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BRIEF COMMUNICATION

Verbal memory deficits associated with fornix atrophy in carbon monoxide poisoning

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Abstract

Magnetic resonance (MR) images and neuropsychological testing data of 69 carbon monoxide (CO) poisoned patients were prospectively obtained within 1 day of CO poisoning, two weeks and six months. CO patients' Day 1 cross-sectional fornix surface area measurements, corrected for head size by using a fornix-to-brain ratio (FBR), were compared to normal age and gender-matched controls. Additionally, a within-subjects analysis was performed comparing the mean areas between CO patients' Day 1, 2 weeks and 6-month FBR. The FBR was correlated with patients' neuropsychological data. There were no significant differences between CO patients' Day 1 fornix measurements compared to normal control subjects. However, significant atrophic changes in the fornix of CO poisoned patients occurred at two weeks with no progressive atrophy at 6 months. By 6 months, CO patients showed significant decline on tests of verbal memory (when practice effects were taken into account), whereas visual memory, processing speed and attention/concentration did not decline. This study indicates that CO results in brain damage and cognitive impairments in the absence of lesions and other neuroanatomic markers. (*JINS*, 2001, *7*, 640–646.)

Keywords: Carbon monoxide poisoning, Morphometric analysis, Fornix, Neuropsychological outcome

INTRODUCTION

Carbon monoxide (CO) exists normally in the body. However, when body stores of CO are increased beyond homeostatic capacity, CO displaces oxygen on blood hemoglobin, forming the carboxyhemoglobin (COHb) molecule, reducing oxygen supply to tissues and resulting in hypoxia (Weaver, 1999). Adverse effects of CO-induced hypoxia are most drastically observed in the brain (Edvinsson et al., 1981). Carbon monoxide poisoning causes hypoxic brain damage and initiates a variety of neuropathological mechanisms including apoptosis, or programmed cell death (Piantadosi et al., 1995), direct histotoxic effect on nervous system parenchyma (Ganong, 1987), lipid peroxidation leading to oxidation injury (Thom, 1990), cerebral edema which may also cause secondary vascular effects (Imaizumi et al., 1994), massive release of excitatory amino acids (Jarrard & Meldrun, 1993), lactic acidosis (Sutariya et al., 1992), binding to intracellular proteins (Piantadosi, 1987) and deposition of peroxynitrate which damages blood vessel endothelium (Thom et al., 1998).

Common areas of CO-induced brain injury include lesions of the white matter, caudate, globus pallidus, and hippocampus as well as nonspecific damage manifested by generalized cortical atrophy (Gale et al., 1999; Hashimoto et al., 1990; Jain, 1990; Kanaya et al., 1992; Klostermann et al., 1993; Kodama et al., 1990; Sovilla et al., 1988; Uchino et al., 1994). Those who survive CO poisoning often suffer a variety of neurocognitive and neurobehavioral impairments that frequently correlate with the severity and localization of brain damage (Gale et al., 1999; Hopkins et al., 1995a; Hopkins et al., 1995b; Nabeshima et al., 1991; Press et al., 1989; Silver et al., 1996).

In previous magnetic resonance (MR) imaging work with CO-induced hypoxic brain injury, we have shown the vulnerability of the hippocampus and the relationship of hip-

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pocampal volume loss to memory deficits (Gale et al., 1999; Hopkins et al., 1995a). In the current study, we are interested in the effect CO-induced hypoxic mediated atrophy of the fornix using a prospective, within subject design. The efferent synaptic projections from the hippocampus through the fornix represent a common functional system, critical to memory (Botez & Botez, 1992; Gaffan, 1992; Kapur et al., 1994; Neave et al., 1994; Squire et al., 1990). Fornix atrophy can occur independently of hippocampal atrophy in certain neuropathological conditions (Kuzniecky et al., 1999). In addition, the fornix can easily be identified on MR scans and has been quantified in other disorders that result in brain injury (Gale et al., 1993).

