Acute NMR Changes During MCA Occlusion: A Preliminary Study in Primates

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SUMMARY  Advancements in computer science and magnet design have resulted in the recent development of high resolution NMR imaging systems. Using our primate model we evaluated the ability of NMR scanning to detect early changes following middle cerebral artery (MCA) occlusion.

Serial NMR scans documented progressive changes secondary to edema and swelling beginning ninety minutes after MCA occlusion. NMR was also able to readily demonstrate the area of cerebral infarct 10 days after a six hour episode of MCA occlusion.

Soft tissue contrast and image resolution were superb. Correlation with pathologic sections was excellent.

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THE PHENOMENON OF NUCLEAR MAGNETIC RESONANCE (NMR) was first reported for the hydrogen nuclei of water and paraffin in 1946. 1, 2 Hydrogen nuclides (protons, deuterium, and tritium) and the isotopes of certain other elements (12C, 13P, etc.) share the common property of having an intrinsic nuclear magnetic dipole moment. As a result they can be thought of as behaving like small bar magnets. Normally in a sample containing the nuclides, these nuclear magnets are randomly orientated so that the net nuclear magnetism is zero (fig. 1a). When such a sample is placed in a strong static magnetic field, however, the nuclear magnets tend to realign themselves with the direction of the lines of force in the magnetic field (fig. 1b) so that the nuclear magnetic forces are additive (fig. 1b). Thermal motions within the sample tend to disturb this alignment. The net effect of these opposing forces is a macroscopic quantity called magnetization. At equilibrium the magnitude of this nuclear magnetization vector is directly proportional to the strength of the applied magnetic field, and inversely proportional to the absolute temperature (Curie’s Law). One of the most common ways to obtain an NMR signal is to use a short, intense radio frequency (RF) pulse applied transverse to the direction of the static magnetic field. By choosing an appropriate frequency for the RF pulse the nuclei of interest (e.g. the hydrogen proton, 1H) can be forced to rotate (or precess) about the axis of the static magnetic field (fig. 2). Following the RF pulse, then, the magnetization of these stimulated nuclei (the sum of the rotating nuclear magnetic vector moments) is no longer in alignment with the static field and undergoes free precession in the magnetic field at an angular frequency characteristic of the nuclide and proportional to the static field strength. The transverse component of this magnetization constitutes the NMR signal. By spatially encoding these signals with a magnetic field gradient it is possible to obtain a map of the density distribution of the mobile nuclei within the sample. 3, 4

With further appropriate processing these signals can be used to generate high resolution images similar to CT, but with the important advantage that NMR scanning uses no ionizing radiation and as far as is known is without harmful effects. Furthermore, because bone has a relatively low mobile proton density RF pulses are able to penetrate it without attenuation and it returns only a weak NMR signal. The result is rich image detail even in tissues adjacent to or surrounded by dense cortical bone.

Recent advances in computer technology, reconstruction algorithms and magnet design have permitted the development of NMR imaging systems capable of scanning the entire human body. Extensive clinical evaluations of these systems are now underway. Preliminary reports have generated great interest and excitement. 5–9

In order to evaluate the ability of NMR imaging to detect early changes following middle cerebral artery (MCA) occlusion in primates and compare the images with those obtained by CT we undertook the following study.

Materials and Methods

We have previously described our primate model of MCA occlusion. 10 Briefly, animals are prepared by implanting our miniature inflatable occluder around the MCA using a transorbital approach. 11, 12 The device consists of a small silastic balloon with arterial hooks, connected via a spring reinforced catheter to a pressure sensitive valve and a small fluid reservoir. Pressure on the reservoir fills the balloon occluding the vessel. The balloon remains inflated until pressure is applied to the valve which deflates the balloon, allowing flow to resume. The valve and reservoir are buried subcutaneously over the skull for easy access. With this device the MCA may be readily occluded at times remote from surgery.

