**Original Contributions**

**True Three-Dimensional Nuclear Magnetic Resonance Neuro-Imaging in Ischemic Stroke: Correlation of NMR, X-ray CT and Pathology**

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**SUMMARY** True three-dimensional proton nuclear magnetic resonance (NMR) imaging was performed on an 84-year-old man following a recent cerebral embolic infarction. NMR data obtained using different pulse sequences were inter-correlated, stressing the significance of image appearance in terms of the NMR tissue parameters. Planes selected for display from the three-dimensional data set allowed optimal visualization of the pathology. Accurate correlations of the NMR data with X-ray computerized tomography scans and with subsequent autopsy findings indicate that NMR may play an important role in the detection and diagnosis of ischemic stroke.

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**THE ADVENT OF X-RAY COMPUTERIZED TOMOGRAPHY (CT)** in 1973 revolutionized the practice of diagnostic imaging to the extent that, at least in neuro-imaging, CT scans now represent the standard against which any new imaging modality must be compared. Such is the case for the most recent addition to the imaging technology armamentarium: nuclear magnetic resonance (NMR).

Because of its inherent three-dimensional (3D) capability, NMR imaging offers the unique possibility of correlating a single 3D data set with any number of CT scans, with other NMR scans and, when the opportunity presents itself, with the definitive standard: pathology.

We present here a case study exemplifying those capabilities. As well as providing a comparison between proton NMR, CT and pathology, two different NMR imaging approaches are inter-correlated. It is concluded that NMR imaging may play an important role in detecting, and monitoring the evolution of, ischemic stroke.

**Materials and Methods**

NMR imaging was performed using a prototype clinical imaging instrument designed and built by Technicare Corporation (Solon, Ohio). The static magnetic field of 0.147 tesla, corresponding to a proton resonance frequency of 6.26 MHz, is generated by a four-coil, resistive electromagnet. The access aperture of this head imaging instrument is 28.0 cm.

Spatial encoding of the NMR signal was achieved using a true three-dimensional technique. For the present studies, a linear magnetic field gradient was rotated through 2π steradians (one half sphere) in a series of predetermined steps. For each gradient angle, an NMR projection profile was obtained following excitation of the nuclear spin system with an appropriate radiofrequency (RF) pulse sequence. Subsequent computer analysis of the NMR projection data allows reconstruction of arbitrarily oriented planar sections, at any location within the confines of the RF coil system. The spatial resolution is approximately isotropic and was set to about 2 mm-3 mm in this case. To provide a more accurate correlation of NMR images with CT scans, the NMR slice thickness (nominally 2 mm-3 mm) was increased to about 10 mm by adding contiguous planes.

The two RF pulse sequences used in this study are sketched in figure 1. The sequence of figure 1(a) is based on a “saturation-recovery” (SR) pulse pattern, and yields an image whose pixel values, \( S_{SR} \), are given by the formula:

\[
S_{SR} = k_p e^{-2\pi/T_2}(1 - 2 e^{-\tau - T/T_1} + e^{-\pi T_1}),
\]

where \( k \) is a constant of proportionality and \( \rho \) is the local nuclear spin density (\( ^1H \) concentration). \( T_1 \) and \( T_2 \) are the local values of the proton spin-lattice and spin-spin relaxation times; \( \tau \) is the interpulse delay times indicated on the diagram. Figure 1(b) depicts an “inversion-recovery” (IR) type pulse sequence, which generates images with pixel values \( S_{IR} \) given by:

\[
S_{IR} = k_p e^{-2\pi/T_2}(1 - 2 e^{-\tau + T/T_1} + 2 e^{-\tau + \tau + \tau/T_1} - e^{-\tau + \tau/T_1} - e^{-\tau + T/T_1}),
\]

where, again, \( \tau \) is the indicated interpulse delays.

The total data acquisition time for the 3D SR study (figure 2(b)) was 18.6 minutes, and for the 3D IR acquisitions was 32.5 minutes (figures 2(c), 3(a)) and 45.9 minutes (figures 3(c), 4(b)).