In the current study, we employed a prospective, within-subjects design to determine if atrophic changes occur in the fornix of CO poisoned patients. We compared the CO patient's Day 1 fornix cross-sectional surface area to that of normal controls, to determine if the Day 1 scans can be used as a measure of preexposure brain morphology. We also examined the CO poisoned patients' impairment in visual and verbal memory functioning, attention/concentration and processing speed associated with fornix atrophy. We expected *a priori* that CO patients would have significant neuropsychological impairments and associated fornix atrophy, when compared to their Day 1 fornix measurements.

METHODS

Research Participants

Sixty-nine CO poisoned patients were enrolled in this study, using a prospective, within-subjects design. Patients were excluded if they did not have at least two MR scans performed, as some patients refused to complete their MR series. The CO patients were administered a neuropsychological screening battery and MR scans were obtained on the day of CO exposure (Day 1), at 2 weeks and 6 months. Our follow-up rates were 97% ($n = 67$) at 2 weeks and 94% ($n = 65$) at 6 months. In order to assess if the patients' Day 1 scans could be used as a baseline, they were compared to scans of normal controls (M age 35.9 ± 11.9 years) from our neuroimaging database (Blatter et al., 1995). Patients had a medically documented exposure to CO with an elevated COHb, and were at least 16 years old. All CO poisoned patients received the current standard of care and were treated with either 100% normobaric oxygen or hyperbaric oxygen (Camporesi, 1996). Informed consent was obtained from each patient or legal surrogate prior to participation in the CO study. Patients received compensation for their time (i.e., $50.00 for a follow-up visit at 6 months). The study had Institutional Review Board approval at LDS Hospital in Salt Lake City, Utah and at Brigham Young University in Provo, Utah.

Of the 69 CO poisoned patients 48 were male and 21 female. The mean age was 34.6 ± 13.7 years (range = 16–86 years) and the mean education level was 11.7 ± 3.2 years (range = 0–17 years). The CO patients had a mean COHb level of 21.4 ± 11.5% (range of 2–39%). Fifty-two percent (52%) of the patients experienced a loss of consciousness associated with their CO exposure. Faulty furnaces were the most common cause of CO poisoning (32%) followed by accidental exposure to automobile exhaust (28%). In self-inflicted poisoned patients ($n = 16$; 23%), the most common source of CO poisoning was automobile exhaust (94%).

Forty-three percent (43%) of patients were clinically depressed as indicated by suicide attempt being the cause of their CO poisoning and/or by a significant Faschingbauer MMPI Depression scale score (T score > 65). Forty-three percent of patients reported a history of smoking (M packs per day = 1.36, $SD = 1.3$; M years = 13.7, $SD = 8.4$), 39% reported a history of alcohol and/or drug use and 24% tested positive for blood alcohol or illicit substances at intake.

Procedures

Imaging

CO patients were scanned within the first 24 hr after arriving at the hospital to be treated for CO poisoning, at 2 weeks and at 6 months following the CO exposure using a 1.5 Tesla MRI scanner (General Electric Medical Systems, Milwaukee, WI). The scans of 46 age- and gender-matched normal controls were obtained from an archival normative imaging database. Both the CO patients and normal controls were imaged supine with the head in a fixed position, using our routine clinical protocol. Controls were not included in the normative imaging database if they had a prior history of head injury with loss of consciousness, neurological disease, psychiatric disorder, alcohol or drug abuse (Blatter et al., 1995). Several of the controls matched more than one CO patient and their data was included for each match, so that every CO patient had a matched control. For the purpose of data analysis there were 69 CO patients and the data from 69 matched controls. The scans of the normal controls were compared to the CO patients Day 1 scans, to determine if there were any brain morphological differences between the groups (Blatter et al., 1995).

The same scanner and scanning protocol were used for the CO patients and for the control subjects taken from the Blatter et al. (1995) normative imaging database. Sagittal and spin echo axial images were collected on a 1.5 Tesla with a quadriture head coil on a GE Signa Scanner (General Electric, Milwaukee, WI). Sagittal scans were T1-weighted, 500/11/2 (repetition time/echo time/excitations) with a 256 × 192 pixel acquisition matrix and a field of view of 2 cm. Sagittal images were 5 mm thick with a 1 mm interspace gap. Axial intermediate and T2-weighted (3000/31,90/1; repetition time/echo time/ excitations) spin echo images were acquired with slice thickness of 5 mm and 2 mm interspace gap, field of view 22 cm, with acquisition matrix of 256 × 192. The scan range extended from the most inferior point of the cerebellum to the most superior

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point of the cerebral cortex on the midsagittal image. Imaging data remained in digital form throughout the entire analysis process.

