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Nuclear Magnetic Resonance Imaging*

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Abstract

The principles of two new techniques of medical physics, nuclear magnetic resonance (NMR) imaging and topical magnetic resonance, are outlined. Progress in the development of these techniques and their application in clinical trials is reviewed. Advantages of NMR methods over existing imaging modalities are discussed. Finally some safety aspects are considered.

1. Introduction

Recently, considerable interest has focused on two new nuclear magnetic resonance (NMR) techniques which show great promise in both medical research and clinical applications. These are NMR imaging (spin mapping) and the related technique of topical magnetic resonance (TMR). Work to date has demonstrated that the NMR imaging method can distinguish detail in living tissue which is difficult or impossible to visualize by established imaging methods such as X-ray computed tomography (CT) or ultrasound. In addition it avoids the problems of exposure to ionizing radiations and may reduce the necessity of using artificial contrast agents in some applications, while in others it may facilitate the development of new and more specific agents for discriminating between different pathological conditions with greater accuracy and without the need for surgery or conventional biopsies. TMR has the potential to provide biochemical information of significance in evaluating the state of a given organ or tissue in a non-invasive manner. If clinical trials, already under way or planned, live up to their initial promise, both modalities may complement information available to clinicians from established techniques of medical physics currently employed in radiology and nuclear medicine.

2. Principles of NMR Imaging

In conventional NMR considerable care is taken to ensure that the applied steady magnetic field is uniform, in order that small chemical shift differences may be resolved. Thus nuclei in identical chemical environments will resonate at the same frequency whatever their position in the sample. Conversely spatial discrimination can be achieved by deliberately applying a field gradient across the sample (see Fig. 1). As a result, ignoring small chemical shift differences, nuclear spins

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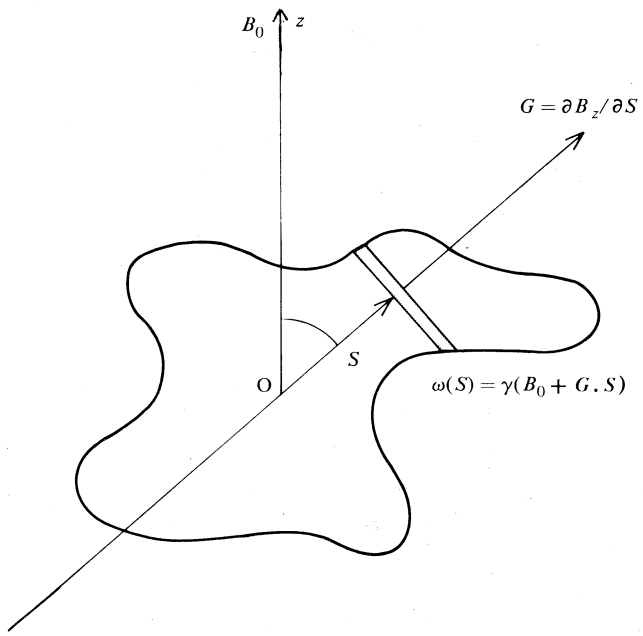

Fig. 1. In the presence of a magnetic field gradient G, nuclei in different slices of the sample, perpendicular to the gradient direction, precess at different frequencies.

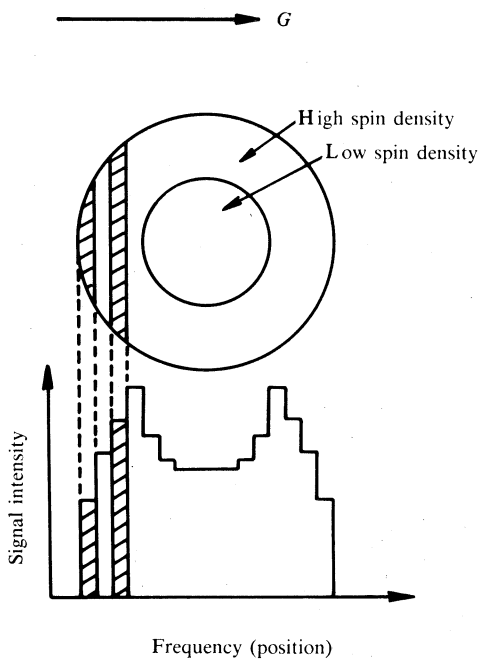

Fig. 2. Schematic spin density projection profile for an inhomogeneous sample comprising an annulus of high spin density (e.g. soft tissue) surrounding a region containing a low density of mobile spins (e.g. bone).

in layers of the sample perpendicular to the gradient $\boldsymbol{G}$ will experience the same total field

$$B = B_0 + \boldsymbol{G}.\boldsymbol{S}$$

and will resonate at the same frequency, but different layers will experience a different resonant frequency dependent on their position $\boldsymbol{S}$. The strength of the NMR signal at a given frequency will depend on the number of resonant nuclei in the appropriate layer so that the NMR spectrum represents a projection of the spin density in the sample onto the magnetic field gradient direction (Fig. 2).