CT scans were obtained on a General Electric 8800...
RF Pulses

Nuclear Signal

Spin echo

\[ t_1 \]

\[ t_2 \]

\[ \tau \]

Figure 1. The data of figure 2 (b) were obtained with a "saturation-recovery" type pulse sequence (a) with interpulse intervals set to: \( t_e = 15.4 \text{ms} \); \( \tau = 268.4 \text{ms} \). All "inversion-recovery" data were obtained with the pulse sequence shown in (b). For the images of figures 2 (c) and 3 (a), the timing parameters were set to: \( t_e = 8.6 \text{ms} \); \( \tau = 400 \text{ms} \); \( t_b = 426 \text{ms} \). For the data of figures 3 (c) and 4 (b), the following parameters were used: \( t_e = 8.6 \text{ms} \); \( \tau = 341 \text{ms} \); \( t_b = 825 \text{ms} \).

scanner without contrast enhancement. A slice thickness of 1.0 cm was selected.

Case Report

This 84-year-old man with chronic intermittent atrial fibrillation sustained a left temporoparietal cerebral infarction eight years previously. His dysphasia and right hemiparesis improved to near normal within two years of the presumed embolic infarct. He had no further embolic phenomena while being treated with warfarin. However, because of frequent falls, warfarin was discontinued in 1979.

On the day of his final admission he had been found in bed stuporous with a left hemiplegia. His head and eyes tended towards rightward gaze, but he maintained full extra-ocular movements on doll’s head maneuvers. He would answer questions only with "ah" but did raise his right hand to command. There was a flaccid left hemiplegia involving face, arm and leg, and moderate residual spastic right hemiparesis. The patient progressed from stupor to coma and expired 74 hours after the onset of his massive embolic right hemispheric infarction.

NMR, X-ray CT, and Pathology Findings

The first CT scan (figure 2(a)), obtained 12 hours after ictus, clearly evidences the old left posterior infarct, but the recent right parietal infarct is not apparent. Saturation-recovery (figure 2(b)) and inversion-recovery (figure 2(c)) NMR imaging studies were obtained six hours later. The SR images at corresponding levels also demonstrate the old lesion. The IR study, in addition to the old lesion, shows extensive areas of heterogeneously-decreased signal intensity on the cortical surface and in the temporal and parieto-occipital lobes in the distribution of the middle cerebral artery.

The 18-hour IR NMR data (figure 2(c)) were reformatted (figure 3(a)), this time to match X-ray CT sections obtained at 48 hours (figure 3(b)). The CT now shows an extensive region of homogeneously diminished attenuation in the right hemisphere, while the IR images (figure 3(a)) show variations in tissue signal within the area of infarction. This orientation of the 18-hour IR data better demonstrates the pathology than does that of figure 2(c).

The images of figures 3(c) and 4(b) were reconstructed from a second IR data acquisition obtained postmortem. The coronal reconstructions of figure 4(b) were selected to correspond to coronal brain sections obtained at autopsy (figure 4(a)). The pathologic sections demonstrate a loss of brain substance and cyst formation consistent with the old left-sided infarct. The recent right-sided lesion shows loss of the gray-white junction. There is sparing of the right sylvian cortex within the massively infarcted right hemisphere. There is good correspondence between the IR...
FIGURE 3. In NMR sections (a) from same data set as Fig. 2 (c) now re-oriented to match CT scan sections obtained at 48 hours (b). Infarct-related changes evident at 18 hours by NMR are now also detected by CT. Postmortem IR NMR images were also obtained (c) for subsequent correlation with pathology.

NMR data acquired at 18 hours post ictus and postmortem, and the autoptic specimen.

Discussion

The pixel values in X-ray CT reflect the local values of the X-ray absorption coefficient. NMR image intensity, on the other hand, depends on several NMR parameters inherent to the signal-emitting nuclei. In proton ('H) NMR imaging, the most important parameters from a diagnostic point of view are the proton density (p), and the proton spin-lattice (T1) and spin-spin (T2) relaxation times. These parameters depend on the physicochemical environment of the nuclei within the tissue, and are therefore sensitive to subtle changes in tissue composition and structure. It was therefore anticipated, well before clinical imaging instruments were available, that NMR might provide a more sensitive means than X-ray techniques for differentiating between diverse normal and abnormal tissues.

