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Michel T. Torbey

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*Stroke* 2000;31;2163-2167

Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231
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Quantitative Analysis of the Loss of Distinction Between Gray and White Matter in Comatose Patients After Cardiac Arrest

M.T. Torbey, MD, MPH; M. Selim, MD, PhD; J. Knorr, DO; C. Bigelow, PhD; L. Recht, MD

Background and Purpose—Anecdotal reports suggest that a loss of distinction between gray (GM) and white matter (WM) as adjudged by CT scan predicts poor outcome in comatose patients after cardiac arrest. To address this, we quantitatively assessed GM and WM intensities at various brain levels in comatose patients after cardiac arrest.

Methods—Patients for whom consultation was requested within 24 hours of a cardiac arrest were identified with the use of a computerized database that tracks neurological consultations at our institution. Twenty-five comatose patients were identified for whom complete medical records and CT scans were available for review. Twenty-five consecutive patients for whom a CT scan was interpreted as normal served as controls. Hounsfield units (HUs) were measured in small defined areas obtained from axial images at the levels of the basal ganglia, centrum semiovale, and high convexity area.

Results—At each level tested, lower GM intensity and higher WM intensity were noted in comatose patients compared with normal controls. The GM/WM ratio was significantly lower among comatose patients compared with controls (P<0.0001, rank sum test). There was essentially no overlap in GM/WM ratios between control and study patients. The difference was greatest at the basal ganglia level. We also observed a marginally significant difference in the GM/WM ratio at the basal ganglia level between those patients who died and those who survived cardiac arrest (P=0.035, 1-tailed t test). Using receiver operating characteristic curve analysis, we determined that a difference in GM/WM ratio of <1.18 at the basal ganglia level was 100% predictive of death. At the basal ganglia level, none of 12 patients below this threshold survived, whereas the survival rate was 46% among patients in whom the ratio was >1.18. The empirical risk of death was 21.67 for comatose patients with a value below threshold.

Conclusions—The ratio in HUs of GM to WM provides a reproducible measure of the distinction between gray and white matter. A lower GM/WM ratio is observed in comatose patients immediately after cardiac arrest. The basal ganglia level seems to be the most sensitive location on CT for measuring this relationship. Although a GM/WM ratio <1.18 at this level predicted death in this retrospective study, the difference in this study is not robust enough to recommend that management decisions be dictated by CT results. The results, however, do warrant consideration of a prospective study to determine the reliability of CT scanning in predicting outcome for comatose patients after cardiac arrest. (Stroke. 2000;31:2163-2167.)

Key Words: coma ■ heart arrest ■ prognosis ■ tomography, x-ray computed

Predicting neurological recovery from coma is important from the perspectives of containing costs, facilitating organ donation, and helping patients’ families reach an easier decision concerning therapy. Since the 1970s, several investigators have tried to better predict coma outcome using predictors such as pupillary and oculocephalic reflexes and variations in pain response, and a number of scoring systems, including the Longstreth scale of awakening and Glasgow Coma Scale, have subsequently been developed.1-6 Clinicians have also investigated the use of the electroencephalogram and somatosensory evoked potentials to predict outcome from anoxic coma.4,7-9 Unfortunately, despite much study, it has remained difficult to predict with certainty those patients who will definitely die.

One of the most frequently used ancillary tests in the comatose patient is the CT scan. At our institution, for example, virtually every patient undergoes this examination within 48 hours of cardiac arrest to rule out possible underlying etiologies. Although not specifically done for prognostic purposes, it has been our impression that those patients for whom the distinction between gray matter (GM) and white matter (WM) on CT was qualitatively diminished always died...
during their hospitalization. Surprisingly, therefore, although occasional reports in the literature attest to this finding,\textsuperscript{10,11} there has never been a systematic study that addressed this question.

At our institution, every patient who is admitted after cardiac arrest is seen by a neurological consultant and then registered in a computerized database. We therefore were able to locate all such patients within a defined time period that had available CT scans for review, as well as a cohort of patients with CT scans that were interpreted as normal. We assessed changes accompanying cardiac arrest–induced coma and the relationship of these changes to outcome for 3 brain areas chosen because of the ability to reproducibly distinguish GM and WM in controls. By measuring GM and WM from small defined areas at commonly imaged levels, we sought to answer 3 questions: (1) What is the range in Hounsfield units (HUs) of GM and WM in normal patients? (2) Is there a difference in these values between CTs from normal patients and those obtained in comatose patients after cardiac arrest? (3) Is there a quantitative difference between those patients who survive their cardiac arrest and those who do not?