Morphometric analysis

The fornix of the CO poisoned patients and the normal controls were quantified using IMAGE computer software (Wayne Rasband, NIMH). The MR scans were loaded into IMAGE and the circumferences of the fornix were precisely traced in the axial plane excluding the septum pellucidum and wall of the anterior ventricles at the level of the frontoparietal opercula following established anatomical guidelines using human brain atlases (Carpenter & Sutin, 1983; Truwit & Lempert, 1986). In each MR scan, the axial section that most closely matched the above orientation was used to obtain the fornix measurements. IMAGE calculates an area measurement based on the circumstances. Fornix was measured following a standardized method (Gale et al., 1993; Synek et al., 1976). Each measurement was taken twice and an average was calculated.

To control for differences in brain sizes, a fornix-to-brain ratio (FBR) was calculated using a method similar to Evans' index (Synek et al., 1976). Brain width was defined as the distance from the outer surface of the brain from one side to the other, across the top of the anterior horns of the lateral ventricle in the same slice used to measure the fornix. A ratio of fornix area to brain width comprised the FBR. The MR scans were cropped such that only the fornix could be visualized to exclude surrounding brain tissue and patient identifiers. The CO poisoned patients' scans were randomly intermixed and measured with those from traumatically brain injured patients, normal controls and all three follow-up dates (i.e., Day 1, 2 weeks and 6 months) such that the researchers were blinded to etiology and scan acquisition dates. Interrater and intrarater reliability correlations of .88 and .94 were obtained using interclass correlations.

Neuropsychological measures

A brief neuropsychological screening battery was administered to all CO patients who were enrolled in this study. The tests administered included digit span from the Wechsler Adult Intelligence Scale–Revised (Wechsler, 1981), Trail Making Tests Parts A and B (Reitan & Wolfson, 1985), Story Recall, Delayed Story Recall, Recall of a Complex Figure (RCF) and Delayed Recall of a Complex Figure (DRCF) from the Denman Neuropsychology Memory Scale (Denman, 1984), on the same dates that MR scans were performed (i.e., Day 1, 2 weeks and 6 months). Delayed Story Recall, Recall of a Complex Figure and Delayed Recall of a Complex Figure were added later in the study. Therefore, less than half of the patients received these measures.

Analysis

Differences among the CO patients were assessed according to the following demographic variables: male, female, loss of consciousness, no loss of consciousness, COHb level above the median (21.3%), COHb below the median, history of smoking, no history of smoking, history of alcohol/drug use, no history of alcohol/drug use, blood test positive for alcohol/drugs, blood test negative for alcohol/drugs, depression and no depression. Since there were no significant differences in FBR or neuropsychological testing scores by independent sample *t* tests for CO patients in the above subgroups, an overall within-subjects analysis was carried out.

A between subject analysis using paired samples *t* tests compared day 1 brain region measurements of CO patients with measurements of normal controls. A within-subjects analysis, using paired *t* tests was performed to compare differences between CO patients' Day 1, 2 weeks and 6 month fornix cross-sectional surface areas. Bonferroni corrections were used due to multiple comparisons.

A repeated measures ANOVA was performed for each of the neuropsychological tests to determine if changes occurred in the CO patients' test data across the three time intervals (i.e., Day 1, 2 weeks and 6 months). Changes in participants' neuropsychological testing results across the three time intervals were also analyzed using the Reliable Change Index (RCI) to correct for practice effects. The RCI is based on a formula derived from a test's standard error of measurement (*SEM*). The RCI yields a range of difference scores that are expected when no real change has occurred, corrected for practice effects. This range is used to determine if test scores on repeated administration decrease, remain unchanged or increase reliably (for detailed methods see (Chelune et al., 1993; Jacobson & Truax, 1991)). Standard error of the measurement for each test was obtained from normative information published in test manuals with the exception of Trail Making Tests as no original published normative *SEM* is available in the test manual. Data from 85 age-, gender-, and education-matched normal controls was obtained, as part of one of our other studies, for comparison with the patients in our prospective clinical trial. Normal controls' Trail Making Test results were used in this study to calculate a *SEM* for the RCI scores in this study. All data from the RCI are reported as the percentage of individuals whose scores declined over time.

