Medical applications of nuclear magnetic resonance

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Summary

A review of the principles, current applications and possible directions for future use of nuclear magnetic resonance in medicine is presented.

Nuclear magnetic resonance (NMR) imaging now regularly provides complete preliminary clinical articles in several respected radiological journals rather than simply headlines, so at this stage of its development a review of its properties and possibilities seems appropriate. This imaging procedure has already been applied to many organs, systems and conditions. Digestion and evaluation of the increasing flow of results is proving to be very exciting. It may seem that the current situation is like the very early days of particle accelerators when Rutherford arrived every morning at the Cavendish Laboratory and said ‘What element shall we put in the beam today, chap?’ (C. H. Collie — personal communication). But current NMR imaging results are not entirely haphazard answers to the question ‘What organ/system/disease state shall we look at today, chap?’ If we can understand some of the principles involved in medical imaging using NMR, the advantages and limitations and hence the role of this novel procedure can be appreciated better. NMR imagers are only available in a few locations today, but within the next few years they seem destined to become as sought after as computed tomography (CT) scanners.

NMR imaging is novel and even its terminology remains unsettled; numar and zeumatography have been proposed, but with little acceptance. Radiologists are likely to be more successful with their wish to alter its name to magnetic resonance. The basic principles of NMR were first described as recently as 1946 and it was subsequently employed as an important tool for laboratory investigations in physics and chemistry, yet the first crude images were produced only in 1973. Further, the principle it uses differs so radically from those of other techniques employed for medical imaging that it seems logical that the information provided by NMR is often not otherwise available. Most NMR images consist of signals derived from hydrogen nuclei. These signals can give information about numbers of atoms and also about the chemical form of the hydrogen and its macroscopic movements, thermal or otherwise.

The ‘nuclear’ part of NMR

Atomic nuclei can each be considered collections of very small magnets which are their protons and neutrons (i.e. nucleons). These identical magnets rotate rapidly and tend to cancel out total magnetic effects by aligning in pairs. If an odd nucleon remains unpaired, the complete nucleus can be affected by magnetic fields, for it then has a net magnetic effect. Protons, or nuclei of normal hydrogen (1H), are very common in living material, which usually contains over 65% of H2O. These protons can interact with applied magnetic fields. So far NMR has been mainly concerned with 1H, although 31P and 13C have also been investigated. Yet there are other nuclei (15N, 17O, 19F, 23Na, 25Mg, 31K, 41Ca) which in principle are also capable of detection by NMR. They are far more difficult to observe, because their concentrations and/or magnetic effects may be extremely small, but in time isotopes of C, F, P and Na may provide as much information as protons.

The ‘magnetic’ part of NMR

When in an external magnetic field (B), magnets in nuclei do not behave like ordinary magnets. ‘Nuclear magnets’ can only be placed at fixed angles with respect to the direction of B and they must hop between these allowed alignment positions if they absorb or emit energy. A further complication is that they are simultaneously spinning around the direction of B (Fig. 1). Each of these allowed alignments is associated with a fixed energy level. This is somewhat analogous to the atomic quantized energy states of the electron in a simple atomic model.

![Fig. 1. The nucleus spins rapidly around its axis (A1 or A2). This axis also rotates about the direction of the magnetic field. B. However, only certain fixed positions of the axis with respect to B are allowed (in this case two such inclinations, A1 and A2).](image-url)
currents can flow. The added complexity of the magnet cooling is compensated by reduced electricity costs and a resulting field that is more uniform and stable than those available from the more usual resistive coils operating at room temperature. The advantages may prove of great importance.

The 'resonance' part of NMR

The essence of NMR for our purposes is the possibility of jumping between those few allowed alignments by the nuclear magnets when a magnetic field is present. A radiofrequency (RF) signal can provide exactly the energy required to enable nuclear magnets to jump up to a higher energy level (say from A1 to A2 in Fig. 1). When the RF is switched off, they jump down again and emit a well-defined and reproducible amount of energy. This is the resonance. The RF frequency (f) is very precisely defined by a simple relation, f = GB (equation 1). G is a constant which depends on the nucleus under study. The sequence of events described is similar to that in the Bohr model of the atom when radiation is emitted after an electron moves up to a higher orbit (and cannot stop on the way) and then returns, again without stopping, to its original low-energy orbit, so giving out a most precise quantum of energy. Information about the detected resonance includes its amplitude, frequency (to less than 1/100) and two relaxation times, T1 and T2. These are related respectively to the rapidity with which it loses energy to its immediate surroundings (T1, the spin-lattice relaxation) and to the time permitting the rotation of the different nuclei about B to become unsynchronized (or, more simply, out of step). This is T2, the spin-spin relaxation. The latter is due to tiny variations in B and interactions between different nuclei.

