Corpus callosum atrophy and neuropsychological outcome following carbon monoxide poisoning

Scott S. Porter\textsuperscript{a,b}, Ramona O. Hopkins\textsuperscript{a,c,*}, Lindell K. Weaver\textsuperscript{c,d}, Erin D. Bigler\textsuperscript{a,c}, Duane D. Blatter\textsuperscript{e}

\textsuperscript{a}Departments of Psychology and Neuroscience, Brigham Young University, Provo, UT, USA
\textsuperscript{b}Department of Psychology, San Antonio State Hospital, San Antonio, TX, USA
\textsuperscript{c}Department of Hyperbaric Medicine, LDS Hospital, Salt Lake City, UT, USA
\textsuperscript{d}Department of Medicine, University of Utah, Salt Lake City, UT, USA
\textsuperscript{e}Department of Radiology, LDS Hospital, Salt Lake City, UT, USA

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Abstract

This study assessed the effects of carbon monoxide (CO) poisoning on the corpus callosum (CC). Sixty-two CO-poisoned patients had MRI scans and a battery of neuropsychological tests within 24 h (day of exposure) of CO poisoning and at 6 months post CO exposure. Serial quantitative magnetic resonance imaging (QMRI) analysis of the CC was carried out, with the day of exposure scans compared to the 6-month scans. There was no difference between normal subjects’ CC and the baseline scans in the CO-poisoned patients. We detected a 15-mm\textsuperscript{2} loss in the cross-sectional surface area of the CC between baseline and the 6-month follow-up scans. The effect on the CC was generalized atrophy rather than CC subregion-specific changes. Neuropsychological test results performed at baseline and at 6 months did not correlate with the level of CC atrophy. Independent of any CC effects, the patients exhibited impaired memory, attention, and executive functioning on baseline testing, with variable improvement in cognitive function at 6 months. Quantitative MRI analysis allows for the detection of subtle CC changes that may not otherwise be observed following CO poisoning. The long-term effects of CO on the brain have been historically underestimated; however, we found subtle but significant CC atrophy and cognitive impairments following CO poisoning. © 2001 National Academy of Neuropsychology. Published by Elsevier Science Ltd.

Keywords: Carbon monoxide poisoning; Corpus callosum; Neuropsychological impairments; Quantitative brain imaging; Hypoxic brain injury

* Corresponding author. Departments of Psychology and Neuroscience, 1001 SWKT, Brigham Young University, Provo, UT 84602-5543, USA. Tel.: +1-801-378-1170; fax: +1-801-378-7862.
E-mail address: mona_hopkins@byu.edu (R.O. Hopkins).

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1. Introduction

Carbon monoxide (CO) poisoning can cause neuroanatomical injury, including white matter damage, affective changes, and cognitive impairments in humans (Weaver, 1999). Cognitive sequelae following CO poisoning includes impaired memory, attention, visual spatial skills, mental processing speed, executive function, apraxia, Parkinson’s like syndromes, and dementia (Hopkins, Weaver, & Kesner, 1993; Min, 1986; Reynolds, Hopkins, & Bigler, 1999). Affective changes also occur following CO poisoning, including depression, anxiety, and emotional lability (Gale et al., 1999; Hopkins, Weaver, & Bigler, 1997). Imaging studies have shown bilateral hyperintensities of the periventricular white matter and centrum semiovale following CO poisoning (Chang, Han, Kim, Wie, & Han, 1992).

Neuropathology due to CO exposure includes lesions of the white matter, globus pallidus, hippocampus, thalamus, and cortical atrophy (Choi, Kim, Choi, Lee, & Lee, 1993; Hopkins et al., 1993; Tom, Abedon, Clark, & Wong, 1996). Both CT and MRI studies following CO poisoning have shown white matter lesions (Bruno, Wagner, & Orrison, 1993; O’Donnell, Buxton, Pitkin, & Jarvis, 2000; Silver, Cross, Fox, & Paxton, 1996). Previous research has shown white matter hyperintensities in the frontal lobes (Choi et al., 1993), centrum semiovale, brain stem and parietal lobe (Silver et al., 1996). White matter degeneration has also been reported in the temporal, parietal and occipital regions, with the most severe degeneration seen in the parieto-occipital region (Uchino, Hasuo, Shida, Matsumoto, & Yasumori, 1994). Damage to cerebral white matter has been observed within the first hours following CO exposure. Choi et al. (1993) found that white matter lesions were more commonly associated with neurologic sequelae compared to lesions in the globus pallidus. Chang et al. (1992) identified three types of white matter anomalies that occur following CO poisoning including: (1) multiple small necrotic foci in the centrum semiovale and interhemispheric commissures, (2) areas of necrosis in the deep periventricular white matter that is associated with axonal destruction and lipid-laden macrophages, and (3) demyelination in the deep white matter. We are unaware of any studies that systematically assess white matter changes in the CC following CO exposure. Recently quantitative magnetic resonance imaging (QMRI) techniques have been used to identify hippocampal and fornix atrophy in CO-poisoned patients (Hopkins et al., 1993; Kesler et al., 1999; Reynolds et al., 1999). One study using quantitative MRI analysis in CO patients found enlarged ventricles, enlarged ventricle-to-brain ratio (indicating diffuse cerebral atrophy), hippocampal atrophy (Gale et al., 1999).