Pearson correlations were calculated to identify relationships between fornix morphology, neuropsychological testing results and non-categorical demographic variables (e.g., age, education, and COHb level). Spearman's rho correlations were used to compare categorical demographic variables such as loss of consciousness, gender and depression (e.g., LOC = 1, no LOC = 0) with fornix measurements and neuropsychological testing results.

RESULTS

Imaging Results

There were no significant differences ($p = .20$) between Day 1 FBR of the CO poisoned patients ($M = 0.11$, $SD =$

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0.02) and the FBR of normal controls ($M = 0.12$, $SD = 0.03$). The within-subjects analysis demonstrated significant differences between CO patients' Day 1 and 2-week FBR ($t = 2.86$, $p = .002$) as well as between Day 1 and 6-month FBR ($t = 3.01$, $p = .002$; see Figure 1), using one-tailed comparisons. A decrease in FBR occurred in 58% of patients between Day 1 and 2 weeks, 49% between 2 weeks and 6 months and 54% between Day 1 and six months. A decrease in FBR was defined as atrophy that was more than 1 standard deviation of the mean on the Day 1 scans.

Neuropsychological Test Results

The patients' neuropsychological test scores are presented in Table 1. The repeated measures ANOVA indicated that CO patients' Story Recall ($p = .000$), Trails A ($p = .000$) and Trails B ($p = .000$) scores increased significantly over time. Digit Span ($p = .09$), Delayed Story Recall ($p = .69$), RCF ($p = .50$) and DRCF ($p = .21$) did not change significantly across time. Since neuropsychological assessment was performed over repeated testing sessions (Day 1, 2 weeks and 6 months), practice effects were taken into consideration using the Reliable Change Index (RCI). The patients' scores showed no significant neuropsychological impairments at 2 weeks post-poisoning using the RCI range. However, 77% of patients demonstrated a significant decline in immediate verbal memory functioning (Story Recall) and 71% demonstrated a decline in delayed verbal memory (Delayed Story Recall) by 6 months using the RCI range. Visual memory (RCF and DRCF), attention/concentration (Digit Span) and processing speed (Trail Making Test) were unchanged using the RCI range. A decreased