Table 1. Nuclei used in NMR imaging
All nuclei have a spin of $\frac{1}{2}$

Nucleus	Nat. abund. (%)	Rel. sens.[A]	Freq. (MHz)[B]	Chem. shift range (ppm)	Signal source[C]	Rel. concn[D]
^{1}H	100	1·0	42·6	12	water, fat	1·0
^{13}C	1	$1{\cdot}8\times10^{-4}$	10·7	350	fat	$\sim10^{-2}$
^{31}P	100	$6{\cdot}6\times10^{-2}$	17·2	700	ATP, PCr, P_i[E]	$\sim10^{-3}$–10^{-4}

[A] Relative sensitivity at constant field.
[B] Frequency in a field of 1·0 T.
[C] Main source of signal in biological tissue.
[D] Approximate relative concentrations of NMR 'visible' constituents.
[E] ATP adenosine triphosphate, PCr phosphocreatine, P_i inorganic phosphate.

In biological tissues the most abundant NMR nuclei are protons. Since these give a strong signal they have been employed almost exclusively in NMR imaging. The main source of protons in tissue is water, with a significant contribution also from fats (Table 1). It should be noted that, as a result of instrumental factors, only nuclei incorporated in mobile molecules contribute significantly to the recorded signal. Thus bone gives a very weak signal while differences in signal intensity between different tissues largely reflect differences in free water content.

All NMR imaging techniques (of which there are now many variations) employ magnetic field gradients to provide spatial discrimination of the signal from different parts of the subject. They differ in the manner in which this information is recorded and used to construct the final image. In the original method described by Lauterbur (1973) projections of the proton density in the sample are recorded for a large number of gradient directions, and the image reconstructed by 'back projection'. Any of the reconstruction algorithms currently employed in X-ray CT can be employed for this purpose (see e.g. Brooks and Di Chiro 1976). Significant variations on this method include sensitive point imaging developed by Hinshaw *et al.* (1976), selective excitation techniques pioneered by Garroway *et al.* (1974) and Fourier imaging by Kumar *et al.* (1975). The sensitive point technique relies on the fact that if a linear field gradient applied to the sample is reversed there will be one plane for which the total field remains unchanged. Thus if three orthogonal time-dependent gradients are employed there will be a single small volume at the intersection of these 'null planes' for which the magnetic field and hence NMR signal frequency is time independent. Suitable filtering removes signal contributions from all other parts of the sample, and image formation therefore simply involves scanning the sensitive point through the region

of interest. In contrast, selective excitation methods employ 'tailored' r.f. pulses of well defined bandwidth which, in the presence of a suitable magnetic field gradient, excite only those nuclei in a limited and well defined region of the sample. Some of the most successful methods employed to date in human whole body and head imaging have utilized a combination of these techniques, together with Fourier transformation to convert the free induction transients to the frequency domain (Edelstein *et al.* 1980; Holland *et al.* 1980; Doyle *et al.* 1981).

Thus the basic instrumental requirements for human whole body scanning or head imaging are a large magnet to provide a uniform steady magnetic field B_0 over the region of interest, ancillary coils for generation of the magnetic field gradients and for production of the r.f. field $B_1(t)$, gradient coil power supplies, a high power NMR spectrometer and a minicomputer for control of the spectrometer and field gradients, signal acquisition and averaging and image reconstruction. Imaging magnets for human subjects are generally of the solenoid type. Both resistive and superconducting magnets have been employed. Superconducting magnets can generate higher magnetic field strengths leading to improved signal to noise ratios and shorter imaging times, but the field strengths which can be employed in human whole body imaging are severely limited by r.f. penetration into the tissue. This restricts operating frequencies to below 6–8 MHz corresponding to magnetic field strengths for protons in the range 0·15–0·20 T.

3. Advantages of NMR Imaging

In addition to the absence of ionizing radiations, NMR imaging offers a number of other advantages over established imaging modalities. It suffers from neither the 'beam hardening' effects of bone which can affect X-ray CT, nor the acoustic mismatch and attenuation problems produced by air (in the lungs and bowel), bone and fat which limit the range of applicability of ultrasound scanning. It eliminates the need for mechanical moving parts (the direction of the applied field gradient can be varied electronically using fixed gradient coils), while allowing complete freedom of choice of the image section. Thus coronal and saggital sections of the human head have been demonstrated without the need for multiple plane imaging and extensive data reprocessing (Holland *et al.* 1980).

