NUCLEAR MAGNETIC RESONANCE (NMR) imaging, now called "magnetic resonance imaging" or "MRI" in the radiologic literature, has become widely available for clinical use. However, application to the cardiovascular system remains predominantly in the research phase. Although the present commercially available systems can generate high-resolution tomographic images, the relatively high cost and rather lengthy acquisition times have limited the cost-effectiveness of NMR as a diagnostic tool when compared with other effective and less expensive noninvasive modalities such as echocardiography and radionuclide procedures. The ultimate importance of cardiovascular NMR imaging will depend on the development of unique applications, including noninvasive angiography particularly of the proximal coronary arteries, noninvasive high-resolution assessment of regional myocardial blood flow distribution, characterization of myocardial pathology by alterations in proton relaxation properties, and evaluation of myocardial biochemistry in vivo by NMR spectroscopy. The advantages of this technology are several: NMR (1) is nonionizing, (2) generates intravascular and soft tissue contrast without the need for contrast medium, (3) is intrinsically three-dimensional, allowing images to be obtained from any plane orientation, (4) can image structures without interference from bone, and (5) has the potential to evaluate biochemical composition and reactions and disease-related changes.

Several clinical applications of proton NMR imaging to the cardiovascular system have been reported and reviewed. Imaging with NMR can depict with excellent detail normal cardiac structure (figure 1) and a multitude of abnormalities (figure 2). Generally, cardiac images are acquired in two-dimensional tomographic slices of 0.6 to 1.0 cm in thickness. The myocardium is depicted in sharp contrast to the moving blood within the chambers so that even the papillary muscles and the moderator band of the right ventricle are often visualized. The interventricular septum is well defined and its unusual configuration in patients with hypertrophic cardiomyopathy or ventricular septal defect can be depicted. Even thinner structures such as the walls and septum of the atria and the pericardium can be visualized. Intravascular blood motion permits imaging of large outflow and inflow blood vessels and occasionally glimpses of the coronary arteries are seen.

The importance of NMR imaging is related not only to its ability to generate high-resolution tomograms demonstrating cardiac morphology but also to extensions of these studies to the assessment of global function, regional characterization of pathologic processes using T1 and T2, and the development of other unique applications that other less expensive technologies cannot perform.

Analysis of structure and function. Since NMR image acquisition generally requires one or more minutes, cardiac imaging must be performed by synchronizing image acquisition with the phase of the cardiac cycle by means of the electrocardiographic R wave. Most studies have been performed with externally defined sagittal, transverse, and coronal planes. Image planes orthogonal to the thorax, however, do not provide optimal display of the heart and great vessels. Not only are these planes oblique to the long and short axes of the heart, but also their angle with respect to those axes varies between individuals. Such tomographic cuts with oblique intersections between image plane and cardiac orientation can lead to erroneous estimates of wall thickness and motion.

Calculations of cardiac chamber volumes, myocardial thickness, and wall motion are most appropriate when tomographic sections are oriented to the intrinsic axes of the heart. Because NMR imaging systems per-
mit data acquisition in any plane by adjusting a set of gradient angles, it is possible in principle to obtain any viewing angle through any part of the patient. Dinsmore et al.\(^5\) used the intrinsic three-dimensional imaging capability of NMR to optimize the selection of imaging planes in this manner. Practical problems exist, however, since appropriate angle selection must be determined by a time-consuming trial and error process. Physically positioning the patient in a 30 degree right anterior oblique orientation, obtaining an initial set of images with one signal average (approximately 1 to 3 min), and determining the appropriate alterations in gradient angles after this initial series has been one solution. Subsequent, optimally oriented, high-resolution, and low-noise images are then acquired with two or more signal averages (figure 3).

During an acquisition period, multiple slices (often six or more) can be obtained. Such multislice acquisition is accompanied by a time delay between consecutive slices so that the various slices do not represent the same phase of the cardiac cycle. Changing the delay time between the gating impulse (usually the R wave) and the radiofrequency (RF) pulses that generate the image allows multiple phases of the cardiac cycle to be obtained for each slice. If end-systolic and end-diastolic images are generated at each of six levels, global volume, ejection fraction, and myocardial mass can be assessed. Compared with other modalities, NMR imaging is well suited to quantify cardiac chamber volumes and myocardial mass because of (1) its three-dimensional nature and (2) the lack of signal attenuation from overlying lung and bone. Attenuation and limitation of view are significant problems for radionuclide and echocardiographic studies. Of course, the long acquisition times and expense are significant limitations of NMR imaging. Recent comparative studies have corroborated the accuracy of NMR measurements of ventricular volumes and myocardial mass.\(^6\)\(^-\)\(^8\)

With continued technologic development, higher speed and true three-dimensional acquisitions will be possible.