We have used this occluder in over 100 primates.
with reliable occlusion documented for up to three months. Two adult male baboons (Papio anubus) were used for this study. Animals were sedated for imaging studies with Ketamine-HCl administered intravenously. The first animal (Baboon I) was scanned using both CT and NMR ten days following a six hour period of MCA occlusion. Clinically this animal had a severe hemiparesis and homonymous hemianopsia appropriate to the side of occlusion. Following these initial scans the MCA occluder was re-inflated and a NMR scan repeated 30 minutes later. The animal was then sacrificed with an intravenous bolus of potassium-chloride and a repeat NMR scan performed 20 minutes after death. Baboon II was scanned with the NMR prior to MCA occlusion, and then at 5, 90 and 180 minutes after occlusion. The occluder was released after six hours (360 minutes) and a final NMR scan obtained 30 minutes after reperfusion. The rapid onset of hemiplegia (which was easily tested despite light anesthesia), and the complete refilling of the fluid reservoir with deflation served to document the proper function of the occluder in this animal. Following the ischemic insult this baboon developed progressive malignant intracranial pressure and died approximately 48 hours after reperfusion.

NMR scans were performed on a prototype system developed by Technicare Corporation. The system utilizes a 100 cm bore diameter superconducting magnet operating at a field strength of 3 kilogauss (0.30 tesla). The images presented in this report were generated using a saturation recovery (3-dimensional) back projection technique, with a recycle delay time of 100 msec in each projection. The number of projections in each scan is 100 over π radians in the azimuthal plane and 50 over π/2 radians in the polar plane. The total scanning time in each case is 20 minutes. Although this is longer than the time necessary for conventional CT imaging, a single scan produces sufficient data to allow generation of images at 1 mm intervals in any desired plane and at any desired level through the brain.

For this study images were displayed on a color monitor after being encoded for color to signal intensity. In order of increasing signal strength each pixel is displayed as brown, light red, blue, green, yellow, or white.

CT scans were performed on a fourth generation system (Technicare* Deltascan 2060) at 1 mm intervals in the coronal plane.

Results

Coronal CT sections through the ten day old infarct in Baboon I, demonstrate a ventricular shift and questionable area of decreased density appropriate to the side of the infarct (fig. 3).

Coronal sections from the NMR scan through the 10 day old infarct are presented in figure 4. Anatomic detail is excellent: The major fissures and the ventricles are well visualized, and the area of the infarct is well delineated from the normal surrounding brain.

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FIGURE 3. Coronal CT sections at two levels through the 10 day old infarct of Baboon I. The ventricles are faintly visualized (small arrows) and a questionable area of decreased density, appropriate to the side of the infarct, is noted (curved arrows).

The NMR scan 30 minutes after re-occlusion of the MCA in this animal revealed no apparent changes (fig. 5). The NMR scan 20 minutes after sacrifice with potassium chloride revealed no appreciable change in the signals from either the normal or infarcted brain (fig. 6).

Comparison of the NMR scans, figures 3 to 6, with a pathologic section through the 10 day old infarct reveals excellent correlation with the tissue specimen on gross exam (fig. 7).

NMR scan of Baboon II prior to MCA occlusion (fig. 8) again reveals the excellent anatomic detail possible with this technique.

Sections from the NMR scan five minutes following MCA occlusion were unchanged (fig. 9).

Ninety minutes after occlusion an area of decreased intensity was apparent in the territory of the middle cerebral artery, and there was mild ventricular enroachment (fig. 10).

At 180 minutes after MCA occlusion changes in image intensity are even more apparent in the ischemic hemisphere and there is further compromise of the ventricle (fig. 11).

FIGURE 4. Coronal sections from the NMR scan of the same animal (Baboon I). Anatomic detail is excellent. The ventricular system is well visualized and an area of increased signal intensity (the infarct) producing a slight mass effect is readily appreciated.
In the final NMR scan at 390 minutes (30 minutes after reperfusion) the ventricle was almost totally obliterated and a slight midline shift is apparent (fig. 12). Reperfusion appears to have masked some of the earlier noted attenuation of signal intensity. However, areas of decreased intensity were still present and overall the image appears to correlate well with changes seen in a pathologic section taken at approximately the same level (fig. 13).