NMR images

At least four different types of information can be presented in an NMR image. We can examine proton-density maps of the human body by examining resonant signal strength. In particular relatively 'mobile' hydrogen atoms can be seen in water and fat. Proportions of water content between different normal soft tissues can vary by up to about 15%. Hence the easy differentiation between various tissues is a basic advantage of NMR over all radiological imaging techniques. Very striking images clearly demarcating grey and white cerebral matter well illustrate this point (Fig. 2). Bone, which contains relatively little water, gives low-amplitude NMR signals; hence regions close to bone suffer neither distortion nor reduced contrast. NMR can therefore be used to study sensitive regions which may be close to bone, such as the cerebral surfaces, the base of the brain and the spinal cord (Fig. 3), another important advantage.

Mappings of T1 and T2 as well as of proton density are possible. For some purposes various combinations of these quantities prove more informative than any one alone. The ratio (T2/T1) is near unity if the hydrogen is in a liquid-like environment. This ratio decreases as thermal motion decreases and the surroundings are more akin to a solid.

Finally, movement of physiological fluids is also shown and there are methods for quantitating flow.

Very accurate measurement of frequency is technically possible; hence for high resolution with little noise, variations in B must be small, since equation 1 shows resonant frequency to be directly proportional to the magnetic field. From these simple facts arises the most difficult and expensive problem in providing good-quality NMR images. Obtaining homogeneity of the magnetic field in which the subject lies to within the required limits is not easy. A substantial fraction of the costs of NMR imaging equipment likely to become available in the future.

Fig. 2. Coronal slices are shown from a cerebral NMR image. White and grey matter are clearly distinguished. Also the skull gives virtually no signal.

Fig. 3. An NMR image of the base of the brain and the upper spinal cord.
near future stems from stringent limitations on the magnetic field. However, the building up of an image from different regions of the subject's body requires a further varying field to be added to the constant field described above. The additional magnetic field usually varies smoothly in a known fashion with distance. If there is only one such extra field steadily increasing from the patient's head to his feet, then there is only one plane through the patient in which the total B has exactly the value required for resonance to occur, as defined in equation 1 (Fig. 4). In this way NMR signals are detected only from one region at a time and so the total three-dimensional image is built up. The region from which signals come is moved in a controlled fashion throughout the patient's volume. Different combinations of space-varying magnetic fields, added to the main constant field, can allow the zone examined at any one time to be a point, a line or a plane. The greater the volume examined at a time the faster the total image is created, if resolution can be maintained. Current research is directed towards speeding up the acquisition of data. The total image is built up from elements of volume selected by variations of sequences of RF pulses as well as the additional magnetic fields. Details of the different methods are very complex, but by increasing the region under investigation at a given instant from a point to a line to a plane, rapidity in obtaining the final image has increased significantly.

Fig. 4. A plot of the magnetic field is shown, which steadily increases from the patient's head to feet. At X alone is this field equal to B, so satisfying equation 1. Hence resonance occurs only in the transverse plane P. Nuclei in plane P but no other nuclei are imaged (unless there are perturbations of the magnetic field which would allow resonance, and hence imaging, to occur out of plane P).

Hazards of NMR

Potential dangers of any new procedure, to which patients and medical staff are subjected, are a most important consideration. This principle is reinforced for the medical profession by a monument in the St Georg Hospital, Hamburg, on which are inscribed over 200 names of those persons known to have died as a result of the overenthusiastic and indiscriminate use of X-rays in the few years after their discovery. It seems virtually certain that no such monument will ever be required after NMR becomes a commonplace medical procedure. On the earth's surface there is a magnetic field which varies with geographical location, and it has known deleterious effects. Those constant fields proposed for NMR imagers are $10^{-6}$ - $10^{-5}$ times greater, and detailed investigations of possible adverse effects of NMR are necessary. Some have already been extensively studied. These include the heating effect in living tissue of absorbed RF radiation and the consequences of steady and varying magnetic fields. The latter can induce voltages in tissues and parts of the body, and physiological electrical signals may already exist, such as muscle and nervous tissue. However, a large safety factor exists between the fields in use and a threshold for induced fibrillation.