**Tissue characterization.** The proton relaxation parameters T\(_1\) and T\(_2\) are related to biophysical and biochemical characteristics of the tissue. These parameters pro-
FIGURE 2. End-diastolic gated spin-echo image at a similar level as figure 1 depicting both left and right ventricles and interventricular septum. This patient had an anteroseptal myocardial infarction, reflected in the thinning and decreased signal intensity of the interventricular septum compared with the posterior left ventricular wall. Note also the excellent depiction of the posterior papillary muscle. Image courtesy of Professor Kutzim, Institute for Clinical and Experimental Nuclear Medicine at the University of Cologne.

provide the basis for the high contrast of NMR images. Variations in the relaxation parameters can be used to characterize tissue, for in virtually all models of myocardial disease $T_1$ and/or $T_2$ become abnormal. For example, laboratory animal and human studies demonstrate alterations in both $T_1$ and $T_2$ with myocardial ischemic insult with or without reperfusion, doxorubicin cardiotoxicity, and allograft rejection. The mechanisms for such alterations in relaxation times have not been fully elucidated, although it is known that factors such as myocardial water and lipid alterations can lead to abnormal increases in relaxation times. In view of the relationship between the presence of myocardial disease and changes in relaxation properties, NMR imaging methods that highlight these properties may be useful for characterizing localized pathologic changes such as myocardial infarction. However, because signal intensity in NMR images is dependent not only on both $T_1$ and $T_2$ but also on proton density and motion, technologic development will need to focus on improved measurement and separation of the effects related to wall motion from those related to relaxation properties. In addition, improved understanding of the mechanisms that influence relaxation in vivo would lead to a more rigorous basis for the design of imaging experiments and equipment, and perhaps a more specific diagnosis of the pathologic states.

Changes in tissue water content play the most important role in the alterations of $T_1$ and $T_2$ associated with disease, particularly coronary artery occlusion followed by reperfusion. Increases in $T_1$ and $T_2$ parallel increases in total tissue water in the ischemically insulted myocardium. Generally, the degree of elevation of the relaxation times in a canine preparation of myocardial infarction is related to the severity of the ischemic insult during occlusion and to the extent of reperfusion with reflow. However, recent data from our laboratory have demonstrated no increases in $T_1$ and $T_2$ in myocardium in which microsphere-determined perfusion indicates ischemia (less than 5% of control flow) for a 4 hr occlusion interval. This absence of $T_1$ and $T_2$ changes was observed even though total tissue water was significantly increased albeit to a lesser ex-
FIGURE 3. End-diastolic gated spin-echo image depicting angulation of the image plane to a nonaxial orientation perpendicular to the long axis of the left ventricle. This approach optimizes a demonstration of the left ventricular wall thickness and chamber dimensions. With the intrinsic three-dimensional nature of proton NMR imaging, this procedure minimizes partial volume distortion. The right and left ventricular cavities are well defined. A papillary muscle is demonstrated within the left ventricular chamber. Image courtesy of Professor Kutzim, Institute for Clinical and Experimental Nuclear Medicine at the University of Cologne.

tent than in less severely ischemic or reperfused zones. Reperfusion of this region was associated with marked elevations in total water, extracellular water, and both $T_1$ and $T_2$. It is still uncertain, however, whether $T_1$ and $T_2$ can be used to assess myocardial viability. It is believed that these measurements reflect the ability of myocardial tissue to maintain normal water balance. At some point in an ischemic insult, tissue water (in the face of some degree of residual perfusion) will increase. This increase ultimately affects $T_1$ and $T_2$ and is likely to be the most important mechanism for their increase. Studies suggest that NMR imaging of relaxation properties, nevertheless, should be helpful in sizing established myocardial infarcts and depicting the severely ischemic necrotic core of an infarct.