**Subjects and Methods**

**Patients**

Using a database in which all neurological consultations performed at University of Massachusetts Medical Center were recorded,\textsuperscript{12} we identified 25 comatose patients in the period between January 1, 1996, and February 1, 1999, who satisfied the following criteria: (1) admission to the cardiac care unit because of cardiac arrest; (2) neurological consultation obtained within 24 hours of event; (3) CT scan performed within 48 hours of event; and (4) no previous history of either coma, severe head trauma, cardiac arrest, or stroke. Patient age, sex, duration of cardiac arrest, hospital and intensive care unit length of stay, discharge status, Glasgow Coma Scale and Glasgow Outcome Scale scores, and Rankin Index were obtained through a review of the medical record. In addition, through accessing Radiology Department records, we identified 25 consecutive CT scans that were interpreted as within normal limits by the radiologist.

**Quantification of GM and WM**

CT scan images were obtained on a GE light speed device and a GE CTI. Three regions of interest were defined on axial imaging (Figure 1): (1) basal ganglia level, defined as the image in which the caudate nucleus, internal capsule, third ventricle, and sylvian fissures were visualized; (2) centrum semiovale level, defined as the image 5 mm above the lateral ventricular system; and (3) high convexity level, defined as the next image 5 mm above the centrum semiovale level.

The measuring cursor was configured as a 10-mm\textsuperscript{2} elliptical surface, and the slice thickness was 5 mm. At both the centrum semiovale and high convexity levels, the GM HU values were taken from the medial cortex of both hemispheres only, to avoid the beam hardening artifact of the bone. Another set of measurements was obtained from the GM of both caudate nuclei and compared with the WM in the adjacent internal capsule. The average of both sides was recorded as the value for GM and WM in that area.

**Statistical Analysis**

Patient characteristics were summarized with the use of frequency distributions, means, standard deviations, and percentiles as appropriate. Box and whisker plots were constructed to summarize the distributions of HU values among controls, comatose patients who survived their hospital stay, and comatose patients who died in-hospital. Group differences in HU and GW/WM ratio values among control and comatose patients were compared with the Wilcoxon rank sum test. A receiver operating characteristic curve (ROC) was constructed to identify the threshold value of the GM/WM ratio that was best predictive of mortality.

**Results**

Twenty-five control patients ranged in age from 21 to 85 years (median age, 49 years); 52\% were men. The scans were all interpreted by the reading radiologist as normal. There was close concordance of HU readings for both GM and WM between the 3 assessed CT levels (basal ganglia, centrum semiovale, and high convexity levels) in all control patients (Table). The GM/WM ratio was also consistent for this group, with median values ranging from 1.42 for centrum...
Assessment of HU of GM and WM at Different Axial Levels

<table>
<thead>
<tr>
<th>Level</th>
<th>Level</th>
<th>Control (n=25)</th>
<th>Comatose (n=25)</th>
<th>GM/WM</th>
<th>Control (n=25)</th>
<th>Comatose (n=25)</th>
<th>GM/WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia</td>
<td>Median</td>
<td>36</td>
<td>32</td>
<td>&lt;10^-5</td>
<td>24</td>
<td>27</td>
<td>&lt;10^-5</td>
</tr>
<tr>
<td></td>
<td>25–75%</td>
<td>34.3–36.5</td>
<td>29.8–34.3</td>
<td>1.45</td>
<td>1.18</td>
<td>1.18–1.27</td>
<td>&lt;10^-5</td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>Median</td>
<td>35</td>
<td>31</td>
<td>&lt;10^-5</td>
<td>25</td>
<td>26</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td></td>
<td>25–75%</td>
<td>34.5–35.5</td>
<td>29.8–32</td>
<td>1.42</td>
<td>1.19</td>
<td>1.19–1.26</td>
<td>&lt;10^-5</td>
</tr>
<tr>
<td>High convexity area</td>
<td>Median</td>
<td>35</td>
<td>31</td>
<td>&lt;10^-5</td>
<td>25</td>
<td>26</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td></td>
<td>25–75%</td>
<td>34.5–35.5</td>
<td>29.4–33</td>
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semiovale and high convexity levels to 1.45 for basal ganglia level. A ratio <1.30 was not obtained for any control patient at any level.

