The Potential Impact of Nuclear Magnetic Resonance Imaging on Cardiovascular Diagnosis

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SUMMARY Nuclear magnetic resonance (NMR) is used to generate cross-sectional images of the human body that show excellent anatomic and functional definition. The NMR imaging process involves interactions between electromagnetic fields and the hydrogen nuclei being imaged. These interactions occur on time scales of milliseconds to seconds. Consequently, the motion of these nuclei, for instance, when carried by blood, produces distinct signatures that are used to assess flow in major vessels. Myocardial dyskinesis also produces visible effects. Because of these effects, NMR imaging may be a safe and effective tool in the diagnosis and assessment of cardiovascular disease.

NUCLEAR magnetic resonance (NMR) imaging has attracted the attention not only of the radiologic community, but also of other medical disciplines, as well as the press and the government. As an unfortunate consequence of this attention, confused raised expectations surround the technique. For example, in oncology, it has been asserted that NMR imaging can not only diagnose cancer, but can cure it as well.1-3 Not surprisingly, systematic investigation has shown that NMR imaging, although highly sensitive to the presence of abnormalities, does not present malignancies in a unique manner.4-6 A more solid basis exists for the expectation that NMR may offer unique capabilities for assessing the cardiovascular system. Fourteen years before the first NMR images were published by Lauterbur,7 Singer8 had demonstrated the ability to measure blood flow by NMR. In the late 1970s, when the medical community became widely interested in NMR imaging, this capability was a significant source of the attention attracted by the technique. Although some capabilities have already been demonstrated in this area, much work remains to be done. In this review, we discuss the principles of NMR imaging to provide a context within which an understanding of the effects of flow on the image can be placed. We also discuss techniques specifically designed to measure flow, and present results that demonstrate some of the effects.

Principles of NMR Imaging

Atomic nuclei with an odd number of protons or neutrons or both have a magnetic moment. When placed in a magnetic field, these nuclei tend to align along the direction of the magnetic field.

Radiofrequency oscillations of energy proportional to the strength of the magnetic field can induce transitions whereby these nuclei align against the field. In the process of returning to equilibrium, the nuclei emit radiofrequency of an energy, or frequency, that depends on the strength of the field at the time of emission.

NMR imaging is based on the ability to induce and monitor resonance of the magnetic moment of nuclei in the presence of large (static), and of weak (varying) magnetic fields. By using magnetic fields whose strength varies with position (gradients), both the location and concentration of resonant nuclei can be defined, and images are created that reflect their distribution in tissue.9 Hydrogen, because it is the most sensitive of the stable nuclei for NMR and also because it is the most abundant nucleus in the body, is ideally suited for NMR imaging.

In understanding the capabilities of NMR imaging, it is important to remember that the intensity of the signal is not simply a reflection of hydrogen density. Actually, the observed intensity is strongly modulated by local physical and chemical factors, including molecular structure, elemental composition, temperature and viscosity. All of these factors affect the rate constant at which nuclei align with the external magnetic field (T1⁻¹) and the rate constant at which nuclear energy emission decays (T2⁻¹). Commonly referred to as "magnetic relaxation times," T1 and T2 are exponential time constants that vary in different tissues. For example, very pure liquids, in general, align less...
quickly and emit energy for a longer time than liquids with proteins.

Varying the interval between the successive excitations of a region of the sample will selectively enhance tissues according to \( T_1 \). If the interval between successive excitations is short, the tissues with a longer \( T_1 \) will yield relatively less signal than those with short \( T_1 \), since the former have less of a chance to become fully aligned before a new excitation is started. Varying the time interval between nuclear excitation and observation of the signal will selectively enhance tissues according to \( T_2 \), the tissues with longer \( T_2 \) values providing relatively larger signals than those with short \( T_2 \).

For an NMR imaging sequence responsive to \( T_1 \) and \( T_2 \), the NMR intensity (I) is given approximately by the expression

\[
I = H \exp(-a/T_2)(1-\exp(-b/T_1)).
\]

This equation is derived in reference 5; \( I = \) the NMR intensity in a particular region of the image, \( H = \) the local hydrogen density, \( a = \) the \( T_2 \) parameter of the instrument, measured in milliseconds and varied within a broad range under computer control, and \( b = \) the \( T_1 \) parameter of the instrument, measured in seconds and also computer-controlled. The parameter "a" can be regarded as the time delay between application of the radiofrequency pulse that excites the nuclei and the receipt of a signal (a pulse or spin echo) from these nuclei. The parameter "b" represents the time between successive applications of the radiofrequency pulses that excite a particular volume of the sample. It also approximates the time allowed for recovery of sample magnetization between excitations.