Proton NMR also has the potential to stage myocardial infarction. The evolution of an infarct from the acute ischemic phase to the formation of myocardial scar is associated with changes in the NMR properties of tissue primarily related to changes in tissue water content. In particular, water content becomes elevated within an hour of onset of ischemia related to the decreased transport ability of the myocardial cell membrane. As fibrous tissue replaces the damaged tissue 2 to 3 weeks after infarction, water content decreases. Lipid and collagen may also play a role in serial $T_1$ and $T_2$ changes associated with myocardial infarction. Proton NMR techniques that depict relaxation times might be useful as a means of characterizing the myocardial ischemic insult because acute myocardial infarction without reperfusion, acute myocardial infarction with reperfusion, and myocardial scar have different relaxation properties.

Factors other than water may have an impact on signal intensity in a gated proton NMR image. Mobile lipids (e.g., fatty acids) can affect water relaxation through cross-relaxation with resultant effects on signal intensity in an NMR image. Alternatively, lipid accumulation in myocardium associated with ischemic insults may be detected specifically because the lipid resonance position is offset from the water resonance. Thus proton NMR imaging has the potential to depict
the accumulation of mobile lipids in vivo. With further technologic advances in NMR imaging methods, such lipid accumulations should be measurable by proton chemical shift or spectroscopic imaging, enabling the ischemic insult to be staged. In addition, the high resolution of the imaging study may permit the identification of the insulted myocardium at a very early stage and accurately and reproducibly quantify the size of the infarct. It is the biophysical (T₁ and T₂) and/or biochemical information that will be derived clinically that is unique to NMR and that will enhance its cost-effectiveness and clinical utility.

**Noninvasive angiography.** Atherosclerotic involvement of the vessels supplying the heart, brain, and other organs is one of the most important diseases facing modern medicine. Current methods cannot adequately assess the severity of such atherosclerosis. NMR, however, has the potential to define the morphology of normal and diseased arteries. Because the NMR signal is affected by macroscopic motion of protons, a reduction in signal intensity can result from blood flow as excited protons move out of the imaging plane. This characteristic loss of signal is the basis for noninvasive NMR angiography without the need for contrast medium. Contrast between arterial lumen and surrounding tissue can be maximized by synchronizing image acquisition to the phase of maximal arterial blood velocity, i.e., early to mid-diastole for the coronary arteries and early to mid-systole for the other systemic arteries.

In addition to providing contrast for angiography, NMR techniques have the potential to quantify flow velocity and, as a result, to evaluate the impact of arterial plaque. Flow velocity measurement is based on the shift in phase of the RF signals that are induced by the movement of protons within a magnetic field gradient. The shift in phase is zero for stationary protons and is proportional to velocity for moving protons. Fourier transform and spin-warp imaging techniques provide means to image the distribution of such phase differences, and hence the velocity of proton flow and diffusion may be mapped. Phase images can be constructed that use color scales to encode the proton velocity in each pixel. Thus flow velocity and turbulence may be depicted. Such images might be useful for detecting impaired ventricular wall motion, vessel obstructions, or intracardiac shunts. Ultimately, it may be possible to assess the severity of valve stenoses by quantifying flow through valve orifices.

Because signal intensity is dependent on phase (i.e., velocity), the subtraction of a systolic image from a diastolic image allows pulsatile flow to be depicted. Structures without flow become in effect transparent and the three-dimensional vascular tree can be projected onto a two-dimensional plane. This technique provides the opportunity to visualize vessels 1 to 2 mm in diameter and may be useful for assessing peripheral vascular disease.17, 18

Although proton NMR has the inherent resolution required for imaging vessels the size of the proximal coronary arteries, their motion and tortuous spatial configuration are technical impediments to consistent imaging. Respiratory motion and the difficulty in predicting location of the vessels reduce the resolution of ECG-gated images of the coronary arteries. Respiratory gating can improve resolution at the expense of increasing imaging time but does not overcome image degradation related to heart rate–dependent fluctuations in ventricular size leading to changes in the location of the coronary arteries. Innovative gating strategies will be required to generate adequate images. Alternatively, high-speed image acquisition techniques such as the echo-planar method of Mansfield and colleagues19 offers the possibility of overcoming these problems by reducing the acquisition period to the 30 msec range, obviating the need for gating. Currently, such methods have resolution too limited to enable satisfactory coronary artery imaging.

