious confounders in this study.

The vibration threshold could be useful for screening for peripheral neuropathy. In a previous study[22)], a significant difference between CS_2 poisoning cases and controls was shown. Carbon disulfide is a solvent which has clearly been associated with sensory motor neuropathy[37)]. In this study, a threshold test of vibration and pain, and an innervation density test with two-point discrimination were selected as peripheral quantitative sensory tests. The innervation density test may remain normal even with moderately advanced nerve dysfunction and may confirm obvious symptoms in advanced and chronic diseases[24)]. The threshold test, however, is more sensitive than the innervation density test in detecting slight, early impairment of peripheral nerve function. As expected, threshod test of vibration and pain showed a difference between cases and controls, but discrimination sense showed only three abnormal cases in which there may be advanced peripheral neuropathy. And among the polyneuropathy patents, a total of seven (58%) complained of subjective symptoms related to peripheral neuropathy.

The distribution of an abnormal rate of vibration threshold did not show a statistically significant difference between CS_2 cases and control workers. And the difference between cases and control workers in the mean threshold was not statistically significant (2.31–10.58 dB vs $-$0.42–4.44 dB). These findings were contrary to Park's previous study[22)]. Comparing this study with Park's, the mean thresholds of cases in this study were higher than those of high exposure workers in Park's study (2.31–10.6 dB vs 2.2–5.5 dB). And the mean thresholds of control workers in this study were also higher than those in Park's study[22)] [$-$0.42–4.4 dB vs $-$3.3–($-$1.4 dB)]. Many factors affect the measurement of vibration perception threshold, such as contact force, temperature, frequency of vibration[38)], lack of standardization of method[39)], and duration and intensity of the initial level of vibration[40)]. The measuring methods were almost the same in the two studies, and a higher mean value for control workers in this study suggested that the vibration threshold of these workers might be increased by their

Table 6. Mean of cummulative exposure indices[a] in carbon disulfide poisoning cases according to the presence of suspected stenotic change[b] in middle cerebral arteries by trans-cranial Doppler

	Suspected stenotic change	Non stenotic change	p-value
All cases	2106.8 ± 1263.2 (N=6)	1176.3 ± 795.0 (N=24)	0.026
< 50 yr old	2274.6 ± 1479.2 (N=4)	1235.4 ± 814.6 (N=15)	0.073
≥ 50 yr old	1771.3 ± 1037.7 (N=2)	1209.6 ± 781.8 (N=9)	0.401

a: Cummulative exposure index was reconstructed based on each worker's work history and CS_2 levels in the working departments of Wonjin company (Lee and Kim, 1998). b: Suspected stenotic change defined as abrupt segmental high blood flow change in TCD.

Table 7. The distribution of subjects who showed above cut-off values in quantitative sensory tests in carbon disulfide poisoning cases (Case) and healthy workers (Worker)

	35–44 yr old		45–59 yr old	
	Case (N=13)	Worker (N=12)	Case (N=18)	Worker (N=9)
Vibration threshold on fingers				
Rt 2nd	2 (15.4%)	2 (16.7%)	9 (50.0%)	2 (22.2%)
Rt 5th	3 (23.1%)	4 (33.3%)	10 (55.6%)	4 (44.4%)
Lt 2nd	2 (15.4%)	1 (8.3%)	10 (55.6%)	3 (33.3%)
Lt 5th	5 (38.5%)	4 (33.3%)	12 (66.7%)	3 (33.3%)
Pain threshold on fingers				
Rt 2nd	8 (61.5%)	6 (50.0%)	14 (77.8%)[a]	2 (22.2%)
Rt 5th	8 (61.5%)	5 (41.7%)	14 (83.3%)[a]	3 (33.3%)
Lt 2nd	9 (69.2%)	5 (41.7%)	16 (88.9%)[a]	1 (11.1%)
Lt 5th	8 (61.5%)	6 (50.0%)	16 (88.9%)[a]	1 (11.1%)
Discrimination threshold on fingers				
Rt 2nd	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)
Lt 2nd	1 (7.7%)	0 (0.0%)	2 (11.1%)	0 (0.0%)

a: $p<0.05$.

use of tools in an automobile company.

There have been few studies evaluating the mechanism of a rise in the vibration threshold caused by CS_2 exposure. Cha *et al.*[4)] reported that carbon disulfide poisoning cases showed both segmental and axonal degenerations. Neurotoxicity of CS_2 could cause an increase in the vibrotactile threshold. In studies of carpal tunnel syndrome, the rationale underlying the use of vibrotactile testing is that large-diameter fibers are affected first, and because sensory (A) fibers are large, their function should be affected in the early stages of compression[41)]. Llewely *et al.*[42)] reported that the vibration sense threshold was positively correlated with the total number of myelinated fibers, but the role of the pacinian corpuscles is also very important in assessing the vibration threshold. Lundborg *et al.*[43)] reported that one of the first changes found in vibration testing is a decrease in sensitivity in the 125- to 250- Hz frequency region, the region mediated by pacinian corpuscles. The age effect on vibration sense was strong[44)], and age-related declines in sensory-motor function were greater in the diabetic group than in the control group[45)]. In the multiple regression analysis, age and smoking variables were statistically significant in the vibration threshold in this study (R^2=0.30–0.43, $p<0.05$). It was very interesting to find that smoking could effect the vibration threshold, but further study is needed to evaluate the effect of smoking on the vibration threshold.

There have been few studies on the pain threshold test for workers exposed to CS_2. The pain threshold seemed to be more affected by CS_2 exposure than vibration sensibility in this study (Table 7). The mean pain thresholds of the case group were 10.19–12.94 g, and those of the control worker were 5.72–7.92 g. The greatest differences between cases and control workers in means were statistically significant. These results suggested that general nerve damage might be a more important mechanism in CS_2 nerve toxicity than damage to specific nerve endings such as the Pacinian corpuscles. In multiple stepwise regression analysis for pain threshold to control age, smoking, drinking variables, only the cumulative exposure index was statistically significant in the regression model (R^2=0.26–37, p<0.0005).

This study had several limitations. This study was done for CS_2 poisoning cases and controls without the blind technique. Examiners knew who were the cases and controls when they conducted the tests. And the number of controls in this study was not large, and control subjects were not selected randomly from general population. The control workers for PQS tests might be exposed to low levels of vibration and showed high thresholds of vibration sense. In spite of these limitations, CO_2 reactivity and the pain threshold test for CS_2 poisoning cases suggested that these tests could probably detect early changes in cerebral vessels and the sensory threshold in CS_2 exposure cases. Further study should be done on workers exposed to CS_2, before the development of CS_2 poisoning, with large number of control subjects.

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