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Magnetic Resonance Imaging: Historical Perspective

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ABSTRACT

Since Paul Lauterbur and Peter Mansfield independently published in 1974 the technique that later became known as magnetic resonance imaging (MRI), this technology has become an invaluable clinical and research tool. Their Nobel Prize-winning discovery, however, was preceded by a series of seminal contributions by scientists from the fields of mathematics, physics, and chemistry dating back to the 19th century and subsequently followed by rapid developments in clinical MRI. This article provides a brief overview of the key developments that have led to today's MRI and its application to the cardiovascular system.

INTRODUCTION

Magnetic resonance imaging (MRI) is a sophisticated imaging technique that has evolved as a clinical modality over the past 30 years. The origins of MRI, or NMR (nuclear magnetic resonance), as it was termed in the past, however, can be traced back for over a century. Along the way, many scientists from diverse disciplines have made remarkable contributions that have brought the field to its present state—a clinical tool capable of real time in-utero cardiac imaging (1) and a research tool capable of imaging a single cell (2, 3). As this powerful imaging modality and scientific tool continues to evolve, it is worthwhile to pause and look back at the evolution of MRI and note the scientists who made the extraordinary contributions that have led to five Nobel Prizes awarded to discoveries related to NMR/MRI.

BEFORE NMR

Jean Baptiste Joseph Fourier (1768–1830) (Fig. 1), a French mathematician and engineer, was, for several years, an officer in Napoleon's army. Fourier served three years as secretary of the Institut d'Egypte at the beginning of the 19th century during Napoleon's reign, and later became prefect of the Isère département in France. However, the focus of his life was mathematics, and without his Fourier transform we would not be able to create MR images. Fourier developed a general mathematical transformation method for analysis of heat transfer between solid bodies (4). His method has made it possible to rapidly process the phase and frequency signals of the NMR data and to efficiently utilize the information for image reconstruction. His mathematical method was first used for magnetic resonance signal analysis and image reconstruction by Richard Ernst in 1975 and has since been used in all modern MRI scanners.

Nikola Tesla (1856–1943) (Fig. 2) was a Serbian-born inventor and researcher who discovered the rotating magnetic field, the basis of most alternating-current machinery (5). He immigrated to the United States in 1884 and sold the patent rights to his system of alternating-current dynamos, transformers, and motors to George Westinghouse the following year. In 1891 he invented the Tesla coil, an induction coil widely used in radio technology. In Colorado Springs, where he stayed from May 1899 until early 1900, Tesla made what he regarded as his most important discovery—terrestrial stationary waves. By this discovery he proved that the Earth could be used as a conductor and would be as responsive as a tuning fork to electrical vibrations of a certain frequency. He also lit 200 lamps without wires from a distance of 25 miles (40 kilometers) and created man-made lightning, producing flashes measuring 135 feet (41 meters). At one time he was certain he had received signals from another planet in his Colorado laboratory, a claim that was met with derision in some scientific journals. The unit strength of a magnetic field is named after Nikola Tesla (1 Tesla = 1 Newton/Ampere-meter). The earth's field $B_E = 0.5 \times 10^{-4}$ T = 0.5 Gauss (1 Gauss = 10^{-4} T)

Sir Joseph Larmor (1857–1942), an Irish physicist, was the first to calculate the rate at which energy is radiated by an

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Figure 1. Jean Baptiste Joseph Fourier.

accelerated electron, and the first to explain the splitting of spectrum lines by a magnetic field (6). He was educated at Belfast and Cambridge and taught at Galway, Ireland from 1880 to 1885. He then went to Cambridge, becoming Lucasian Professor there in 1903. He worked on electricity and thermodynamics and wrote Aether and Matter in 1900. Knighted in 1909, Larmor served as MP for the University of Cambridge from 1911 to 1922. The Royal Society awarded him its Royal Medal in 1915 and its Copley Medal in 1921. He was also awarded the De Morgan Medal of the London Mathematical Society in 1914. He is most famous in the field of NMR for the equation that bares his name—The

Figure 2. Nikola Tesla.

Larmor equation. It states that the frequency of precession of the nuclear magnetic moment (ω) is directly proportional to the product of the magnetic field strength (B_0) and the gyromagnetic ratio (γ): $\omega = \gamma B_0$. The Larmor equation is important because it is the frequency at which the nucleus will absorb energy. The absorption of that energy will cause the proton to alter its alignment and ranges from 1–130 MHz in MRI.