The tortuous nature of the coronary arteries also precludes adequate diagnostic study with two-dimensional tomographic sections. Three-dimensional imaging could solve this problem, but such imaging increases the complexity and duration of the NMR procedure. In summary, proton NMR imaging of the proximal coronary arteries will be technically difficult; nevertheless, the potential exists for developing high-resolution, noninvasive NMR techniques to depict these and other vessels and to measure blood flow and velocity. Such an application of NMR imaging would be quite cost-effective.

**Evaluation of regional pathophysiologic impact of coronary artery disease.** The assessment of regional myocardial blood flow during exercise stress or in conjunction with the vasodilator dipyridamole by means of radionuclide methods has been of value for prognostication in coronary artery disease. The extent of the perfusion defect(s) has been shown to predict survival.20 However, the low spatial resolution of radionuclide imaging methods justifies development of new high-resolution NMR techniques to evaluate perfusion. In addition to considerable improvement in spatial resolution in comparison with radionuclide procedures, proton NMR image intensity is not attenuated by overlying soft tissue (a limitation of thallium imaging, in which
the emitted photons have relatively low energy) and NMR contrast agents are stable and will not decay or require specialized licensure. Paramagnetic agents enhance contrast in NMR images by facilitating relaxation. An agent designed for myocardial extraction (like thallium) would permit NMR imaging of regional myocardial blood flow distribution.

The major problem with the strategy of using paramagnetic reagents is their toxicity in the concentrations needed to generate adequate NMR contrast. Early studies in canine preparations of myocardial infarction used ionic manganese (Mn⁺⁺). Although manganese ion distributes to myocardium in proportion to regional blood flow, it is quite toxic in quantities adequate for imaging. Toxicity considerations have led to the study of chelated metals, such as gadolinium-DTPA (Gd-DTPA). Although these complexes alter relaxation rates of tissue in proportion to their concentration and consequently increase contrast in the presence of concentration differences, they distribute nonspecifically; that is, they are not specifically deposited in myocardial cells or zones of infarcted myocardium. The increase in extracellular water associated with a myocardial ischemic insult results in a transient concentration differential of the contrast agent between vascular and extravascular space. This dynamic gradient will lead to less image contrast as equilibrium is restored. The studies of Wesbey et al. illustrate these points. Gd-DTPA was administered after 24 hr of coronary artery ligation in dogs. Myocardium from nonischemic zones excised 90 sec after injection of Gd-DTPA had significantly shortened relaxation times relative to those of infarcted zones. In contrast, 5 min after administration the infarcted myocardium had reduced relaxation times and those of noninfarcted myocardium were increasing back toward control. These results are consistent with early accumulation in and clearance from normal myocardium and delayed accumulation in infarcted myocardium. The challenge is to develop an agent that is specifically, rapidly, and efficiently deposited in viable myocardial cells and has no toxicity. Such an agent would depict regional myocardial blood flow distribution, and when administered during exercise or with dipyridamole would provide a means for improved pathophysiologic assessment of the extent of coronary artery disease.

**Myocardial biochemistry.** NMR has the unique clinical potential to monitor biochemical processes in vivo with spectroscopy. This is accomplished either by (1) generating spectra from a smaller volume of the total volume of the body within the magnet or (2) imaging the spatial distribution of a preselected portion of the spectrum. The latter has been performed by acquiring three-dimensional data sets in which the x and y dimensions contain spatial information and the z dimension is that of the spectrum. A single tomographic slice (e.g., through the mid thorax) and a portion of the spectrum (e.g., lipid resonances) are selected. The distribution of lipid within that slice is then depicted. Moreover, paging through the z axis shows images from one end to the other end of the spectrum. In contrast to conventional NMR images in which signal intensity distribution is related to all mobile protons in the region imaged, these images depict only the mobile protons of the selected molecular type. The proton spectrum depicts peaks for water, the methyl and methylene groups of lipids, lactic acid, and other molecular species. Water and lipid are present in higher concentrations than other molecules and are most readily detected. Chemical shift images have been generated that depict the distribution of water and that of lipid in the head and abdomen. The difficulty in obtaining high-resolution proton NMR spectra of sufficient quality to allow spectroscopic observation of relevant metabolites of the heart in vivo is related to the interference by the intense water signal. The application of surface coils permits definition of a limited volume of interest, optimization of the magnetic field homogeneity over that volume, and the implementation of spectroscopic techniques to suppress the water resonance. With this approach, millimolar concentrations of metabolites have been observed in humans.