Discussion

The images presented in this report document the exquisite anatomic detail possible with NMR scanning. The soft tissue contrast and image resolution of the baboon brain are far superior to that obtainable on the present generation of CT scanners. The baboon brain lends itself poorly to discriminating tissue densities by CT: The brain is relatively small and encased in high density bone with a high riding sella and clivus that produce extensive beam attenuation and imaging artifact, thus, accounting in part for the relatively poor resolution observed in the CT scans presented here. Since bone gives virtually no signal during proton NMR imaging it does not interfere with NMR resolution. We have previously reported on over 500 sections of CT scans in twelve baboons and observed inconsistent low density changes after brief periods of MCA occlusion. However, the scans failed to demonstrate the ventricular system making it difficult to interpret any subtle changes in brain swelling. With the NMR scanner we have demonstrated progressive alteration of intensity in the ischemic MCA territory with ventricular encroachment and obliteration. It is reasonable to assume that the changes observed

FIGURE 5. Coronal NMR section through the infarct 30 minutes after repeat MCA occlusion in Baboon I: No changes are noted.

FIGURE 6. Coronal section from the NMR scan 20 minutes after sacrifice of Baboon I: Unchanged.

FIGURE 7. Pathologic section through the infarct in Baboon I revealing the excellent correlation between the NMR images and the actual tissue specimen. The area of infarct (arrow) is producing a slight mass effect.

FIGURE 8. Coronal NMR sections of Baboon II prior to inflating the MCA occluder. The major fissures and ventricular system are well visualized (Normal Control Scan).
in Baboon II are reflections of progressive edema leading to mass effect. That these changes can be observed as early as 90 minutes after MCA occlusion is remarkable. Although edema has been appreciated as early as 30 minutes following MCA occlusion by direct measurement, up to now no diagnostic tool has been able to observe these early changes in vivo.

Reports by other investigators have demonstrated the time course of cerebral edema using pulse NMR studies in models of both cold and triethyl tin injury. However, in these reports the animals were sacrificed at appropriate intervals and tissues directly examined.

The ability to detect and quantify edema in vivo without the need for invasive procedures may be of importance in assessing any treatment designed to influence the natural course of cerebral edema.

The interpretation of NMR images requires an understanding of how pulse techniques may affect signal intensity. Unlike the CT scan which measures only one variable, the attenuation of an X-ray beam by the tissue in its path, proton NMR images are a reflection of multiple influences, the contributions of which can be altered by the RF pulse sequence.

After an RF pulse the intensity of the NMR signal is proportional to the mobile proton density, and has a varying dependence on two parameters, $T_1$ and $T_2$. $T_1$, known as the spin-lattice relaxation time, is phenomenologically the characteristic time required for the longitudinal component of the magnetization to recover from RF excitation and any other disturbances of its equilibrium value. Spin-lattice relaxation is due to the interaction between the nuclei in question and the ther-
mal lattice which includes all molecular degrees of freedom coupled to the nuclear spins. The second parameter $T_2$, the spin-spin relaxation time, characterizes the time necessary for the transverse magnetization to decay to zero. This decay is a result of internuclear magnetic interactions that cause individual nuclei to spin (precess) at slightly different frequencies during free precession. As a result, the spins become progressively out of phase with each other, reducing the net transverse magnetization signal (thus the term spin-spin relaxation). In biological tissues, as in most any substance except simple pure fluids, $T_2$ is always smaller than $T_1$.

The scanning technique used for NMR imaging in this study involves application of a series of equally spaced 90 degree pulses. If sufficient time, $t$, is allowed for near complete relaxation (complete realignment) of the nuclei between repeated 90 degree RF pulses (i.e. when $t \gg T_1$ for all tissues in the sample) and provided that data is collected in a time shortly after the RF pulse in comparison with $T_1$, then the intensity of the returned signal will be essentially independent of $T_1$ and $T_2$, and will be a reflection of only the mobile proton density. However, if the repetition time, $t$, is shortened so that it is less than $T_1$ for some segments of the sample then there will be only partial recovery of the protons in those segments between pulses subsequently leading to a reduction in NMR signal intensity from tissues in which $T_1 > t$. The whole volume technique used for imaging in this study takes advantage of shortening repetition time to enhance the contrast between tissues with varying $T_1$'s, as well as decrease total scanning time.

The result is that in the images we present tissues or fluids with a relatively long $T_1$, such as CSF which is composed almost entirely of free water, and those with a low mobile hydrogen proton density, such as bone, give a weak signal and appear light red. Tissues with a relatively short $T_1$, such as the cortex in which all but a small fraction of the water is restricted in motion by its interaction with larger molecules, give a strong signal. An exception to these rules is the effect seen when blood is moving. Blood, because of its long $T_1$, would be expected to give a low signal. However, blood that flows into a tissue between pulses will not have previously been exposed to an RF pulse and will thus appear to have fully recovered as though it had a short $T_1$, and will, therefore, produce a strong signal.