EARLY NMR

Gerlach and Stern: The roots of nuclear magnetic resonance (NMR)—the term used through the mid-1980's—can be traced to the work of **Walter Gerlach** (1889–1979), who worked in Munich and **Otto Stern** (1888–1969), who worked in Hamburg. In 1924, they published the results of an experiment that demonstrated the quantum nature of the magnetic moment of silver atoms by molecular beam deflection in an inhomogeneous magnetic field (7).

Isidor Rabi (1898–1988) (Fig. 3), a native Austrian who worked in the Department of Physics at Columbia University in New York, whose early work was concerned with the magnetic properties of crystals. In 1930, he began studying the magnetic properties of atomic nuclei, developing Stern's molecular beam method to great precision as a tool for measuring these properties. His apparatus was based on the production of ordinary electromagnetic oscillations of the same frequency as that of the Larmor precession of atomic systems in a magnetic field. He succeeded in detecting and measuring single states of rotation of atoms and molecules, and in determining the magnetic moments of the nuclei (8). For his discoveries, he was awarded the Nobel Prize in Physics in 1944. CJ Gorter, attributing the term to Rabi, coined the term 'Nuclear Magnetic Resonance' in 1942 (9).

Figure 3. Isidor Rabi.

Figure 4. Edward M. Purcell.

Figure 5. Felix Bloch.

Bloch and Purcell: In 1946, two scientists in the United States, Felix Bloch, working at Stanford University, and Edward Purcell from Harvard University, independently of each other, described a physicochemical phenomenon, which was based upon the magnetic properties of certain nuclei in the periodic system. **Edward M. Purcell** (Fig. 4) was born in Illinois, worked at the Massachusetts Institute of Technology, and later joined the faculty of Harvard University. **Felix Bloch** (Fig. 5) was born in Zurich in 1905 and taught at the University of Leipzig until 1933; he then immigrated to the United States and was naturalized in 1939. He joined the faculty of Stanford University at Palo Alto in 1934 and became the first director of CERN in Geneva in 1962. He died in Zurich in 1983.

Bloch and Purcell found that when certain nuclei were placed in a magnetic field they absorbed energy in the electromagnetic spectrum, and re-emitted this energy when the nuclei returned to their original state. The strength of the magnetic field and the radiofrequency matched each other according to the Larmor relationship. They measured the precessional signal of spins in water and paraffin samples subject to a magnetic field (10, 11). They jointly received the Nobel Prize in Physics in 1952.

Erwin L. Hahn developed a method to study molecular diffusion in liquids by the spin-echo method using a gradient approach to create a storage memory (12).

NMR RESEARCH 1940's THROUGH 1970's

During those three decades, the field of NMR saw many investigations of non-biological and biological samples, including measurement of relaxation times in living cells, excised animal tissues, whole blood, plasma, red blood cells, skeletal muscle of frog, and living human subjects. In 1971, **Raymond Damadian,** who worked at Downstate Medical Center in Brooklyn, New York, measured T1 and T2 relaxation times of excised normal and cancerous rat tissue and stated that tumor tissue had longer relaxation times than normal tissue. Damadian thought that he had discovered the ultimate technology to detect cancer and, in 1972, filed a patent claim for an 'Apparatus and Method for Detecting Cancer in Tissue' (Damadian R. United States Patent no. 3789832. Filed 17 March 1972, awarded 5 February 1974. Apparatus and method for detecting cancer in tissue. Inventor: Raymond V. Damadian). The patent included the idea but no description of a method or technique to use NMR to scan the human body. In February 1973, **Abe** and his colleagues applied for a patent on a targeted NMR scanner [Abe Zenuemon, Kunio Tanaka, Hotta Masao and Imai Masashi: [Patent] Application. Measurement method from the outside [to obtain] information in the inside applying nuclear magnetic resonance. Japanese patent application 48-l3508, 1973 (application day: February 2, 1973)]. They published this technique in 1974 (13). Damadian reported a similar technique in a publication two years later, dubbed 'field-focusing NMR (Fonar),' which contained an image of scanned volume elements through a mouse (14, 15).

ORIGINS OF BLOOD FLOW MEASUREMENT BY NMR

In 1959, **Jay Singer**, working at the University of California at Berkley, published an NMR method for measurement of blood flow in mice tails (16). In 1967, **Alexander Ganssen** filed a patent for a whole-body NMR machine to measure the NMR signal of flowing blood in the human body. The machine was designed to measure the NMR signal of flowing blood at different locations of a vessel using a series of small coils.