Application to the cardiovascular system may include assessing myocardial lipid accumulation associated with ischemic insults. Such accumulation may be related to the reversibility and viability of myocardial tissue. The utility of evaluating the distribution of water compared with lipid is presently under investigation and ultimately may provide a means to evaluate a myocardial ischemic insult. Of course, the ability to determine the spatial distribution of lactic acid, which is known to accumulate in ischemic tissue, also would be of great importance. Unfortunately, the relatively low concentration of lactic acid and its spectroscopic proximity to the position of the lipid resonance present difficult technical challenges to be overcome before clinical images of the distribution of lactic acid can be generated.

Other nuclei such as phosphorus-31 (P), sodium-23 (Na), and carbon-13 (C) have important biological potential. P spectroscopy can be used to evaluate high-energy phosphate metabolism and intracellular pH; Na imaging might depict intracellular sodium accumulation related to the inability of ischemic cells...
to maintain an energy-dependent sodium gradient; and
$^{13}$C spectroscopy might be used to monitor myocardial
substrate metabolism by tracing endogenous or admin-
istered, specifically enriched $^{13}$C-containing com-
ounds. By combining a pulsed magnetic field gradient
with surface coil techniques, spatially localized $^{31}$P
spectra have been recorded noninvasively from the
human heart in vivo. Although noninvasive $^{13}$C studies
of the heart in vivo have not been yet reported, glyco-
gen metabolism has been investigated in an open-chest
guinea pig model preparation.25

Recent and future developments. Although NMR
imaging techniques have enormous potential to yield
important and unique clinical and research insight,
several problems limit its routine clinical application
to cardiac imaging: (1) data acquisition time is long rela-
tive to the cardiac cycle and thus gating is required; (2)
NMR is difficult to apply in acutely ill patients or
infants and young children because of its prolonged
acquisition time and the requirement that the patient
remain still; (3) NMR studies are contraindicated in
patients with cardiac pacemakers or metallic implants;
and (4) an NMR system and facility are expensive.

Strategies for decreasing acquisition time and im-
proving resolution are under investigation. Methods
using reduced RF excitation angles allow image acqui-
sition in substantially less time while maintaining ade-
quate contrast and high spatial resolution. Preliminary
data show that imaging of a cardiac cycle within a
single plane can be acquired within 45 sec. Presently,
three-dimensional data acquisition strategies are under
development. These will allow visualization of virtu-
ally any image plane. Such acquisitions allow appro-
priate evaluation of the course of structures such as
the coronary arteries, which have a tortuous spatial ori-
teation. Nevertheless, three-dimensional imaging sub-
stantially increases the time required for data acqui-
sition and display.

New innovative strategies are being investigated to
decrease imaging time, such as the echo planar meth-
od, which allows acquisition of an image plane in 30
msec but which yields poorer image resolution.

Surface coil imaging — a technique that uses an RF
coil placed directly over the anatomic region of interest
— characteristically demonstrates high sensitivity and
relatively uniform response to signals in proximity to
the coil. Because of the size of the coil, limited field of
view, and the proximity to the area being imaged, a
three to five times greater signal-to-noise ratio is often
achieved compared with conventional whole body
coils. Consequently, high-resolution, low-noise im-
ages are obtained in standard image acquisition times.

Advances in coil design and techniques to increase the
homogeneity of the RF excitation pulse may increase
the application of surface coil methods to the heart and
blood vessels.

Another approach to obtain NMR signals from a
localized area of myocardium in vivo has used a cat-
ther with a small RF coil at its tip.26 This technique
permits phosphorus spectra of myocardium in close
proximity to the coil to be obtained. However, such an
approach might not be easily applied clinically to dis-
ease in which involvement tends to be focal (such as
coronary artery disease).

Conclusion. Despite its relatively recent emergence
as an imaging modality and the cost of NMR facilities,
it has become apparent that NMR imaging techniques
could have a substantial impact on cardiovascular di-
agnosis. The combination of excellent resolution, in-
herent contrast, sensitivity to blood flow, three-di-
ensional nature, lack of ionizing radiation, morphologic
imaging, and the potential to assess metabolic and
tissue function provide ample justification for cardio-
vascular applications. The success of unique applica-
tions of NMR methods will ultimately decide its cli-
nical utility and cost-effectiveness.

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