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 neuroradiological 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 consistently 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

Experimental studies have addressed various aspects of transient forebrain or global brain ischemia. Very few reports are available on serial changes in human brain following reperfusion after complete global ischemia. We investigated chronological changes in the brain of patients who remained in a persistent vegetative state after cardiac arrest using computed tomodographic (CT) scanning and high-field magnetic resonance (MR) imaging.

Subjects and Methods

Subjects satisfying the following criteria were included in this study: persons without preexisting neurological disease suffering out-of-hospital cardiac arrest followed by successful resuscitation at Nara Medical University Hospital during the period September 1991 to July 1993 and the ability to undergo multiple neuroimaging studies. During this period there were 10 such patients, but 2 (1 each with cardiac arrest due to subarachnoid hemorrhage and lightning) were excluded from the present study because direct effects on the brain could not be ruled out. The Table summarizes the clinical features of these 8 patients, who ranged in age from 30 to 86 years (mean±SD age, 61.6±15.3 years). This study protocol was approved by the ethics committee of our university hospital.

On admission, the electrocardiogram showed cardiac arrest (isoelectric) in 5 of the 8 patients and ventricular fibrillation in the remaining 3. Four of the patients were female. The cardiac arrest was estimated to have lasted for 10 to 25 minutes (mean, 17.1±5.0 minutes), and the time needed for cardiac output restoration ranged from 5 to 18 minutes (mean, 8.5±3.9 minutes). All patients in this study within the first few minutes to hours after resuscitation recovered brain stem function, such as spontaneous respiration and cranial nerve reflexes, and other aspects of vegetative behavior. After the patient was transferred to the intensive care unit, various physiological parameters were monitored continuously and maintained within the normal ranges. All the patients remained in a persistent vegetative state throughout the study period. Persistent vegetative state was diagnosed in accordance with the published criteria of the American Neurological Association. Informed consent was obtained from each patient's nearest relative before the study began.

CT scanning was performed using an Xpeed scanner (Toshiba) with 10-mm cuts displayed on a 512x512 matrix (5-second scan time). All patients underwent precontrast CT scanning daily for the first 3 days (days 1 through 3) after cardiovascular stability was assured, and thereafter repeatedly every 1 to 5 days. Postcontrast CT scanning was performed in 2 patients (patient 4 on days 4 and 25, and patient 6 on day 20) with intravenous administration of iodinated contrast medium.

MR imaging was performed twice per patient with a superconductive unit (Picker, Vista MR system) operating at a field strength of 1.5 T. The timing of MR imaging is indicated in Fig 1. Axial, coronal, and sagittal T1- and T2-weighted sequences were obtained using a spin-echo technique, with repetition time (TR) of 500 or 200 milliseconds and echo time (TE) of 20 milliseconds for the short TR/TE images and TR of 2000 milliseconds and TE of 100 milliseconds for the long TR/TE images. Other imaging parameters included 5- or 7-mm slice thickness with an intersection gap of 0 to 5 mm, matrix size 256x256 or 192x256, and 25-cm field of view. During patient transport and throughout CT scanning and MR imaging, electrocardiogram and arterial blood pressure were continu-
Clinical Features of Eight Patients With Global Brain Ischemia

PtNo. | Age, y | Sex | Cause of CA | ECG on Admission | Duration, min | Distribution Pattern of Low Density on CT (Time of First Detection) | Outcome
-----|-------|-----|-------------|-----------------|--------------|-------------------------------------------------|------
1    | 30    | F   | Chest trauma | Flat            | 20           | B (day 6)                                      | PVS  
2    | 86    | M   | Suffocation | Flat            | 18           | B (day 3)                                      | D on day 53
3    | 60    | F   | Anaphylactic reaction | VF    | 10           | A (day 2)                                      | D on day 32
4    | 69    | M   | Suffocation | Flat            | 10           | B (day 4)                                      | PVS  
5    | 58    | M   | Asthma attack | VF              | 17           | A (day 3)                                      | D on day 36
6    | 74    | F   | Unknown (sudden collapse at home) | Flat  | 22           | C (day 6)                                      | D on day 37
7    | 54    | M   | Acute alcoholism | Flat    | 15           | N                                             | PVS  
8    | 62    | F   | AMI         | VF              | 25           | B (day 2)                                      | D on day 33

(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, SLDLs in the caudate and lenticular nuclei; C, SLDLs in the thalamic nuclei; N, no SLDLs; PVS, persistent vegetative state; and D, death. Values in parentheses are mean±SD.

ously monitored in all patients. While the patient was in the scanner or imager, the respiration was assisted by manual ventilation with a Jackson-Russ circuit.

Five of the 8 patients died during the study period of systemic complications such as respiratory, cardiac, and/or renal failure. Unfortunately, permission for autopsy was not obtained in any case.

Results

Both the CT scans and MR images of our patients illustrated noteworthy changes with time in the basal ganglia, thalami, 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.

Specific Changes with time on MRI

Specific Changes with time on MRI

Case | Initial MRI | Second MRI |
-----|-------------|------------|
1    | T1WI day 3  | T1WI day 6 |
2    | T2WI day 4  | T2WI day 20 |
3    | T2WI day 5  | T2WI day 27 |
4    | T2WI day 6  | T2WI day 30 |
5    | T2WI day 8  | T2WI day 17 |
6    | T2WI day 11 | T2WI day 23 |
7    | T1WI day 13 | T2WI day 23 |
8    | T2WI day 15 | T2WI day 20 |

Fig 1. Chart shows serial changes on high-field magnetic resonance images (MRI) in each patient. These specific changes are considered to reflect hemoglobin degradation products. T1WI indicates T1-weighted image; T2WI, T2-weighted image.

Discussion

In humans, brief cardiac arrest typically leads to transient complete global brain ischemia. Previous CT
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and pathological studies revealed that hypoxic-ischemic insult predominantly affects the cerebral cortex, basal ganglia, thalamus, hippocampus, and brain stem.\(^5\)\(^\text{-}\)\(^12\) Cohan et al\(^13\) 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\(^14\) 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, Roine et al\(^15\) 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.\(^16\) 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\(^17\) and Hecht-Leavitt et al,\(^18\) the most consistent MR imaging patterns were isointensity/hyperintensity in the basal ganglia, thalami, and/or substantia nigra on the initial T\(_1\)/T\(_2\)-weighted images, respectively, followed by hyperintensity/hyperintensity or hyperintensity with central hypointensity in the same sites on the later T\(_1\)/T\(_2\)-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.\(^16\)\(^\text{-}\)\(^18\) 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\(^19\) reported that increased signal intensity on T\(_1\)-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.
permeability in particular areas, including the striatum and thalamus, after transient global cerebral ischemia. Some combination of the following factors may play a role in the selective damage to the basal ganglia, thalamus, and substantia nigra: uncoupling of heterogeneous regional cerebral blood flow and regional cerebral metabolic rate, iron-catalyzed reaction-associated reperfusion injury 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, 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/hyperintensity 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 edema 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. 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, thalamus, 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. Fujikoma and M. Onoue 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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