Standards already exist which give an upper limit for deposition of heat in humans by RF. This heating is due to energy dissipation in the resistive part of tissues. It seems reasonable to prevent extraneous heat energy from exceeding the basic metabolic rate. No NMR device in existence, or under consideration, approaches this limit. Unchanging magnetic fields can perturb the function of proteins and normal enzymatic function can be upset in this way. Similarly these fields, if sufficiently large, can wreak havoc with the passage of ions and compounds through cell membranes. The controlling mechanism, although poorly understood, is associated with cell proteins. Animal experiments with steady magnetic fields have demonstrated protein malfunction, but again this takes place with field strengths far higher than those planned for NMR imaging. Blood moving through a region of constant magnetic field induces a voltage proportional to the vessel diameter and across its full width. This effect is used as a non-invasive flowmeter. Yet potentials across individual cells fall far short of the depolarizing thresholds, and in humans no effects have been detected in the ECG for static fields up to five times those likely to be used in future NMR tomography scanners. The voltages induced by varying magnetic fields can have striking effects. For over a century it has been known that a signal of 30 Hz applied to a human head in total darkness can cause visual hallucinations in the form of apparent flashes of 'light' or phosphenes. Fortunately similar effects at RF require far higher induced currents. Not unexpectedly, excitation of nervous or muscular tissue has never been reported in patients undergoing examinations with NMR, although the size of the eddy current loops is not well understood. Protection against commoner hazards such as electric shock, falling from an examination couch, etc., should not be ignored. Sharp ferromagnetic objects such as a nurse's scissors can be lifted, even at distances of 6 m from the magnet. This probably provides the worst recognized problem with NMR, apart from those patients with pacemakers or large metal implants for whom whole-body NMR imaging is usually not possible.

The dismissal of possible long-term complications such as teratogenicity or oncogenicity is not as easy as for the physical effects mentioned already, and no work has been done on possible synergism between them. However, careful follow-up of the few thousand patients who have already been studied with NMR does suggest that no sinister dangers associated with its use are so far apparent. Measurements with bacteria, various cell cultures and frog embryos have likewise failed to show any evidence of mutation after exposure to NMR fields. In Britain pregnant women may now receive NMR examinations after the first 3 months.

NMR and CT scanners

The imaging devices most similar to NMR are CT scanners. Comparisons between the two are often made, and indeed their costs, complexity, size and staffing needs may be similar. Also both can produce transverse slice images, but their
differences are much more significant than their similarities. Most importantly, NMR uses non-ionizing radiation and is particularly appropriate for many paediatric studies. Also, since it is based on physical principles unique in imaging it is reasonable to expect information to be provided that is not otherwise available.

Further differences must be emphasized. The regions displayed by NMR as images are selected electronically and so any plane can be presented (Fig. 5). Coronal, sagittal or other views are often more useful than transverse slices. No moving parts mean greater reliability and reduced upkeep costs compared with CT. Significant improvements in software and hardware have reduced imaging and processing times, and many procedures require comparable or shorter times than do those utilizing CT. Hearts can now be imaged in real time non-invasively. Current resolution is under 2 mm for static images and is likely to improve. Since bone signals with NMR are weak, adjacent structures are clearly seen (Fig. 6), but also bone erosion and calcification are poorly presented. Respiratory and bowel gas causes little problem and moving blood presents a readily identifiable image.

![Fig. 5. A sagittal slice from an NMR image of the lumbar and pelvic regions in a normal subject. Intervertebral discs are clearly seen.](image)

Running costs of most present-day NMR units which rely on resistive coil magnets include about R30,000 annually for electricity bills alone. Superconducting magnets keep a current flowing indefinitely but require complicated and expensive refrigeration, involving liquid helium.

All radiological images produced by conventional and CT means depend on the relative attenuation of X-rays by different tissues for their variations of contrast. This cannot easily be changed, although improvements in the most recent CT units allow some slight differentiation between cerebral white and grey matter.

NMR images which depend strongly on T₂ can show far higher contrast. By varying the different components contributing to an NMR image, the grey-scale order and other characteristics can be changed greatly to suit the observer's needs, unlike CT. Although this is one of the basic practical advantages of this modality, some knowledge of the principles involved in obtaining an NMR image will probably be essential to obtain optimal results from the first generation of commercial devices at least, for there is no agreement among different manufacturers and users with regard to image component parameters.