The term \( f(v) \) is included because in general, motion of nuclei through the volume being imaged will also change NMR intensity during an imaging sequence, the change also depending on the \( T_1 \) and \( T_2 \) of the fluid, direction of motion, and imaging procedure. These changes have significant implications.

The Effects of Blood Flow on the NMR Image

Imaging sequences apply carefully tailored radiofrequency pulses and magnetic field gradients designed to produce optimal amounts of signal from a volume in the subject. Apparently, then, moving nuclei would observe a disrupted sequence and consequently produce little or no signal. In a simple manner, we would expect that signal would disappear if all the nuclei transverse the imaged volume in the time it takes to carry out a single sequence. Consider, for instance, a 70-msec sequence. Nuclei moving across an imaged plane 7 mm thick will take 70 msec to traverse this distance if their velocity is 10 cm/sec. For this case, cutoff velocity (the velocity above which the moving nuclei produce no signal) should be about 10 cm/sec.

Consider now a very low velocity regimen across the section, low enough that few nuclei leave the imaged volume. Loss of signal is not appreciable, and the small fraction of nuclei leaving the volume are being replaced by nuclei that have not undergone pre-vious irradiations. While the stationary nuclei may recover only half of their magnetization, nuclei that enter this volume between successive excitations have not undergone a prior irradiation and are fully magnetized, consequently providing full signal. Thus, if 10% of the flowing nuclei in a pixel are replaced by fresh nuclei providing twice as much signal as the remaining ones, we should expect that the net signal should be 0.9 \( \times 1 + 0.1 \times 2 = 1.1 \), or 10% higher than for stationary fluid. We called this effect paradoxical enhancement. The exact behavior of signal intensity depends on the relaxation time of the fluid, which determines how much magnetization is lost between excitations and between excitation and signal reception, the interval between these excitations, and the delay between excitation and signal reception; that is, the length of the sequence. Figure 1 shows the relative intensity as a function of velocity for blood. Curves are shown for different values of \( a \) and \( b \).

In imaging, not only the quantitative but also the qualitative behavior during flow can change from that described above if the process has added complexities. Let us consider flow in the plane of the section being imaged. The flowing nuclei are being irradiated at the

**Figure 1.** The nuclear magnetic resonance (NMR) intensity of whole moving blood relative to the intensity of stationary blood as a function of flow in a 9.6-mm-diameter tube. Blood hematocrit (which affects \( T_1 \) and \( T_2 \) relaxation times) is 44%. Response varies as a function of \( a \) and \( b \) parameters. Relative intensity is higher for longer values of \( a \) and for shorter values of \( b \).
same rate as the stationary ones, and paradoxical enhancement will not occur. Consider also an imaging method where more than one section is imaged at the same time. This is a desirable imaging mode because it allows for higher utilization of the total imaging time. For instance, if the sequence is 70 msec long and the interval between excitations 0.5 second, seven sequences could be fit in each interval. Although the same section cannot be irradiated, another six can, so that a total of seven contiguous sections are imaged in one 0.5-second interval. This is an effective method of multisection imaging. In this case, only the nuclei entering the first (outside) section have not undergone a previous irradiation and show paradoxical enhancement. As they enter subsequent sections, paradoxical enhancement is decreased or disappears. The effect is illustrated in figure 2.

Finally, if an imaging technique irradiates a volume much larger than that being imaged, stationary and flowing blood may appear almost identical, because nuclei outside and inside the imaged volume undergo similar sequences.

Flow-sensitive Sequences

Although flow effects appear in NMR images incidentally to the imaging process, it is desirable to design sequences specifically for blood flow imaging. Probably the simplest way to highlight blood flow is to decrease interval b, so that stationary nuclei lose as much signal as possible compared with the incoming nuclei. This technique has been demonstrated by Gore. More sophisticated techniques can conceptually be used. These derive from Singer’s work, and are based on two principles. In the first, a bolus of excited hydrogen nuclei is produced and either its disappearance from the site of production or arrival distal to it is used to quantitate flow. A potentially more powerful method to quantitative capillary blood flow involves the generation of “flow graphs.” These graphs plot the number of nuclei flowing within a velocity interval and can therefore produce maps of blood flow in terms of ml of blood/gram of tissue/min.