Although still in an early stage of clinical trials, NMR appears to offer a greater sensitivity than X-ray CT for detecting demyelinating disease and low grade tumors, some of which may not be visualized on CT even after administration of double doses of iodinated contrast materials. Although contrast agents may also play an important role in NMR, as they do in CT studies of certain pathologies it is possible to obtain a remarkable degree of soft tissue contrast resolution by virtue of the significant relaxation-time differences inherent to the tissues. The extent to which such variations in relaxation parameters are exhibited in the NMR image depends on the particular RF pulse sequence used. For example, the inversion-recovery pulse sequence can provide an astonishing degree of discrimination between gray and white matter in the brain.

Some of our early experimental in vitro studies, directed towards the detection of ischemic stroke by NMR, indicated that T1 and T2 of affected cerebral hemispheres increased significantly in symptomatic

FIGURE 4. Sylvian cortex is relatively preserved amidst the extensive right hemispheric infarct noted on the coronal brain sections (a). There is good correspondence between postmortem IR NMR images (b) re-oriented from the same data set shown in figure 3 (c).
gerbils as early as two hours post ligation of the carotid artery.\textsuperscript{10} Such parametric alterations were responsible for early changes of intensity in in-vivo NMR images.\textsuperscript{2,11} Sensitivity to tissue ischemia and infarction was also noted in the cat brain.\textsuperscript{12} These experimental data were obtained using the steady-state-free-precession (SSFP) pulse sequence, in which the image intensity is a complicated function of $p$, $T_1$, and $T_2$. In this case, $T_1$ and $T_2$ enter the equation as a ratio, and interpretation of SSFP data is especially difficult. Saturation-recovery and inversion-recovery pulse sequences in general present rather fewer interpretational difficulties, since the data are more amenable to quantitative analysis.

The image intensity functions for the SR and IR pulse sequences, as defined by equations 1 and 2, are plotted versus $T_1$ in figure 5. Curves are drawn (solid lines) for the conditions $T_1/T_2 = 1$ and $T_1/T_2 = 5$; the majority of tissue protons contributing to image intensity will have $T_1/T_2$ ratios within this range (shaded portion of graphs). (The ratio $T_1/T_2$ can never be less than unity.) The broken lines in figure 5 show how the image intensity would vary with $T_1$ if free induction decays following the 90° pulses, rather than spin echoes,\textsuperscript{13} were used to generate the images. In the case of the SR pulse sequence, this corresponds to setting $T_1 = 0$ in equation 1, which then reduces to:

$$S_{SR} = kp(1 - e^{-T_1/t_1}).$$

(3)

This is the more familiar expression for image intensity in SR.\textsuperscript{8} The more common expression for IR images is:

$$S_{IR} = kp(1 - 2e^{-T_1/t_1}),$$

(4)

which is obtained from equation 2 again by setting $t_1 = 0$ and, in addition, by ensuring that the repetition interval $t_e$ of the pulse sequence is very long compared to the maximum $T_1$ value of the sample (typically, $t_e \gg 5(T_1)_{max}$).

(Equations 1 through 4 are generally considered valid only for $T_1 \ll T_e$, since then unwanted refocusing of magnetization by successive RF pulses is avoided. In our case, however, such refocusing is avoided by application of magnetic field gradients.)

