Specific Changes in Human Brain Following Reperfusion After Cardiac Arrest

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Background and Purpose
Very few reports are available on serial changes in human brain after cardiac arrest. The primary objective of this study is to investigate sequential neuro-radiological changes in patients remaining in a persistent vegetative state following resuscitation after cardiac arrest.

Methods
We repeatedly studied eight vegetative patients resuscitated from unexpected out-of-hospital cardiac arrest using computed tomographic (CT) scanning and high-field magnetic resonance (MR) imaging at 1.5 T.

Results
In seven of the eight patients, CT scans obtained between days 2 and 6 featured symmetrical low-density lesions in the bilateral caudate, lenticular, and/or thalamic nuclei. These ischemic lesions were persistently of low density on serial CT scans. In these seven patients, MR images demonstrated what were thought to be hemoglobin degradation products derived from minor hemorrhages localized in the bilateral basal ganglia, thalami, and/or substantia nigra. Diffuse brain edema in the acute stage and diffuse brain atrophy in the chronic stage were consistent neuroradiological findings. No abnormal enhanced lesions were demonstrated by CT scans.

Conclusions
The most characteristic findings on high-field MR images were symmetrical lesions in the bilateral basal ganglia, thalami, and/or substantia nigra with specific changes suggestive of minor hemorrhages that were not evident on CT scans. We speculate that these minor hemorrhages result from diapedesis of red blood cells in these regions during the reperfusion period through the endothelium disrupted by ischemia-reperfusion insult. (Stroke. 1994;25:2091-2095.)

Key Words • cerebral ischemia, transient • heart arrest • hemorrhage • magnetic resonance imaging • reperfusion
Clinical Features of Eight Patients With Global Brain Ischemia

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Cause of CA</th>
<th>ECG on Admission</th>
<th>Duration, min</th>
<th>Distribution Pattern of Low Density on CT (Time of First Detection)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>F</td>
<td>Chest trauma</td>
<td>Flat</td>
<td>20</td>
<td>B (day 6)</td>
<td>PVS</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>M</td>
<td>Suffocation</td>
<td>Flat</td>
<td>18</td>
<td>B (day 3)</td>
<td>D on day 53</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>F</td>
<td>Anaphylactic reaction</td>
<td>VF</td>
<td>10</td>
<td>A (day 2)</td>
<td>D on day 32</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>M</td>
<td>Suffocation</td>
<td>Flat</td>
<td>10</td>
<td>B (day 4)</td>
<td>PVS</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>M</td>
<td>Asthma attack</td>
<td>VF</td>
<td>17</td>
<td>A (day 3)</td>
<td>D on day 36</td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>F</td>
<td>Unknown (sudden collapse at home)</td>
<td>Flat</td>
<td>22</td>
<td>C (day 6)</td>
<td>D on day 37</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>M</td>
<td>Acute alcoholism</td>
<td>Flat</td>
<td>15</td>
<td>N</td>
<td>PVS</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>F</td>
<td>AMI</td>
<td>VF</td>
<td>25</td>
<td>B (day 2)</td>
<td>D on day 33</td>
</tr>
</tbody>
</table>

(61.6±15.3) (17.1±5.0) (8.5±3.9)

Pt indicates patient; CA, cardiac arrest; ECG, electrocardiogram; CPR, cardiopulmonary resuscitation; CT, computed tomogram; AMI, acute myocardial infarction; VF, ventricular fibrillation; A, symmetrical low-density lesions (SLDLs) in the caudate, lenticular, and thalamic nuclei; B, SDLIs in the caudate and lenticular nuclei; C, SDLIs in the thalamic nuclei; N, no SDLIs; PVS, persistent vegetative state; and D, death. Values in parentheses are mean±SD.

Results

Both the CT scans and MR images of our patients illustrated noteworthy changes with time in the basal ganglia, thalamus, and substantia nigra bilaterally (Table, Fig 1).

Precontrast head CT scanning performed on day 1 demonstrated no abnormal findings in any patient. In 7 of the patients, CT scans obtained between days 2 and 6 revealed symmetrical low-density lesions in various combinations of localized areas (in the bilateral caudate, lenticular nuclei, and thalami in 2, in the bilateral caudate and lenticular nuclei in 4, and in the bilateral thalamic nuclei in 1) (Table). The subsequent CT scans showed these lesions as low-density areas consistently throughout the study period. In all 8 patients, diffuse brain edema with effacement of the cerebral sulci appeared on CT scans in the acute stage (within 1 week of onset) and gradually resolved with time. CT scans in the chronic stage (from 1 week to 2 months after onset) exhibited diffuse brain atrophy in all patients except patient 1. Postcontrast CT scans in 2 patients (patients 4 and 6) showed no evidence of abnormal enhanced lesions.

Fig 1 shows the serial changes on high-field MR images in each patient. The most common pattern was isointensity/hyperintensity on the initial T1/T2-weighted images, respectively, in the caudate nuclei, lenticular nuclei, and/or thalamic nuclei followed by hyperintensity/hyperintensity or hyperintensity with central hypointensity in the same sites on the later T1/T2-weighted images, respectively. In addition, in 1 patient (patient 4) isointensity/hyperintensity followed by hyperintensity/hyperintensity was found in the substantia nigra on the initial and later T1/T2-weighted images, respectively (Figs 2 and 3). In 1 patient each (patients 6 and 1), hyperintensity/hyperintensity was found in the substantia nigra on the initial and later T1/T2-weighted images, respectively.

This pattern of specific changes was found in all but 1 of the patients (patient 7), in whom neither CT nor MR imaging detected any symmetrical ischemic lesions.