The median age of the 25 comatose patients was 64.5 years (range, 22 to 84 years); 56% were men. The duration of the cardiac arrest lasted from 3 to 45 minutes (median, 25 minutes). Only 24% survived the hospitalization; the majority of the survivors were moderately disabled. Only 1 patient regained functional independence.

On CT scans performed within 48 hours of arrest, the GM/WM ratios were much lower than those of the control patients, with median values of 1.18, 1.19, and 1.18 being obtained for basal ganglia, centrum semiovale, and high convexity levels, respectively (P<0.00001, rank sum test for all 3 comparisons) (Table). The lower ratios were due mainly to a decreased intensity of GM that was nearly the same for all 3 levels (P<0.00001, rank sum test for all 3 comparisons). In contrast, the increase in WM intensity was less homogeneous, and an equally significant difference was only noted at the basal ganglia level (P<0.00001, rank sum test). Interestingly, there was virtually no overlap of the distribution of GM/WM ratios for comatose and control patients at the basal ganglia and centrum semiovale levels (Figure 2).

In an analysis that investigated the relationship of GM/WM ratios to functional outcome, we found no association of this ratio and functional status as measured by either the Rankin Index or Glasgow Outcome Scale. Patients who survived their arrest had, on average, a slightly higher GM/WM ratio. In terms of the GW/WM ratio, the only area in which a marginally significant difference could be detected between dying and surviving patients was at the basal ganglia level (median, 1.16; 25% to 75%, 1.15 to 1.25 versus median, 1.24; 25% to 75%, 1.20 to 1.24; P<0.05, 1-tailed r test). At the basal ganglia level, it is notable that no patient survived who had GM/WM ratio <1.2.

Using ROC analysis, we determined that a GM/WM ratio <1.18 at the basal ganglia level was 100% predictive of death in this cohort. At the basal ganglia level, none of 12 patients below threshold survived, whereas the survival rate was 46% among patients in whom the difference was >1.18. The risk of death associated with HU ratio <1.18 was 21.67.

**Discussion**

The difference on CT between GM and WM arises because the higher water and lower lipid content in GM results in higher oxygen and lower carbon concentrations, with a resultant increased photoelectric absorption. In the 1970s, Hounsfield described the use of the CT to discriminate between GM and WM. Several studies have since used HU as a measure of this difference. Various methods of quantification have been used, including subtracting values of GM and WM from cerebrospinal fluid or measuring both against a skull water phantom. The CT scan is frequently abnormal after anoxic or ischemic insults and reflects the propensity for these injuries to cause a variety of neuropathologic abnormalities, including neuronal necrosis, watershed infarcts, and periventricular leukomalacia. Tissue anoxia underlies many of these abnormalities and is the primary cause of central nervous system ischemic damage. The inadequate production of ATP that accompanies ischemia disrupts both the sodium-potassium pump and the homeostatic properties of the cell membrane, which results in an overall increase in water content (ie, cytotoxic edema).

Compensatory mechanisms that attempt to offset these damaging effects also occur in this situation. A delayed hyperemia after resuscitation has been described that can lead to increased intracranial pressure and occasionally acute brain edema and, therefore, increased HU values. The GM/WM ratio has been found to be increased in patients with acute ischemia, with a resultant increased photoelectric absorption.

**Figure 2.** Box plot of CT GM/WM ratios of 25 control (Cont) and 25 comatose patients (Coma). Slash marks represent 25% to 75% values; filled circles represent outliers. BGL indicates basal ganglia level; CSOL, centrum semiovale level; and HCL, high convexity level.
This increase in intracranial pressure can partially occlude the subependymal veins and impede deep venous outflow. Initially, the cerebral blood vessels collapse so as to decrease intracranial volume and prevent further increases in intracranial pressure. If systemic hypotension is corrected, however, such as happens in the acute management of cardiac arrest, cerebral blood flow increases, resulting in the deep medullary veins becoming distended.\textsuperscript{24–26} This results in a situation in which white matter becomes distended with blood and appears more dense on unenhanced CT scans.\textsuperscript{11,27} Therefore, a loss of distinction between GM and WM after arrest could result from some combination of a decreased GM intensity due to cytotoxic edema and an increased WM intensity due to distention of the medullary draining veins. Therefore, one would expect that the GM/WM ratio would be a more sensitive indicator of a loss of distinction than measurement of either alone.