NMR studies by other investigators have documented that edema, by increasing the percentage of free water in a tissue, increases $T_1$. The pulse technique that we used for NMR imaging should therefore result in reduced signal intensity from edematous tissue as was appreciated in figures 10 and 11 at 90 and 180 minutes after MCA occlusion respectively. Following reperfusion the rapid flow of blood through the previously ischemic tissues can be expected to partially mask the changes produced by edema as in figure 12. These explanations are only preliminary and based on our limited experience with this new technique. Studies are planned to further evaluate the changes produced by focal cerebral ischemia, and also to document the effects of increasing blood flow.

Conclusion

The capacity of NMR scanning to provide images with both high spatial resolution, and tissue contrast has been demonstrated. Proton NMR imaging was readily able to document changes due to chronic infarction, as well as detect early changes produced by tissue edema and swelling during MCA occlusion.

The results of this preliminary study hint at the enticing prospects of NMR imaging for the evaluation of pathological processes without the need for invasive methods or ionizing radiation.

References

Chronological Sequences and Blood-Brain Barrier Permeability Changes in Local Injury as Assessed by Nuclear Magnetic Resonance (NMR) Images from Sliced Rat Brain

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SUMMARY Two experiments were done with a prototype mini-NMR imager to evaluate the potential application of nuclear magnetic resonance (NMR) imaging in neuropathology. Cryo-injury-induced brain edema in brain slices from 22 adult male rats was imaged for observing the chronological sequences. Blood-brain barrier permeability changes were evaluated in 12 other brain slice images. EDTA-2Na-Mn solution was intravenously injected as an indicator of blood-brain barrier permeability. Contrast enhancement was achieved by changing the NMR imaging parameters. High resolution imaging permitted visualization of the corpus callosum, the thickness of which was only 0.2-0.4 mm. The extent of edema in gray matter was clearly shown with a striking contrast; no consistent findings were seen with slight differences in water content between edema and the surrounding normal cortex. As a result, the chronological sequences of brain edema were clearly observed. Mn-EDTA leaking from the circulating blood through the damaged capillary wall had a “paradoxical enhancement” effect on the NMR images; this effect might be suitable for evaluating blood-brain barrier permeability changes in NMR images.

NUCLEAR MAGNETIC RESONANCE (NMR) imaging is very sensitive to physico-chemical changes in tissue characteristics. Images obtained not only possess high spatial resolution but also show striking contrast between normal and pathological tissues. Although several imagers for human application are now available,1 and many clinical investigations have already been published,2,3 there are only a few reports on its application to experimental studies in animals.4-6 A new imaging technique was safely developed for animal experiments. It is of interest to evaluate the characteristics of NMR imaging and its potential application to neuropathology, based on an experimental model such as brain edema induced by cryo-injury.

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1. Animal Preparation

Thirty-four adult male Wistar rats (300–350 g) were used. Edema was produced as described by Klatzo.7 Animals were anesthetized with intraperitoneal pentobarbital and a midline scalp incision was made. The right side of the skull was exposed, and a 2 mm burr hole was made 2 mm posteriorly from the coronary suture and 3 mm laterally from the sagittal suture. The Klatzo procedure often causes macroscopic hemorrhages in rats as a result of direct cooling of the exposed pial brain surface. Thus, in our experiments, the 2 mm burr hole did not penetrate the very thin bone layer, to which a pre-cooled metal plate was applied. A standard lesion time of 30 sec was used. By this modified technique, we could produce a highly uniform local injury in rat brain without any hemorrhages; after the operation the scalp was completely closed. Eleven pairs of rats were sacrificed by intraperitoneal exsanguination at the following time intervals: 10 minutes; 2, 6, 12, 24, 48, 72 hours and 4, 5, 6, 7 days after injury. The brain was rapidly excised in a highly humidified box and a 2-mm coronal slice was made through the cryo-lesion. Then the brain slice was put during ischemia and after restoration of blood flow: Measurement of water, potassium content and plasma protein permeability. Stroke 10: 542–547, 1979

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