Since CO frequently causes white matter lesions (Choi et al., 1993), we were interested in the effect of CO poisoning on the corpus callosum (CC), the largest white matter commissure in the central nervous system (CNS). We are unaware of any study that has assessed the effects of CO poisoning on the CC. The purpose of this study was to assess the effects of CO poisoning on the integrity of the CC and on neuropsychological performance. In the current study, we used a prospective within-subjects design to determine if atrophic changes occur in the CC of CO-poisoned patients. We also examined the CO-poisoned patients’ cognitive function using a neuropsychological test battery. We hypothesize that patients exposed to CO will exhibit CC atrophy and concomitant neuropsychological impairments.
2. Methods

2.1. Subjects

Using a prospective within-subjects design, 62 consecutively CO-poisoned patients were included in this study. All patients were seen at the LDS Hospital Hyperbaric Medicine Department in Salt Lake City, UT. This study had IRB approval and informed consent was obtained. There were 43 men and 19 women between the ages of 19 and 86. The mean age of the CO subjects was 37 ± 13 years (range 16 to 86 years) and a mean educational level of 12.0 ± 3.3 years (range = 0 to 17 years). Forty-eight percent of the patients experienced loss of consciousness (LOC). The patients initial mean carboxyhemoglobin (COHb) was 22.4 ± 10.61% (range 0% to 39%). Seventy-four percent of the patients were accidentally exposed to CO and 26% attempted suicide. The CO exposure from internal combustion engine was 69%, 23% from natural gas furnaces, 6% from charcoal briquettes, and 2% from fire.

2.2. Procedures

2.2.1. Imaging

All CO-poisoned patients were scanned within 24 h after hospital arrival (baseline scan) and at 6 months following exposure. Additionally, the patients’ baseline scans were compared to age- and gender-matched normal control subjects, obtained from an archival database (Blatter et al., 2000). Sagittal and spin echo axial images were collected on a 1.5-Tesla GE Signa Scanner with a quadrature head coil (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 24 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 24 cm, on a 256 × 192 pixel matrix. Imaging data remained in digital form throughout the entire analysis process.

The cross-sectional surface area of the CC of the CO-poisoned patients and normal controls were quantified using the midsagittal slice using the methods of Johnson, Pinkston, Bigler, and Blatter (1996). The cross-sectional surface area of the CC was determined on the sagittal slice defined as midsagittal, using the cerebral aqueduct and the cribiform plate as defining midline structures. The overall cross-sectional surface area of the CC and seven subregions of the CC were obtained and analyzed using the NIH image (Johnson et al., 1996). The CC subregions include the genu, rostral midbody, anterior midbody, posterior midbody, isthmus, and splenium, and are chosen due to their relationship to specific brain regions (Witelson, 1989). Angular variation was corrected using a line that bisected the maximal distance between the posterior and anterior parts of the CC, then rotating the scan to make the angle reach 0 degrees. Thus, the perpendicular axis was consistent across scans. Morphometric analysis was performed using the Macintosh based NIH IMAGE software (Rasband, 1995). The interrater reliability was 0.95 for the six CC divisions and the total CC area. Each scan was measured on two separate occasions with the mean of the two measurements used for analysis. The researcher (S.S.P.) doing the CC quantitative analysis was blinded to patient
and scan acquisition date. The baseline CC cross-sectional surface area was compared to that of normal control subjects. Atrophy was defined as a decrease in the cross-sectional surface area from the baseline scan to the 6-month scan in the CO-poisoned patients.