It has been a general impression that a decreased distinction between GM and WM on CT predicts poor outcome after cerebral insults. Prior reports have been qualitative and descriptive and have demonstrated visual changes on CT that occur with anoxia.\textsuperscript{10} Certain signs, such as the “reversal sign,” have been coined to denote this qualitative change in CT characteristics in patients who generally have a bad outcome.\textsuperscript{27} Our own clinical impression supported this association, and we sought first to assess this question qualitatively. However, our analysis revealed that while clinicians could predict outcome after cardiac arrest on the basis of a loss of distinction between GM and WM, the finding was only 90\% predictive and had a low interrater reliability (0.465).\textsuperscript{28}

We hypothesized that this predictive capacity could be increased if the analysis was more quantitative. To address this question, we located 25 patients after cardiac arrest, 6 of whom survived. The axial images assessed were the same as those used by George and colleagues\textsuperscript{17} and are routinely obtained in virtually all patients undergoing this procedure. We used the ratio of GM to WM (instead of the difference) to control for possible technical variability that might occur between examinations because of differences in exposure or other uncontrollable factors. We found that in patients with normal scans, reproducible values for GM, WM, and their ratios are obtainable when HUs are calculated from small defined areas. Standard deviations of $<5\%$ of the mean values were noted at all 3 levels.

Despite the retrospective nature of this study, therefore, several findings merit comment. First is the observation after cardiac arrest of a quantitatively significant loss in the distinction between GM and WM in comatose patients. In terms of GM/WM ratio, an average decrease of 18\% in the median values below that of the corresponding median control value was noted. This loss reflected more a loss of the intensity of GM than a gain in WM intensity. There was a complete lack of overlap of GM/WM ratios at both the basal ganglia and high convexity levels between comatose and control patients. Thus, virtually all patients who are comatose after cardiac arrest have a loss of GM-WM differentiation that can be detected by CT measurement. This probably explains both why our initial qualitative study had such a low interrater reliability and why a quantitative analysis is likely to yield a more consistent result.

Another important observation was that the basal ganglia level was the best level for assessing this difference. This is consistent with its known sensitivity to injurious stimuli. The head of the caudate and putamen are especially at risk during periods of low perfusion in view of their high metabolic activity and their location in the boundary zones of perfusion. Loss of the distinction between GM and WM in this area is a frequent finding in a number of other conditions associated with either metabolic insult or hypotension, including carbon monoxide poisoning, hypoglycemia, barbiturate overdose, cyanide poisoning, and closed head injury.\textsuperscript{29–32}

Our findings also suggest that there is a quantifiable threshold value below which there is no chance for survival. Using ROC analysis, we determined that a value of $<1.18$ for GM/WM ratio at the basal ganglia level predicted death. While almost half the patients who had values higher than this survived, every patient with a lower value died. Since this is a preliminary, retrospective study, however, this must be interpreted very cautiously. For example, the results could be skewed if the physicians’ decision to pursue a do not resuscitate order was based on their learning that there was a loss of GM-WM differentiation on CT. While we cannot rule out such a possibility, as far as we could determine, the physicians were not aware of this since such a result was rarely recorded on the CT report. Nevertheless, further studies will be necessary to determine the validity of this value.

We conclude therefore that HU values can be reliably measured with modern CT technology and that a very small range of values is obtained when normal scans are assessed. We also conclude that most, if not all, comatose patients after a cardiac arrest have a diminished GM-WM differentiation on CT scans obtained within 48 hours of ictus. Given the retrospective nature of this study, we cannot be as confident that there is an absolute threshold of GM-WM differentiation below which all patients will die, although our preliminary data suggest that such a value may exist. Finally, it is notable that the measures used here are readily available in most hospitals and require less time to obtain than either an electroencephalogram or somatosensory evoked responses. A prospective study is therefore conceivable, and if it confirms these preliminary data, it could establish CT scanning as a readily available, useful ancillary test in the prediction of outcome after cardiac arrest or other causes of coma.

References