Table 2. NMR T_1 relaxation values for rabbit tissues at 2·5 MHz

Tissue	T_1 (ms)	Tissue	T_1 (ms)	Tissue	T_1 (ms)
Liver	141	heart ventricle	243	lower lung	303
Skeletal muscle (thigh)	182	spleen	258	grey cerebral tissue	332
Skin (fur removed)	198	white cerebral tissue	264	kidney medulla	426
Kidney cortex	206	upper lung	283		

Perhaps more importantly, the intrinsic contrast between different organs and soft tissues is greater than that found with X-ray methods, since differences in water content for such tissues ($\sim 15\%$) are greater than the corresponding electron density variations. These differences are further enhanced if NMR techniques are employed which render the signal intensity sensitive to the spin-lattice relaxation time T_1. This parameter has been shown (Ling *et al.* 1980) to vary by a factor of ~ 3 at 2·5 MHz between different organs and soft tissues in the rabbit (see Table 2). Recently

a number of human whole body and head images employing this technique have appeared in the literature. These results demonstrate excellent intrinsic contrast, facilitating the resolution of white and grey matter in the brain and the identification of tumours without the need for artificial contrast agents (Doyle *et al.* 1981; Smith *et al.* 1981). The ability of NMR to discriminate between tumour and normal tissue, as a consequence of a significant difference in T_1, was first demonstrated by Damadian (1971), although it would appear that such differences probably stem from differences in free water content and are common to both malignancy and benign neoplastic and oedemous tissue.

NMR 'T_1' images are also very sensitive to fluid flow. Thus major blood vessels can be identified with excellent contrast in such images (Edelstein *et al.* 1980). Since the NMR signals can be rendered sensitive to both the magnitude and spatial distribution of flow rates (Garroway 1974), the possibility exists of measuring blood flow rates in NMR images, an application of potential significance in the study and treatment of heart disease, circulatory disorders such as atherosclerosis, and stroke.

Thus, although the resolution of NMR images at present is inferior to that of X-ray CT, its improved contrast often results in images which contain more useful information. While imaging times are also currently longer (typical imaging times are presently around 1–3 min), these can be expected to improve by an order of magnitude. However, it is unlikely that high resolution real time NMR imaging will develop as a competitor to ultrasound in the foreseeable future.

4. Topical Magnetic Resonance

Topical magnetic resonance is a development stemming from ^{31}P NMR experiments on perfused organs and tissues from animals carried out during the 1970s (Gadian *et al.* 1979). These studies showed that the ^{31}P NMR spectra from living tissues are relatively simple to interpret and contain information of considerable biochemical significance. In general the major peaks arise from adenosine triphosphate ATP, phosphocreatine PCr and inorganic phosphate P_i, with smaller contributions from adenosine diphosphate ADP, sugar phosphate and nicotinamide adenine dinucleotide NAD. Other phosphorus containing metabolites occur at too low a concentration or in an insufficiently mobile form to produce an appreciable contribution to the spectrum. Thus the spectra contain information on the relative concentrations of these metabolites in free solution *in vivo*. Additionally the frequency of the inorganic phosphate peak relative to the other major peaks is a sensitive measure of intracellular pH. Recently Nunnally and Bottomley (1981) have applied such methods to a study of regional ischaemia in a rabbit heart.

In order to extend such techniques to non-invasive measurements on whole animals and humans it is necessary to confine the sensitive region from which the NMR signal is derived to a single organ or tissue within the overall sample volume. The simple artifice of employing linear magnetic field gradients as in NMR imaging cannot be used here, since this would broaden the spectrum from the region of interest to such an extent that individual peaks could not be resolved. The problem can be partially overcome by the use of small 'surface coils' for application of the resonant time-dependent field $B_1(t)$ and detection of the signal. These are simply attached to the skin of the subject over the region of interest giving some spatial selectivity. Indeed it is necessary to employ such coils in human TMR. Coils large enough to

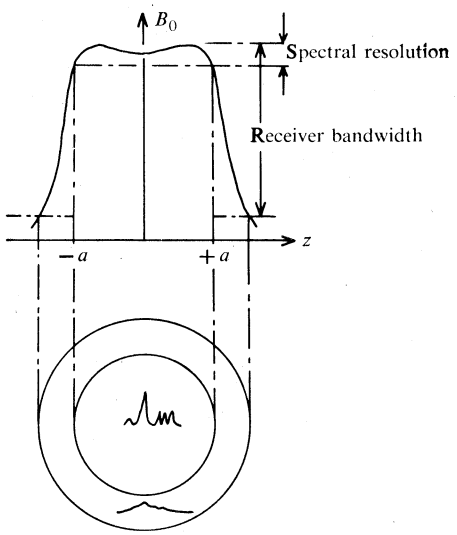

Fig. 3. Typical field profile employed to provide spatial discrimination in TMR. [Courtesy of Oxford Research Systems.]