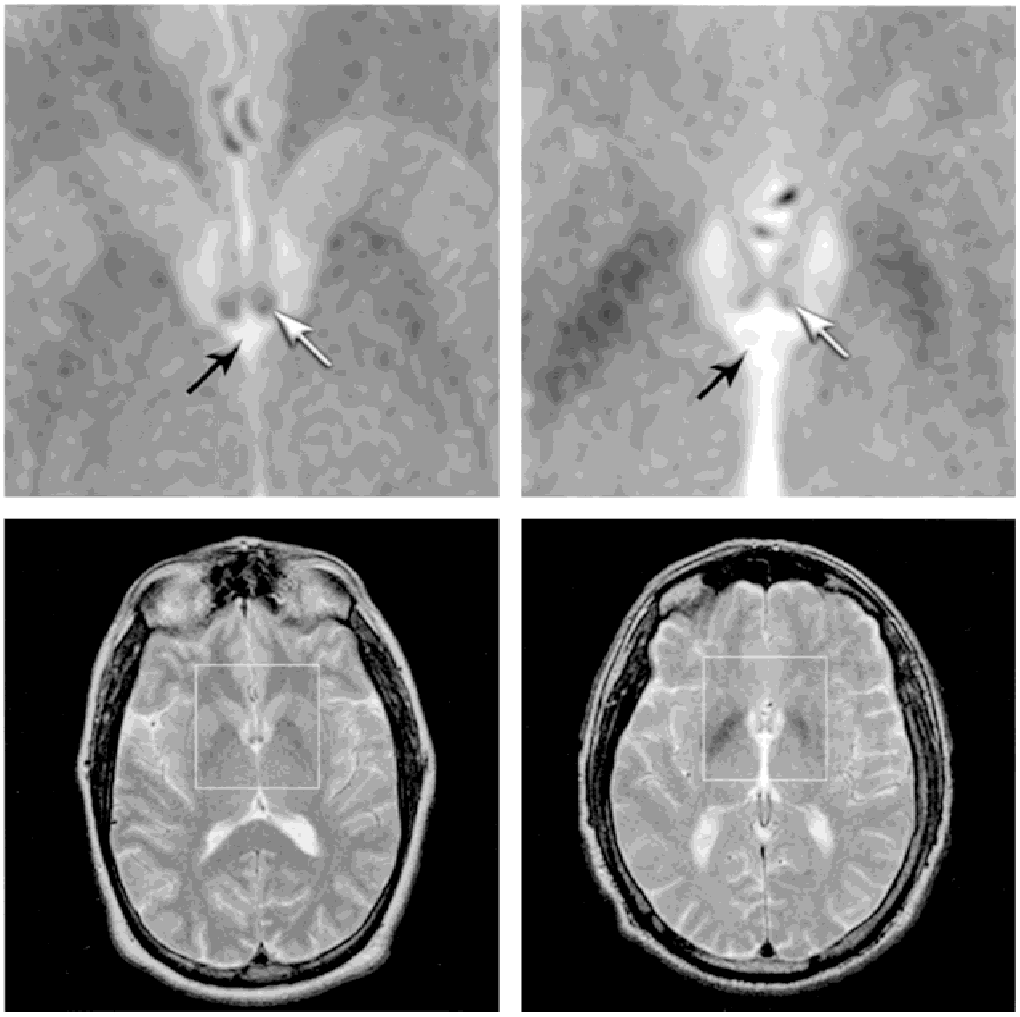

Fig. 1. The bottom brain MR scans show axial slices at the level of the frontoparietal opercula, with the box marking the area that is seen in the enlarged view (top row). On the top row in the enlarged sections of the MR scans the white arrows point to the fornix and the black arrows point to the anterior portion of the lateral ventricles. The MR scans on the left side show a CO patient's fornix on Day 1. The same patient's fornix at 6 months is shown in the scans on the right side and demonstrates marked atrophy. Note the ventricular dilation, another indication of atrophic change in the brain.

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Table 1. Mean neuropsychological testing scores not corrected for practice effects

Test name	Time of test	Standard scores $M \pm SD$
Story Recall	Day 1	7.0 ± 3.9
	2 weeks	11.0 ± 3.5
	6 months	10.0 ± 3.5
Delayed Story Recall	2 weeks	11.2 ± 2.5
	6 months	12.1 ± 2.0
ROCF Immediate Recall	2 weeks	13.7 ± 3.2
	6 months	13.8 ± 1.9
ROCF 15′ Delayed Recall	2 weeks	9.1 ± 3.7
	6 months	11.6 ± 2.8
Digit Span	Day 1	8.8 ± 3.1
	2 weeks	9.6 ± 3.2
	6 months	9.6 ± 3.6
		T Scores
Trails A	Day 1	45.0 ± 13.0
	2 weeks	51.1 ± 13.1
	6 months	52.6 ± 14.1
Trails B	Day 1	44.0 ± 13.7
	2 weeks	52.1 ± 15.6
	6 months	54.0 ± 13.9

FBR was correlated with impaired immediate verbal memory ($r = -0.32$, $p = .009$). Impaired verbal memory was defined as a decline in verbal memory test score, using the RCI range. No other correlations between imaging results and neuropsychological testing were found.

There were no significant relationships between any of the demographic variables (i.e., age, sex, smoking history, drug/alcohol history, COHb, LOC, or depression), neuropsychological testing, or quantitative imaging results. However, we found a significant correlation between LOC and COHb ($r = 0.21$, $p = .04$).

DISCUSSION

Significant atrophic changes were found in the fornix of CO patients over time (Figure 1). Most of the atrophic change in the fornix occurred within the first 2 weeks of exposure. Based on our data, this atrophy occurred in approximately 50% of patients indicating that volume loss is relatively common in patients with CO poisoning.