Most of our evaluation of NMR considers only its representation of the morphological features of different normal and pathological tissues; already advantages are clearly apparent. But its greatest benefits will probably come from functional investigations. In this way it has much in common with in vivo nuclear medicine.

Biochemical investigations have been made non-invasively in living tissue to detect one of ¹H, ³¹P or ¹³C. This procedure is sometimes called topical magnetic resonance (TMR), for surface-coil techniques can be used. Some current and projected whole-body imagers also have this facility. Relative quantities of molecules containing the nucleus and their variation in time can easily be measured. Different electronic surroundings of the nucleus provide signals which would indicate for ³¹P how much adenosine triphosphate, phosphocreatine, inorganic phosphate, sugar phosphate and phosphodiesters are present. Each species of molecule bathes the ³¹P nucleus in a slightly different magnetic field, and hence each NMR signal has a frequency characteristic of the molecule from which it originates. Relative amounts of the different molecules are related to the different signal amplitudes. Continuous biochemical analyses in vivo have been made on a human limb or a small animal's heart, brain, etc. under a variety of conditions including ischaemia, exercise and drug administration. Already this technique has allowed a diagnosis of McArdle's syndrome to be made by comparing the relative abundance of different molecules containing ³¹P, after exercise, in normal subjects and in a patient suspected of having the condition. Such biochemical or spectroscopic information is not available from CT.

**NMR imaging today**

The accomplishments of NMR imaging can form a long list of comparisons with other modalities, usually CT, but it is equally important to recognize those situations where the disadvantages of NMR exceed any advantages.
Ferromagnetic life-support systems, the cost of the study and claustrophobia (in 1 - 5% of patients) may all prevent use of NMR. Investigations of gallstones, small amounts of calcification, the larynx, the tongue base and the prostate gland are better done with X-rays. Also, NMR imaging is not suitable for patients with pacemakers or large metal implants. NMR shows most promise in investigating the central nervous system, heart and kidney.

There is no doubt that NMR is already the equal of CT for examination of the central nervous system and that in some respects it surpasses CT, in particular for the investigation of posterior fossa disease and demyelinating conditions. The different types of soft tissue, notably grey and white, are clearly distinguished and structures such as the basal ganglia, substantia nigra and cerebellar peduncles can be defined clearly. NMR has been shown to be very sensitive in recognizing head trauma and following up its sequelae.

Although the smaller brainstem nuclei usually cannot be resolved, this is liable to change with technical advancement. Even so, brainstem lesions are more readily apparent with NMR. Grey and white matter can be distinguished throughout the medulla and spinal cord, and some infarcts, haemorrhages and inflammations not recognizable with CT have been demonstrated clearly by NMR. Another most striking advantage concerns the recognition of myelin. Both demyelinating diseases and the process of postnatal cerebral myelination can be studied in much greater detail by NMR than by other means. However, there is current uncertainty over the role of NMR in the investigation of brain tumours. Some reports suggest that NMR may be superior to CT and others that it may confuse tumour and peritumoral oedema.

Blood in cardiac cavities can readily be distinguished from myocardium and an 8 mm slice of 32 pixels has been obtained in 35 ms, so ventricular motion need not cause artefacts. Lungs and bones give no problems, unlike the case with ultrasound, and identification of infarcts by NMR is superior to that with 201Tl tomography. Coronary arteries can be seen and there is a clear difference between flowing blood and atherosclerotic lesions. Thrombotic filling defects and left ventricular wall thickness can be recognized. The optimist equates this to a combination of the best aspects of cardiac catheterization and nuclear medicine investigation, but obtained non-invasively and without injections (Fig. 7).

In renal investigations NMR usually gives better results than CT (with or without contrast medium) and provides better spatial resolution than ultrasound. A distended ureter can be seen clearly in the absence of excretion. With a paramagnetic contrast medium NMR can quantify kidney function. Acute renal failure is recognizable from a different T1 in renal parenchyma. Renal tumour, thrombus, carcinoma and cysts can all easily be observed with NMR, the latter better characterized than with other modalities.

With further studies NMR has also shown many advantages, especially in investigating soft tissues, fluids and regions near to bone. Adrenal medulla and cortex may be differentiated, as can the parts of a lumbar disc, marrow infiltration, vessel invasion and compression and small lymph nodes with metastatic deposits not recognizable otherwise.