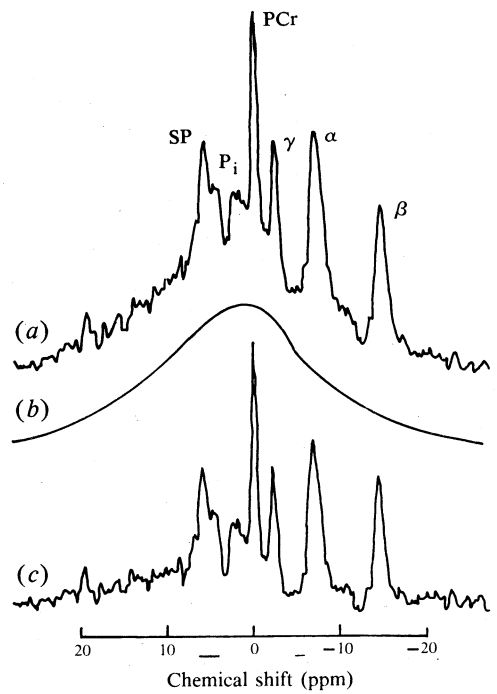

Fig. 4. Typical ^{31}P TMR spectrum: (*a*) Raw data; (*b*) spectrum broadened by exponential multiplication; (*c*) difference spectrum (*a*)−(*b*). [Courtesy of Oxford Research Systems.] Note the peaks due to ATP (α, β, γ), phosphocreatine (PCr), inorganic phosphate (P_I) and sugar phosphate (SP).

accommodate even a human limb cannot be tuned to the high frequencies necessary to provide adequate signal and dispersion of the chemically shifted peaks. (Typical magnetic field strengths for TMR are an order of magnitude higher than those necessary for imaging.) Further spatial selectivity can be achieved by tailoring the profile of the steady magnetic field B_0, so that it is very uniform over the region of interest but varies rapidly over adjacent regions (see Fig. 3). In this respect the method is analogous to an early version of NMR imaging due to Damadian *et al.* (1976). The high resolution spectrum from the region of interest is then superimposed on a broad background which can be subtracted off by the technique of 'convolution difference' (Fig. 4).

To date the method has been employed in studies of human limbs and animal organs (Ackerman *et al.* 1980; Gordon *et al.* 1980; Ross *et al.* 1981). It may prove of great value in studies of peripheral vascular disease and the efficacy of drug therapy in the treatment of localized ischaemia. Other potential applications include assessment of whole organ transplant viability and monitoring following transplantation. Recently ^{1}H and ^{13}C TMR spectra have been demonstrated and shown to provide a means of monitoring tissue fat content (triglyceride and lipid), providing information of potential value in the study and treatment of muscular dystrophy.

5. Safety Aspects and Conclusions

A consideration of paramount importance in considering any new imaging technique is its safety. While only limited experience has been gained so far with NMR imaging of human subjects, all the indications suggest that it is a very safe method (Budinger 1981). At the power levels employed in NMR, the rate of dissipation of energy in the body tissues is unlikely to exceed the basal metabolic rate. For exposure periods of perhaps 10 min the body can easily handle this additional heat load, although in the vicinity of implanted metal objects and prosthetic devices local heating could prove more serious. Similarly, considerable experience exists of human exposure to steady magnetic fields in the range 0·1–1·0 T for long periods without any appreciable side effects. Perhaps of more concern is the effect of rapidly switched magnetic field gradients employed in some imaging techniques. Fortunately a number of imaging methods for both whole body (Edelstein *et al.* 1980) and head (Holland *et al.* 1980; Doyle *et al.* 1981) scanning have been developed which avoid the use of very rapid gradient switching. However, it can be anticipated that an extensive program of clinical trials will be necessary before NMR techniques can be introduced at a more general level.

In summary, NMR has the potential to provide information which is difficult or impossible to obtain by other methods, at reduced risk and without discomfort to the patient. In addition the promise of *in vivo* monitoring of tissue biochemistry may reduce the need for time consuming and costly biopsies and lead to improved techniques for evaluating drug therapies and the progress of organ transplants.

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