For both of these pulse sequences, the $T_1$ contrast may be altered by changing the interpulse delays $t$ and $t_e$. For example, the differential contrast observed between the IR images of figures 3(a) and 3(c) is due mainly to an alteration in interpulse intervals, rather than to any postmortem tissue changes. However, this latter effect cannot be ruled out completely, especially as far as flow and motion effects are concerned.\textsuperscript{12}

The effect of employing spin-echoes to acquire the data is to reduce the signal intensity in general, but especially in regions characterized by short $T_1$ relaxation times. The degree of $T_1$ contrast may be minimized by reducing the 90°–180° pulse interval, $t_e$. A more serious consequence of using spin-echoes to acquire $T_1$-weighted data is that the image intensity no longer decreases monotonically with increasing $T_1$ (solid curves, figure 5). This is in contradistinction to the image intensity functions obtained when spin echoes are not used (dotted curves in figure 5). Thus, for example, pathologies for which $T_1$ and $T_2$ are both elevated compared with their normal tissue counterparts may not be visualized in a single study. This is because the decrease in intensity due to a prolongation of $T_1$ may be offset by an increased signal strength due to the concomitant $T_1$ elevation. Fortunately, this problem may be overcome by obtaining additional images with different pulse sequences or with different timing parameters. Thus, in the patient reported here, the recent, right hemispheric infarct which was not seen on the 18 hour SR study (figure 2 (b)) was readily apparent on the 18 hour IR study (figure 2 (c)). Other factors also play a role, however: several institutions\textsuperscript{4,14} have noted an inferior detection sensitivity for SR as compared to IR which may be largely a result of the lower dynamic range obtainable from the SR pulse sequence.\textsuperscript{15} Notwithstanding, the inherently faster data acquisition rate of the SR pulse sequence allows generation of higher spatial resolution images than does the IR sequence, for equal imaging times. Thus, SR is particularly useful for the accurate depiction of abnormalities which alter the physical shape or size of organs.

The IR images of figures 2–4 show the recent stroke in this patient as an area of heterogeneously reduced signal intensity. In general, as discussed above, such an effect may be ascribed to either local elevations of $T_1$, reductions in $T_2$, or depressions of spin density.
However, the last two parametric alterations might be expected to produce regions of decreased intensity on the SR scan also, and this was not found to be the case (figure 2 (b)). Thus, the abnormally low signal intensity in the right hemisphere of the IR scans is most probably a result of a prolonged $T_1$. In concurrence with this conclusion, we have documented that elevated $T_1$ and $T_2$ relaxation times accompany the early tissue changes associated with ischemic stroke.\(^8\)

Subsequent to these studies, the implementation of other pulse sequences has provided us with the facility for obtaining quantitative, \textit{in-vivo} $T_1$ data.\(^6\) Further, images which preferentially emphasize or quantitate $T_2$ may be obtained by using significantly longer delays $t_e$.\(^4\) Such advances may be of help in the bid to characterize tissue and disease by virtue of their inherent NMR parameters.

X-ray CT, whilst immensely valuable in diagnostic medicine, has the significant drawback that only transverse or oblique transverse planes may be obtained, as a result of the mechanical nature of the scanning procedure. Thus to obtain coronal or sagittal views, useful in general diagnosis and for many specialized procedures (stereotactic biopsy; radiotherapy planning; etc.), it is necessary that many closely spaced planes be acquired, and the data re-formatted appropriately. The fact that no mechanical motion is required to acquire NMR image data (the magnetic field gradients are rotated electronically) means that single two-dimensional sagittal or coronal tomograms may be selected at will prior to starting the scanning procedure.\(^17\) However, it is only with true three-dimensional imaging technology that sagittal, coronal, transverse or oblique planes may be selected for display after data acquisition is complete. This obviates the necessity of precise patient positioning, and ensures the possibility of accurate correlation with other imaging modalities.

Although the total data acquisition time for a true 3D study is usually rather longer than that of a single-slice 2D study, an extremely large number of 2D views can be reconstructed at leisure from the former data set, and the imaging time \textit{per plane} is therefore much reduced. Indeed, 3D imaging represents the most efficient way to acquire NMR data.\(^18\) In addition, 3D data presents the possibility of employing surface detection algorithms,\(^19\) enabling the determination of the volume of lesions and organs. In the head, therefore, where involuntary motion frequently is not problematical, we have found that true 3D imaging is almost always the preferred mode of data acquisition. Some decrease in the data acquisition time and/or increase in spatial resolution can be expected with the use of higher magnetic fields and other advances in instrument design.

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