Although neither the NMR bolus nor flow graph techniques have been used to map blood flow distributions, these methods are conceptually capable of doing so, and are likely to be demonstrated in the future.

Potential Applications of NMR Imaging in Studies of the Circulatory System

Clinical evaluations of NMR imaging are too new to have resulted in definitive publications dealing with the efficacy of this technique. Nevertheless, studies in animals and human subjects indicate an impressive potential for use in evaluating the circulatory system noninvasively.

While the interaction of the NMR imaging process and motion permits visualization of the vessel lumen (within the technique’s ability to spatially resolve that lumen), the properties of the tissues making up a lesion should allow for an assessment of its composition. Principally, lipids will provide high-intensity signals as a result of their combination of short T1 and long T2 times. Necrotic and calcified tissues will provide little signal, and connective tissues are intermediate between these two. Figure 3 is an example of an NMR image of a freshly excised vessel. With adequate spatial resolution, even lesions that do not intrude the lumen become visible because they are compositionally different from the vessel wall (fig. 4).

In NMR images of normal volunteers, vessels in the head are clearly seen (fig. 5). The vessels associated with an arteriovenous malformation are shown in figure 6. In the neck, normal vasculature is dark because of flow. In a patient with unilateral obstructive diseases, a clear asymmetry is observed (fig. 7). A “textbook” example of paradoxical enhancement is shown in figure 8, from a patient with partial obstruction of the jugular vein secondary to a neck tumor.

Because of motion, the normal heart is ill-delineated in ungated images, i.e., images obtained without synchronization with the heart beat. In figure 9, from a patient with an aneurysm, the akinetic portion of the myocardium is imaged because there is little motion. The normal and stenotic aorta are shown in figures 10 and 11.
FIGURE 3. (A) Five contiguous nuclear magnetic resonance (NMR) sections of an excised iliac artery. In section 2, advanced plaque is visible, with dense connective tissue around the periphery. The central area (appearing darker in the photograph of the lesion (B) and bright in the NMR image) is filled with amorphous lipid-containing debris and lipid-laden phagocytic cells. In section 4 of the NMR image, the lipid-laden region runs parallel to the luminal surface and extends slightly toward the media of the vessel. (C) A photograph of the specimen through this section.

FIGURE 4. Five contiguous nuclear magnetic resonance sections of an excised carotid artery with a lesion containing an orderly increase of connective tissue with moderate number of lipid-laden phagocytic cells. The lesion is evident in the five sections, and rotates counterclockwise along the wall, as indicated by the markers. (B) Photograph of the vessel through section 4.

Paradoxical enhancement can be used to advantage in identifying vessels. In figure 8, the bright vessel was identified as a jugular vein because it was brightened in the most cephalad of five sections, indicating that blood flow was from head to foot in the vessel. In a less obvious case, a duplicated inferior vena cava is distinguished from a similarly shaped aorta by observing enhancement in the most caudal of five sections (fig. 12). This enhancement is most evident in the second pulse echo (large value of "a"), as indicated by the data in figure 1.

These examples demonstrate the capabilities of NMR imaging of the circulatory system. By observing asymmetries in flow between left and right carotids, patients who need angiography may be identified safely and conveniently. In some cases, angiography may be obviated. NMR imaging may become a safe way to follow patients who undergo experimental treatments designed to arrest the growth or regress the size of atherosclerotic lesions and to evaluate bypass patients.
(fig. 13). The potential to evaluate the nature of a lesion is clear but not yet demonstrated.

Experiments have been carried out where the imaging procedure is optimized for highlighting flow by using short intervals between excitations as discussed above, but the images thus obtained do not provide unambiguous imaging of flow distributions.11

As of this writing, imaging of the coronary arteries remains an elusive goal. Two approaches may be used. The first involves gating to the heart beat, so that the imaging procedure is repeated at the same time in the heart cycle.13 It is not clear if spatial resolution sufficient for delineating the coronary arteries can be obtained in this manner. The second approach involves obtaining “freeze” frames of the heart by NMR. To do so, the procedure must be completed in a fraction of the heart cycle (50 msec or less). Ordridge et al.14 demonstrated NMR images of the intact rabbit chest obtained in 32 msec with a spatial resolution of $32 \times 32$ points. This technique requires rapid switching of magnetic field gradients, a technically demanding task that becomes more so as the imaged object increases in size. Scaling from rabbit to adult human size is not a trivial task, but probably can be done if we place the time and funds needed to do so within the context of other current efforts aimed at obtaining rapid images of the heart.