There were no differences between CO patients' Day 1 imaging results compared to normal controls. As with traumatic brain injury (TBI), the day of injury scan may be too early in the pathological process to display the neuropathological effects of CO-induced hypoxic brain damage (Bigler et al., 1994). Further, this observation suggests that day of injury imaging results can be used as a baseline or estimate of premorbid brain morphology in CO patients as well as for TBI patients.

Our study demonstrated that CO patients experience verbal memory deficits but do not have impairments on processing speed or attention/concentration. This finding is consistent with the results of Gale et al. (1999) and supports the idea that CO poisoning damages or disrupts neural structures that are involved in verbal memory. Other researchers have found similar impairments in patients with fornix lesions caused by various etiologies, where the memory impairments are specifically associated with fornix lesions (Araki et al., 1994; Kuzniecky et al., 1999; McMackin et al., 1995) or occur with fornix damage in combination with other lesions, such as in the hippocampus and thalamus (Calabrese et al., 1995; Markowitsch et al., 1990; Oxbury et al., 1997). Although we did not find an attentional impairment in our study with our measures, attentional impairments following CO poisoning may be observed using other more challenging measures of attention like the Pace Auditory Serial Attention Test, consonant trigrams, Stroop Test or Continuous Performance Test.

The analysis of patients' neuropsychological test results in this study illustrates that practice effects associated with repeated testing may obscure neuropsychological impairments. Without considering the impact of practice effects, patients' scores for all neuropsychological measures were within normal limits. However, practice effects artificially inflated the patients' scores resulting in the appearance of an improvement in cognitive functioning over time. The RCI method, which corrects for practice effects, may be more sensitive to impairments in patients' neuropsychological test scores than analyses using raw test data. Practice effects should be considered when dealing with repeated testing.

In addition to fornix atrophy and impaired verbal memory, LOC was related to increasing COHb levels. However, neither of these variables was significantly associated with neuropsychological nor brain morphological outcomes. Previous work has shown that COHb levels are not a reliable predictor of the severity, symptoms, or outcome following CO poisoning (Jain, 1990; Martindale, 1989). Some studies have shown that the length of LOC is related to outcome (Jain, 1990). Alternatively, Hopkins et al. (1995) found that loss of consciousness was not required in order for CO poisoned individuals to develop cognitive sequelae.

All the CO patients in our study received high fractional concentrations of supplemental oxygen therapy (standard of care) using 100% normobaric oxygen or HBO_2 (Camporesi, 1996). It is commonly thought that HBO_2 decreases the incidence of neuropsychological sequelae following CO poisoning. Whether HBO_2 is advantageous in CO poisoning is presently unclear. Data from randomized clinical trials that compared the outcome of CO poisoned patients treated with HBO_2 with those treated with normobaric oxygen are conflicting. Two studies that compared CO poisoned patients treated with HBO_2 or normobaric oxygen, found a significant difference in quantitative electroenceph-

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alograms and cerebral vascular responsiveness to acetazolamide (Ducasse et al., 1990) and a decrease in the incidence of neuropsychological sequelae (Thom et al., 1995). Alternatively, there are four clinical trials that demonstrate no differences in neuropsychological outcomes between CO patients treated with HBO_2 therapy and normobaric oxygen (Mathieu et al., 1996; Raphael et al., 1989; Scheinkestel et al., 1999; Weaver et al., 1995). The effectiveness of HBO_2, in improving outcome is unclear at the present time.

The long-term adverse effects of CO on the brain have historically been underestimated. Carbon monoxide poisoning is common, often is unrecognized and may result in permanent brain injury. This study demonstrates that following CO poisoning, fornix atrophy occurs by 2 weeks and is relatively stable by 6 months. CO poisoned patients also exhibited concomitant verbal memory impairments. Because other clinical findings and demographic and poisoning variables do not reliably correspond with outcome, establishment of neuroanatomic and neuropsychological changes may offer additional diagnostic and prognostic information concerning outcome following CO poisoning. Further study is required to determine the extent and severity of the neuroanatomic changes and associated neuropsychological deficits following CO poisoning. Given our findings of fornix atrophy and impaired verbal memory, it is important to prevent CO poisoning through education and the use of CO detectors.

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