2.2.2. Neuropsychological testing

Each patient received a brief neuropsychological screening battery using standard administration within 24 h of CO poisoning and at 6 months postexposure. Given time constraints due to the large number of patients and repeated test times, only a brief neuropsychological test battery was administered. Tests included digit span, digit symbol and block design from the Wechsler Adult Intelligence Scale-Revised, Trail-Making Test Parts A and B, and story recall from the Denman Neuropsychological Memory Scale. Cognitive impairments are defined as any test score that was more than one standard deviation below the mean T score for that measure (T score mean = 50, standard deviation = 10). At the 6-month follow-up visit the Geriatric Depression Scale (GDS) was administered to assess symptoms of depression (Yesavage, Grind, Rose, & Lum, 1983). The GDS was chosen for two reasons. First the GDS has been shown an effective and reliable screening tool for depression and second, other depression measures are heavily loaded toward measuring the somatic symptoms of depression, while the GDS does not focus on somatic complaints. Somatic symptoms such as sleep disturbances, aches, and pains are frequent complaints of individuals with brain injury such as occur following CO exposure.

2.2.3. Statistics

A multivariate analysis of covariance (MANCOVA) assessed CC atrophy as a main effect and the covariates were COHb and LOC. The main effect takes into account the seven subregions and the repeated scans, correcting for family-wise error rates. A MANCOVA assessed CC atrophy as the main effect and the covariates were suicide and test time (baseline and 6 months) and a second MANCOVA assessed neuropsychological performance as the main effect, suicide and test time as the covariates. Paired t tests were used to compare the seven subregions over time using Bonferroni corrections. Paired t tests were used to compare the baseline total CC cross-sectional surface area to the total CC cross-sectional surface of the normal control subjects. Pearson’s correlations were used to compare CC area to the neuropsychological data.

3. Results

The mean cross-sectional CC surface area at baseline was $664.61 \pm 125.28$ mm$^2$. Paired t tests that compared the seven subregions of the CC on the baseline scans with the CC on the 6-month scans, showed no significant differences for any of the CC seven subregions. Therefore, the CC was reported as total CC cross-sectional surface area. A within-subjects repeated measures MANCOVA revealed a main effect for total CC atrophy [$F(1,60) = 4.51$, $P < .03$], but no interactions were significant. We found that the average atrophy of the CC cross-sectional surface area was $15 \text{ mm}^2$ comparing the baseline to the 6-month scans, with 80% of the patients showing atrophic changes (Fig. 1). The baseline CC cross-sectional
surface area was not significantly different from that of demographically matched normal control subjects ($t = 0.23, P < .82$). A MANCOVA revealed no significant effect on CC atrophy for COHb levels, LOC, or neuropsychological test performance. A MANCOVA revealed no significant effect of suicide with CC atrophy or test time. A third MANCOVA revealed no significant effect of suicide with neuropsychological performance or test time.

Neuropsychological test data are summarized in Table 1. A MANOVA showed a main effect for neuropsychological test [$F(1,8) = 21.02, P < .001$] comparing baseline data to the 6-month follow-up data. At the 6-month follow-up all test scores showed significant improvement, with digit span showing the least improvement (Table 1). The patients exhibited impaired memory, attention and executive functioning on baseline testing as can be observed from the mean $T$ scores on story recall, digit span and Trail-Making Test Part B. Table 2 shows the percent of patients at baseline and 6 months that had neuropsychological test scores more than one standard deviation below the mean $T$ score of 40. Although the CO patients improved, at 6-month follow-up 52% of the patients still exhibited cognitive impairments. The mean GDS scores at the 6-month follow-up were $10.1 \pm 8.3$ (range 0 to 28) [normative data for the GDS: normal; $M = 5.75$, S.D. = 4.34 and mild depression; $M = 15.05$, S.D. = 6.5].

![Mean CC cross-sectional surface area at baseline and 6 months post CO exposure with 95% confidence intervals.](image.png)

**Fig. 1.** Mean CC cross-sectional surface area at baseline and 6 months post CO exposure with 95% confidence intervals. The CC cross-sectional surface area at baseline (mean $= 664.61 \pm 125 \text{ mm}^2$) and at 6 months (mean $= 649.64 \pm 125 \text{ mm}^2$).