Detection of infarcts in gated or freeze-frame imager should be possible, as NMR is very sensitive to the

![Figure 5](image1.png)  
**Figure 5.** Transverse nuclear magnetic resonance section through a normal head shows internal carotids. The a and b image acquisition parameters are indicated. In the normal subject, carotid arteries are dark because of rapid flow.

![Figure 7](image2.png)  
**Figure 7.** A patient with unilateral obstructive disease demonstrates an asymmetric nuclear magnetic resonance image through the neck. On the obstructed side, the vessels are light because of lack of flow.

![Figure 6](image3.png)  
**Figure 6.** Nuclear magnetic resonance image of patient with an arteriovenous malformation, which appears dark. Near the malformation, there are some light areas that indicate regions of brain edema.

![Figure 8](image4.png)  
**Figure 8.** Most cephalic of five nuclear magnetic resonance sections through the neck of a patient with a neck tumor located caudal to this image. The tumor reaches the carotid artery and jugular vein. In this image the vasculature on the left side of the patient (reader’s right) is normal, but the image shows some signal intensity on the tumor side. In the images with longer value of $a$ (right), the jugular demonstrates paradoxical enhancement (PAR ENH), thus becoming the brightest area in the image. This indicates that flow is impaired but not fully obstructed.
edema associated with infarction. No demonstration of the effects of ischemia has been published, but changes are visible in hearts excised from dogs after the administration of manganese, a paramagnetic ion. The differential uptake of manganese in normal and ischemic myocardium changes the relaxation time of the hydrogen present in the muscle, thus outlining the pathologic area. Unfortunately, with the imaging techniques used, when physiologic amounts of contrast agents were injected, no changes in the dog heart were evidenced in vivo.13

Potential Hazards Associated with NMR Imaging

Three kinds of fields are associated with the imaging process: static magnetic fields of moderate strength (400 G to 3.5 kG), switched weak magnetic field gradients (changing from 0 to 30 G in 1 msec) and radiofrequency magnetic fields. Budinger15 presented an exhaustive review of possible damage mechanisms and experimental information. We place the physical fields associated with NMR imaging within the context of other frequently occurring exposures.

The energies associated with the imaging process are on the order of $10^{-3}$ eV/quantum, and are too low to cause ionization or breaking of chemical bonds. (Note that the energies associated with body temperatures are...
10⁵ to 10⁶ times larger, so that temperature effects are far more disruptive of bonds than NMR imaging can be.) Thus, it is not surprising that tests for genetic damage have been negative.¹⁶

The static magnetic fields are six or seven times weaker than these found in particle accelerators, where many have been exposed over the last 5 decades. No detrimental effects due to long exposures at these fields have been identified, and the short exposures associated with NMR imaging are unlikely to produce any. The switched magnetic field gradients could heat tissues by current induction or induce voltages that would disrupt normal function. Whatever heating can occur has been small enough that monitoring of subject temperature has not evidenced it. As for the production of voltages, a sensitive indicator would be the occurrence of phosphorescence. These have not been reported by any worker in the field. If phosphorescence do not occur, it is hard to postulate a mechanism by which more dangerous voltage induction (i.e., defibrillation) could happen.

Radiofrequency radiations are known to heat objects, but high power levels are needed. In our imager, average power input ranges from 0.5 W in the head coil to 7 W in the body coil. Even if all of this power were deposited in the patient and no heat dissipation occurred, it is unlikely that the temperature could increase by more than 0.1°C during an imaging procedure. Both frequency and power levels are in the range of citizen band radio emissions.

As with any environmental factor, we may find that NMR poses some kind of somatic hazard. As we understand them today, the hazards associated with NMR imaging are posed by ferromagnetic objects, such as tools or oxygen cylinders, that are accelerated toward the center of the magnetic field, and if carelessly handled can seriously damage patients, attending personnel and equipment. Sudden and extensive rupture of the vessel could spill cryogenic liquids used in superconducting magnets. (Quenching, or loss of superconductivity, is an extremely infrequent and benign event that poses no hazards.) With these considerations in mind, some patient populations should be excluded until more is learned about potential hazards. These populations include patients with pacemakers, extensive prostheses that could, under certain circumstances, be heated,¹⁷ and pregnant women.

**Conclusion**

Enough capabilities have been demonstrated by NMR imaging to assure its role in the assessment of the cardiovascular system. Over the next 5 years, as the technology matures and time and resources become available for exploring its full range, we may better appreciate what this imaging modality can contribute to the study of circulation in the human.

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