Discussion

In humans, brief cardiac arrest typically leads to transient complete global brain ischemia. Previous CT
and pathological studies revealed that hypoxic-ischemic insult predominantly affects the cerebral cortex, basal ganglia, thalamus, hippocampus, and brain stem. Cohan et al suggested that cerebral hyperemia in the resuscitated patient induced increased blood-brain barrier permeability and might contribute to the development of cerebral edema or increased intracranial pressure, leading to a poor outcome. Martin et al considered that the heterogeneous cerebral metabolic response to the global ischemia might result from inhomogeneous cerebral blood flow due to a "no-reflow" phenomenon. Recently, Reine et al reported that cardiac arrest was significantly associated with deep cerebral infarcts in the first controlled MR imaging study that used a 0.02-T ultra-low-field scanner.

The results of the present study can be summarized as follows. First, specific and symmetrical ischemic brain damage was demonstrated neuroradiologically in the brains of humans in a persistent vegetative state after cardiac arrest. Second, these ischemic lesions were distributed bilaterally in the basal ganglia, thalami, and/or substantia nigra. Third, high-field MR images showed what were thought to be minor hemorrhages in the ischemic lesions. Fourth, diffuse brain edema in the acute stage and diffuse brain atrophy in the chronic stage were consistent neuroradiological findings.

MR signal characteristics of hemorrhagic cerebral infarcts can be explained on the same basis as those of intracranial hematomas. MR imaging is most sensitive for detecting hemorrhage into cerebral infarcts. In this study, in which hemorrhagic transformation on MR images was diagnosed according to the criteria of Gomori et al and Hecht-Leavitt et al, the most consistent MR imaging patterns were isointensity/hyperintensity in the basal ganglia, thalami, and/or substantia nigra on the initial T1/T2-weighted images, respectively, followed by hyperintensity/hyperintensity or hyperintensity with central hypointensity in the same sites on the later T1/T2-weighted images, respectively. These patterns of changes on MR images were interpreted to suggest the presence of methemoglobin inside or outside red blood cells during the process of hemoglobin degradation. This type of hemorrhage with its characteristic distribution seems to differ from the usual hematomas caused by vascular destruction because CT scans consistently showed the hemorrhagic lesions as low-density areas. In our patients, we speculate that transient global brain ischemia associated with cardiac arrest induced diapedesis of red blood cells in the basal ganglia, thalami, and/or substantia nigra during the reperfusion period through the endothelium disrupted by the ischemia-reperfusion insult. Bryan et al reported that increased signal intensity on T1-weighted MR images in patients with cerebral infarction without high density on CT scans resulted from ischemic lesions with damaged capillary endothelium through which red blood cells had leaked. The mechanism of this type of hemorrhage is undoubtedly a remarkably complex and dynamic process, involving a combination of vascular disruption with altered permeability and reperfusion of the damaged vascular bed.

The precise mechanism of selective damage to the basal ganglia, thalami, and substantia nigra could not be elucidated by our study. However, the present findings are consistent with several animal experiments that have noted a heterogeneous increase in blood-brain barrier...
permeability in particular areas, including the striatum and thalamus, after transient global cerebral ischemia.20-22 Some combination of the following factors may play a role in the selective damage to the basal ganglia, thalami, and substantia nigra: uncoupling23,24 of heterogeneous regional cerebral blood flow25,26 and regional cerebral metabolic rate,14,27,28 iron-catalyzed reaction-associated reperfusion injury29,30 due to the fact that iron is unevenly distributed in brain tissues, and selective neuronal vulnerability.

A hyperintensity on T1-weighted MR images could just as well represent ectopic calcifications as hemorrhagic transformations. According to the early literature,31-33 calcified lesions of the brain occasionally appear bright on T1-weighted MR images at 1.5 T. However, they report that such calcified lesions appear hypointense on T2-weighted images and of high density on CT scans. Based on these reports, the specific changes in the present study, which exhibit hyperintensity/hypointensity or hyperintensity with central hypointensity on T1/T2-weighted MR images, respectively, and appear of low density on CT scans, are thought unlikely to represent ectopic calcifications.

Diffuse brain edema8,15,34 due to cytotoxic and vasogenic causes in the early stage has been shown to occur in ischemic-anoxic encephalopathy, consistent with the neuroradiological findings in the present study. Brain edema as observed in our patients has been proposed to predict a poor neurological outcome after cardiac arrest.8,15,34 Diffuse brain atrophy was a common finding in our patients and could be interpreted as diffuse loss of neurons and glial cells.

Conclusions

To our knowledge, this is the first study on serial changes in the brain of humans remaining in a persistent vegetative state following resuscitation after cardiac arrest using high-field MR imaging. MR images, but not CT scans, revealed what were thought to be hemoglobin degradation products derived from minor hemorrhages localized in the bilateral basal ganglia, thalami, and substantia nigra. We speculate that these minor hemorrhages on MR images result from diapedesis of red blood cells through the damaged vascular wall exposed to ischemia-reperfusion insult. Further studies on larger series of patients will be needed to determine the clinical and prognostic significance of these findings. It is not clear from this study whether the presence of such minor hemorrhages on MR images indicates a need for a change in therapy, but it is hoped that a better understanding of the mechanisms involved will help to identify areas of the human brain at particular risk of ischemic injury and rationalize the treatment of postischemic-anoxic encephalopathy.

Acknowledgments

We greatly appreciate the thoughtful comments and expert assistance of H. Nakagawa, MD, Y. Tatematsu, MD, Y. Kamada, MD, I. Hayashi, MD, A. Fujikawa, MD, A. Nishimura, MD, J. Sogami, MD, N. Doi, MD, Y. Inada, MD, and K. Nishio, MD. We also thank K. Fujoka and M. Omoue for their secretarial help.

References

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Stroke. 1994;25:2091-2095
doi: 10.1161/01.STR.25.10.2091

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