FROM NMR SIGNAL TO IMAGE FORMATION

All the experiments up to now had been one-dimensional and lacked spatial information. Nobody could determine exactly where the NMR signal originated within the sample. In 1974, **Paul C. Lauterbur**, working in the United States, and **Peter Mansfield**, working in England, without knowledge of each other's work, described the use of magnetic field gradients for spatial localization of NMR signals. Their discoveries laid the foundation for **M**agnetic **R**esonance **I**maging (MRI). For their contributions, Lauterbur and Mansfield were jointly awarded the 2003 Nobel Prize in Physiology or Medicine.

Paul C. Lauterbur (Fig. 6) was born in 1929 in Sidney, Ohio. He received a Ph.D. degree in Chemistry from the University of Pittsburgh in 1962, and from 1969 to 1985 he was a Professor of Chemistry and Radiology at New York University at Stony Brook. While at Stony Brook, he had the idea of applying magnetic field gradients in three spatial dimensions and used the computer-assisted tomography (CAT)-scan back-projection approach to create 2D NMR images. He published the first images of two 1 mm capillaries filled with water submerged in heavy water in March 1973 in the journal Nature (17). The article was initially rejected due to lack of interest for a wide readership. This was followed later in the year by the picture of a living animal, a clam, and in 1974 by the image of the thoracic cavity of a mouse. Lauterbur called his imaging method *zeugmatography*, a term which was later replaced by (N)MR imaging.

Figure 6. Paul C. Lauterbur.

Figure 7. Peter Mansfield.

Peter Mansfield (Fig. 7) was born in 1933 in London, UK. He studied physics at Queen Mary College in London where he received a Ph.D. degree in 1962. He worked in the Department of Physics at the University of Nottingham until retiring in 1994. Mansfield worked on studies of solid periodic objects such as crystals. In a letter to the editor in 1973, Mansfield and Grannell, who was a postdoctoral fellow at the time, described the use of magnetic field gradients to acquire spatial information in NMR experiments (18). At a Colloque Ampère conference in Cracow, Poland later that year, he and Grannell presented a one-dimensional MR interferogram to a resolution of better than 1 mm (19). While this cannot be considered an MR image, one year later, Garroway and Mansfield filed a patent and published a paper on image formation by NMR (20).

In 1975, **Richard Ernst** described the use of Fourier transform of phase and frequency encoding to reconstruct 2D images. This technique is the basis of today's MRI. In April 1974, Paul Lauterbur gave a talk at a conference in Raleigh, North Carolina. Richard Ernst attended this conference and realized that instead

Figure 8. Prototype MR scanner in Aberdeen, Scotland with Dr. Hutchinson.

of Lauterbur's back-projection, one could use switched magnetic field gradients in the time domain. This led to the 1975 publication that described for the first time a practical method to rapidly reconstruct an image from NMR signals (21). Richard Ernst was rewarded for his achievements in pulsed Fourier Transform NMR and MRI with the 1991 Nobel Prize in Chemistry.

The early contribution of computed tomography (CT) to MRI is worth noting. Hounsfield introduced x-ray-based CT in 1973 (22, 23) the same year that Lauterbur and Mansfield introduced spatial localization of NMR signals to produce two-dimensional images. This date is important to the MRI timeline because it demonstrated the interest of the scientific and clinical communities in noninvasive cross-sectional in-vivo imaging. These two imaging technique have continued to this day to both compete and complement each other. Allan Cormack and Godfrey Hounsfield received the 1979 Nobel Prize in Physiology or Medicine for the development of computer assisted tomography.

LATE 1970's: EARLY MR IMAGES

By 1975, Peter Mansfield and Andrew Maudsley proposed a line scan technique, which, in 1977, led to the first image of in vivo human anatomy, a cross section through a finger. In 1977, Hinshaw, Bottomley, and Holland succeeded with an image of the wrist (24) and Damadian et al. created a cross section of a human chest (25). More human thoracic and abdominal images followed, and, by 1978, Hugh Clow and Ian R. Young, working at the British company EMI, reported the first transverse NMR image through a human head (26). Two years later, William Moore and colleagues presented the first coronal and sagittal images through a human head. In 1980, Edelstein et al. from Aberdeen University in Scotland demonstrated imaging of the body using Ernst's technique (Fig. 8) (27). A single image could be acquired in approximately five minutes by this technique. By 1986, the imaging time was reduced to about five seconds without sacrificing too much image quality.