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline Mean</th>
<th>Baseline S.D.</th>
<th>6-Month follow-up Mean</th>
<th>6-Month follow-up S.D.</th>
<th>$P$</th>
</tr>
</thead>
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<tr>
<td>Digit span</td>
<td>40.1</td>
<td>15.7</td>
<td>44.7</td>
<td>11.8</td>
<td>.01</td>
</tr>
<tr>
<td>Trails A</td>
<td>40.6</td>
<td>16.9</td>
<td>50.4</td>
<td>12.5</td>
<td>.001</td>
</tr>
<tr>
<td>Trails B</td>
<td>40.1</td>
<td>17.2</td>
<td>52.5</td>
<td>13.1</td>
<td>.001</td>
</tr>
<tr>
<td>Digit symbol</td>
<td>44.6</td>
<td>17.1</td>
<td>56.0</td>
<td>13.2</td>
<td>.001</td>
</tr>
<tr>
<td>Block design</td>
<td>47.5</td>
<td>17.6</td>
<td>59.1</td>
<td>14.6</td>
<td>.001</td>
</tr>
<tr>
<td>Story recall</td>
<td>33.1</td>
<td>11.2</td>
<td>37.0</td>
<td>10.5</td>
<td>.001</td>
</tr>
</tbody>
</table>

The data are presented as $T$ scores with mean $= 50$ and S.D. $= 10$. 

Table 1

CO subjects’ neuropsychological test results at baseline and 6-month follow-up
A t test compared the GDS scores of those with accidental exposure to those who attempted suicide and found no significant differences between the two subgroups of CO subjects. Pearson’s correlations compared the total CC atrophy with the neuropsychological test data. There were no significant correlations between CC cross-sectional surface area and neuropsychological performance at baseline or 6 months post CO exposure. The overall CC cross-sectional surface area did not correlate with COHb levels or LOC. Although there were no significant correlations between neuropsychological scores and CC atrophy, the patients did experience significant cognitive impairments.

4. Discussion

To our knowledge, this is the first study that has assessed the effects of CO poisoning on the CC. Using serial QMRI we were able to detect small but significant changes in the CC cross-sectional surface area at 6 months in a group of consecutively CO-poisoned patients. The data show that CC atrophy was generalized and was not subregion specific. We detected a 15-mm² loss in the cross-sectional surface area of the CC using a within-subjects design. Our results are consistent with previous reports showing white matter damage following CO poisoning in humans and in primates (Chang et al., 1992; Choi et al., 1993; Ginsberg, Myers, & McDonagh, 1974).

The MRI scans taken within 24 h of CO exposure provide a reliable neuroanatomical baseline. Our patients’ baseline CC cross-sectional surface area on day of injury was no different than those of normal controls (Choi et al., 1993; Johnson, Bigler, Burr, & Blatter, 1994; Levin et al., 1990). Our results also do not differ from a meta-analysis of 26 studies in normal subjects, where the CC cross-sectional surface area mean was 667 ± 87 mm² (Johnson et al., 1994). These results indicate that the day of exposure scans can be used as baseline scans in CO-poisoned patients. These findings are similar to previous studies in traumatic brain injury in which the day of injury scan has been shown to be an index of pre-injury brain morphology (Bigler et al., 1994). On average, we observed a 15-mm² decrease in the CC. It is possible that the decrease in CC cross-sectional surface area may be due to measurement error; however, given the intra- and interrater reliability, we feel this is unlikely.

Although we found significant CC atrophy, we found no relationship between CC atrophy and COHb and LOC, which are markers of poisoning severity. Even with significantly

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Table 2
Shows the number of CO subjects and percent of their neuropsychological test scores that fall more than one standard deviation below the mean at baseline and 6-month follow-up

<table>
<thead>
<tr>
<th></th>
<th>Digit span</th>
<th>Trails A</th>
<th>Trails B</th>
<th>Digit symbol</th>
<th>Block design</th>
<th>Story recall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N more than 1 S.D.</td>
<td>28</td>
<td>19</td>
<td>19</td>
<td>16</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>Percent</td>
<td>45%</td>
<td>31%</td>
<td>31%</td>
<td>26%</td>
<td>18%</td>
<td>46%</td>
</tr>
<tr>
<td><strong>6-Month testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N more than 1 S.D.</td>
<td>5</td>
<td>26</td>
<td>9</td>
<td>8</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Percent</td>
<td>8%</td>
<td>43%</td>
<td>15%</td>
<td>14%</td>
<td>7%</td>
<td>16%</td>
</tr>
</tbody>
</table>

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elevated COHb levels and LOC in half of the patients, these markers of severity did not correlate with CC atrophy or to cognitive impairments. This finding is not unexpected as previous research has shown that COHb and LOC do not correlate with symptoms of poisoning, neurologic, and/or cognitive impairments (Gale et al., 1999; Garland & Pearce, 1967). Our results are similar to those of other studies reported in the literature where COHb levels do not correlate with severity of poisoning or clinical outcome (Camporesi, 1996; Hopkins, Weaver, Larson-Lohr, & Howe, 1995; Meyers and Britten, 1989; Winter and Miller, 1976). Research on CO exposure in primates has shown that neither severity nor duration of CO exposure is related to the severity of white matter damage (Ginsberg et al., 1974). The lack of correlations between COHb and outcome measures are due in part to the variability in COHb levels in CO-poisoned individuals. The variability in COHb levels is partly due to delay from removal from the CO environment to medical treatment and the amount and duration of supplemental oxygen administration prior to COHb measurement (Sokal, 1985; Sokal and Kralkowska, 1985).