The future

NMR imaging seems here to stay. Its advantages, already considerable, are likely to increase and so it is not surprising that over 80 units are installed or on order in Europe alone (in early 1984). In one small US city (population 66,000) approval for two NMR scanners has already been granted. Climbing on a bandwagon must be resisted, but for the investigation of certain problems NMR is already the best modality.

NMR is unlikely to replace most other imaging methods, in spite of excessive enthusiasm in certain quarters. The complementary nature of its contributions is the most pressing topic which requires investigation, as part of the fullest evaluation of the information which it can provide. The present impression of an extremely sensitive but relatively nonspecific diagnostic modality may change as further refinement of its in vivo biochemical properties comes about, imaging of several elements becomes possible with a single machine, and paramagnetic species are investigated. These ions and compounds give a strong signal in NMR images and they function both like the gamma-emitting part of a radiopharmaceutical and like an X-ray contrast medium. The ions of Mn, Cu, Cr, Fe and Gd show great promise and can be chelated to a wide range of molecules ranging from ethylenediamine tetra-acetic acid to monoclonal antibodies. Other species, such as O2 and nitrooxide-stable free radicals, are likely to become as indispensable as their X-ray and scintigraphic counterparts.

The main effort devoted to NMR in the short term will be to determine: (i) optimal sequences of magnetic field variations and RF signals; (ii) the optimal type of magnet and its field strength to be used; (iii) the relative roles of spectroscopic analysis and imaging in the same machine; and (iv) the place of paramagnetic species.

This review is necessarily short and selective, but it attempts to convey something of contemporary excitement about NMR, what it has attained non-invasively and without ionizing radiation, and more importantly where work remains to be done. The different concentrations and molecular environments for protons and other species can now be recognized and already provide much unique information about many organs, systems and disease states. More will undoubtedly become available soon.

We wish to thank the following suppliers of commercially available NMR imaging systems for providing the illustrations used in this article: the General Electric Company (Medical
Products Division) (Fig. 2), Philips Medical Systems (Fig. 5), Siemens Medical Engineering Division (Fig. 3), the Technicare Corporation (Fig. 6) and Picker International (Fig. 7). The careful preparation of the typescript by Mrs E. Mostert is gratefully acknowledged.

REFERENCES


Uterine contraction patterns in abruptio placentae

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Summary

Tocographic monitoring of 21 patients with grade III abruptio placentae revealed the following: (i) the tocographic pattern can be of diagnostic aid; (ii) the tocograph is of no value in measuring progress, because there is no significant change in uterine tone and contraction frequency and amplitude from the time the membranes are ruptured until the delivery of the fetus; and (iii) the tocographic patterns in abruptio placentae are probably of diagnostic value as regards the coagulation defect, but further proof of this is necessary.

Abruptio placentae is the pathological condition in obstetrics in which the placenta separates in part or as a whole from its normal insertion in the uterine wall. The perinatal mortality rate in severe abruptio placentae can be as high as 75%. At the Pelonomi Hospital, Bloemfontein, where we carried out this study, 25% of intra-uterine fetal deaths are caused by this complication. Abruptio placentae is also the commonest cause of coagulation failure in pregnancy, and in grade III abruptio placentae the maternal mortality rate can be as high as 11%.

Uterine contraction frequency in abruptio placentae has been studied previously but no in-depth study of the contraction patterns as a whole or of uterine tone in particular has been published. We therefore undertook the following study.

Patients and methods

Patients with severe clinical abruptio placentae were entered into the study if the fetus was dead (no fetal heartbeat demonstrable with Doppler apparatus or by means of ultrasound examination), vaginal delivery was possible, and the expected duration of labour was at least an hour. Twenty-five patients met these criteria, but of these 4 were subsequently excluded from the study because of faulty recording of uterine contractions.

After the diagnosis of abruptio placentae, the patients were admitted to the labour ward where resuscitation continued. The membranes were ruptured as soon as possible (in 1 case the membranes were already ruptured).

The uterine contractions were monitored through an open-ended polyethylene catheter introduced into the uterine cavity and connected to a Corometric III fetal monitor at a paper speed of 1 cm/min. The recording needle was calibrated to the zero line by closing the catheter to the uterus and opening the pressure transducer to atmospheric pressure. Calibration was done at the beginning and then every 30 minutes or when it was suspected that the catheter had become blocked. Care was taken to ensure that the pressure transducer stayed at the level