EARLY 1980's–PRESENT: CLINICAL APPLICATIONS

The early 1980's saw an intense interest in clinical applications of this new technique, which was still called NMR. Early clinical imaging was extremely difficult, time-consuming, and often disappointing. Spin-echo imaging was the workhorse of clinical MRI and was mainly based upon proton-density differences. Later, spin echo sequences also incorporated differences in T1-weighting. By 1982–1983, several groups pointed out that long, heavily T2-weighted spin echo sequences were better at highlighting pathology (28, 29).

CARDIAC MRI

It is difficult to determine with certainty when cardiac MRI was first performed. The heart and great vessels could be recognized on some of the early MR images that included the chest, but these investigations were not directed at the cardiovascular system. In 1980, Goldman and colleagues from the Massachusetts General Hospital and Harvard Medical School in Boston predicted the future of clinical cardiac MR (30). Most of their predictions were realized in the course of the ensuing quarter century. In 1981, Hawkes and colleagues from the University of Nottingham in the UK published a paper that was specifically directed at NMR imaging of the heart (31). Acquisition of a single image took 150 seconds with pixel dimensions of $4 \times 4 \times 10$ mm, interpolated to in-plane image display of 2×2 mm. The resultant images required corresponding anatomical sections and line drawing for illustration of the anatomy but were of sufficient quality to excite the investigators to realize the clinical potential of cardiac MRI. In the introduction to their paper, the authors point out the advantages of MRI in terms of avoiding the hazards of ionizing radiation and the lack of known biological damage, and recognize the limitations imposed by cardiac and respiratory motion. They pointed out to the potential to overcome image blurring due to cardiac motion by using ECG-triggering, a technique that was first described by Berninger et al. in 1979 in a CT experiment in dogs (32). Paul Lauterbur's group, in an experiment in dogs, first reported ECG-gated cardiac MRI in 1983 (33). A year later Higgins and colleagues from the University of California in San Francisco (UCSF) reported cardiac imaging using gated MR in 3 volunteers who were study investigators.

They tested three gating signal methods—peripheral pulse signals; Doppler flow signal; and ECG signal. The ECG triggering method proved superior to the other two and provided "sharp definition of internal cardiac morphology" (34).

Rob Hawkes may not only have made the first image of a heart but have also worked on the earliest versions of the steady state free precession (SSFP) imaging sequence, which is now the workhorse of cardiac MRI. Hawkes joined the faculty at the Brigham and Women's Hospital and Harvard Medical School in the early 1980's, following his mentor Bill Moore, for whom an ISMRM prize is awarded every year. Bill Moore died on the squash court at Harvard while playing squash with Rob Hawkes (Robert V. Mulkern, PhD: personal communication). SSFP faded after its first incarnation due to inferior image quality as compared with other gradient echo imaging techniques. In the late 1990's and early 2000's, it came roaring back once magnets had better homogeneity and the echo and repetition times have dropped down due to advances in fast switching gradient hardware.

In 1982, Peter Mansfield's group from Nottingham reported real time cine MRI of live rabbit heart. Using single shot echo planar imaging (a technique previously described by the same group), they produced cine loop images consisting of 6 frames, each taking 32 ms to acquire (32×32 pixels interpolated to 128×128) (35). In 1983, the group from UCSF reported NMR imaging of the heart and great vessels in 244 volunteers using a 0.35 T scanner (36). In the same year, Leon Axel's group published a 3D display of cardiovascular anatomy imaged by NMR, demonstrating the 3D nature of MRI (37). In the ensuing years, the field of cardiac MRI has witnessed rapid growth in the clinical and research arenas (Fig. 9). Table 1 summarizes some of the milestones in the development of cardiovascular MR.