Similar to markers of poisoning severity, CC atrophy did not correlate with cognitive sequelae, although the patients had impaired attention, memory and executive function on baseline testing. Since we found mild generalized CC atrophy, one would not expect a strong relationship between CC atrophy and specific cognitive functions. Had we found more severe atrophy, we may have found a relationship between CC atrophy and cognitive function. The fact that we find no relationship between CC atrophy in cognitive function following CO poisoning is in contrast to previous studies. Previous studies have shown relationships between CC atrophy and neuropsychological performance in conditions such as multiple sclerosis, traumatic brain injury, and Alzheimer’s disease (Huber et al., 1992; Johnson et al., 1996; Yamaguchi et al., 1993). One explanation for our result is that our patients ranged from mild to severe CO exposure and were not a select subset of only the most severely poisoned patients. If only patients with severe CO exposure were assessed, they may be more likely to have more severe CC atrophy and cognitive impairments, thus the probability of a significant relationship would be expected to increase.

One important finding is that the within-subjects repeated measures design provides baseline brain morphology that enabled us to detect mild but significant CC atrophy that may have otherwise been missed. This study demonstrates that the day of exposure scans can provide significant information about preexposure brain morphology that can be used for postexposure comparisons. Another advantage of the within-subjects design was that we did not need to correct for head size to adjust for intracranial volumes. Head size correction may increase the error term and decrease the power of the study.

Given that 26% of the patients enrolled in this study were exposed to CO due to suicide attempts raises the concern of interpretive issues surrounding the results of the neuropsychological test scores. In order to address this issue, we analyzed suicide and neuropsychological performance and found no significant effects of suicide on neuropsychological performance. In addition at 6 months, CO-poisoned patients were administered the GDS in order to determine if depression contributed to the cognitive impairments that we observed. The results of the GDS showed no difference between accidental and intentional CO exposure for self-reported symptoms of depression. There is currently little evidence in the literature demonstrating that mild depressive symptoms can cause decrements in cognitive performance (Breslow, Kocsis,
Belkin, 1980; Caine, 1986). These results suggest it is unlikely that depression contributed to the neuropsychological performance observed in our CO-poisoned subjects.

There are several limitations of this study. CO poisoning can cause other white matter lesions that were not assessed in this study. An analysis of white matter lesions may provide further understanding of the effects of CO on white matter in the brain (Chang et al., 1992; Choi et al., 1993). Given the generalized CC atrophy observed in this study, a volumetric study of the total white matter volume, assessing possible diffuse white matter damage is needed. More research is needed to further explore the question of white matter changes in CO poisoning and the relationship to cognitive sequelae. A second limitation is that of the effect of practice on repeated neuropsychological testing. Previous research has shown that repeated testing can increase neuropsychological test scores from 1% to 5%, depending on the task (Hopkins, Weaver, & Churchill, 1999; Temkin, Heaton, Grant, & Dikmen, 1999). In order to address this issue, we are currently conducting a study of demographically matched control subjects tested at the same time intervals as in this study. Preliminary data from this study indicates that normal control subjects tested at the same times (day of exposure and 6 months following exposure) as CO-poisoned individuals, performed significantly better than CO-poisoned subjects on the day of CO exposure. However, the CO-poisoned individuals approached to level of the control subjects by 6 weeks (Hopkins et al., 1999). A third limitation is the brief neuropsychological screening battery that was administered in this study, due to time constraints. It is possible that if more detailed neuropsychological tests were administered to the CO-poisoned patients that assessed other cognitive functions such as visual processing, executive function, attention, then we might have found neuropsychological impairments and significant relationships between neuropsychological testing and the severity of CO poisoning. The long-term effects of CO on the brain have been historically underestimated. This study shows subtle but significant CC atrophy and cognitive impairments following CO poisoning. The atrophic changes occur by 6 months and half of the patients exhibited cognitive impairments. Future research should investigate volumetric changes in other white matter structures following CO poisoning in order to determine if the white matter changes are generalized. Our findings illustrate the importance of preventing CO poisoning using CO detectors and education.

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References

Blatter, D. D., Bigler, E. D., Gale, S. D., Johnson, S. C., Anderson, C. V., Burnett, B. M., Parker, N. P., Kurth, S.,