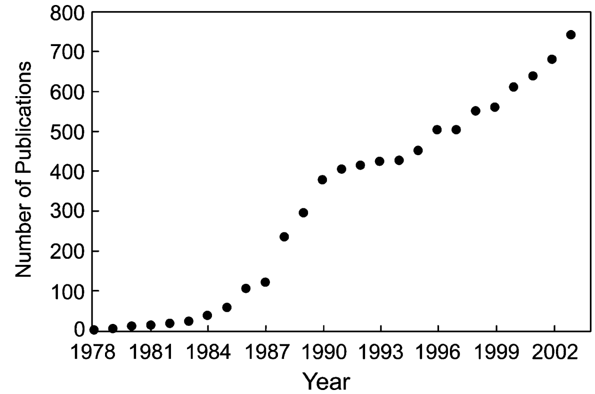

Figure 9. The graph shows the annual number of publications identified by a search of the National Library of Medicine from 1977 through 2004 for the terms *NMR and cardiac, NMR and heart, MRI and cardiac, or MRI and heart.*

MRI OF CONGENITAL HEART DISEASE

The same difficulty in ascertaining "firsts" in other areas of MRI exists when it comes to MRI of congenital heart disease. In 1982, Paul Lauterbur's group published the first paper I could identify that specifically targets a congenital cardiac anomaly. They used NMR to produce 3D images of artificially created muscular ventricular septal defect in preserved lamb hearts (38). They concluded, "Results of these experiments suggest that NMR zeugmatography will become a valuable addition to existing imaging techniques for the study of congenital heart disease." (39). Their prediction has manifested itself the quarter century that followed.

Table 1. Milestones in cardiovascular MR

MR Technique or Application	Year	Reference
Static cardiac imaging	1981	(31)
Dynamic cardiac imaging ("real time" echo planar gradient echo cine)	1982	(35)
MR evaluation of congenital heart disease (ventricular septal defect)	1982	(38)
Electrocardiographically-triggered cardiac MR	1983	(33)
MR assessment of myocardial infarction	1983	(56)
Blood flow measurements using phase velocity mapping	1984	(57, 58)
Clinical use of Gadolinium-enhanced MRI	1984	(59–62)
Steady state free precession MR	1986	(63)
MR imaging of coronary artery anomaly	1987	(64)
Myocardial tagging	1988	(65)
Assessment of myocardial viability using late gadolinium enhancement*	1988	(66)
First pass myocardial perfusion	1990	(67)
Dipyridamole stress CMR	1990	(68)
Dobutamine stress CMR	1992	(69)
In-vivo MR catheter tracking	1995	(70)
MR-guided cardiac catheterization in children	2003	(54)

Note: As with other developments in science and medicine, it is difficult to determine with certainty when and by whom new techniques were invented or were first applied in the clinical arena. In most circumstances, progress is built upon prior work. The dates reflect the first published clinical application.
*Use of gadolinium-DTPA in myocardial infarction was first published in 1984 (59).

Early applications of MRI in pediatric cardiology mainly involved static imaging using ECG-triggered spin echo techniques (39). Beginning in the late 1980's and early 1990's, the use of ECG-triggered gradient echo cine MR has gained acceptance as a useful tool for the assessment of ventricular function and blood flow in patients with congenital heart disease (40–43). During the same period, reports on measurements of blood flow rate and velocity by phase velocity cine MR in patients with shunt lesions and other congenital and acquired cardiac anomalies were first published (44–46). In the ensuing years, cardiovascular MRI rapidly gained acceptance as a useful clinical and research tool in patients with virtually all forms of congenital heart disease, ranging in age from newborns to adults (47, 48). Today, MRI is gradually replacing diagnostic cardiac catheterization in a variety of clinical circumstances such as anomalies of systemic and pulmonary venous anomalies (49), congenital anomalies of the coronary arteries (50), pre-bidirectional Glenn (or hemi-Fontan) shunt (51), coarctation of the aorta (52), before and after pulmonary valve replacement in patients with tetralogy of Fallot (53), and other conditions. Concurrently, new frontiers in pediatric cardiac MRI—MRI-guided cardiac catheterization (54) and fetal cardiac MRI (1)—are evolving.

The maturation of cardiac MRI has brought with it new challenges. As a growing number of pediatric cardiac programs endorse MRI as integral to their practice, the demand for trained experts exceeds the number of physicians with sufficient training. In 2005, new ACC/AHA/AAP guidelines for training in pediatric cardiology recommended, for the first time, that every pediatric cardiology fellow be trained in cardiac MRI (55). Indeed, the evolution of congenital cardiac MRI during the past quarter century has sustained Paul Lauterbur's 1982 prediction that ". . . MRI will become a valuable addition to existing imaging techniques for the study of congenital heart disease" (38).

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