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iSTORY

HISTORICAL PERSPECTIVE

The History of Cardiovascular Magnetic Resonance

Gerald M. Pohost, MD, FACC, FAHA

Los Angeles, California

The most beautiful experience we can have is the mysterious. It is the fundamental emotion that stands at the cradle of true art and true science . . .

Albert Einstein (1)

Cardiovascular magnetic resonance (CMR) has developed progressively during the past 3 decades. It began in the 1970s as a means for assessing high-energy phosphate myocardial metabolism in vitro with ^{31}P spectroscopy to measure adenosine triphosphate, phosphocreatine, and inorganic phosphate in isolated, perfused, rat hearts (2,3). It progressed in the 1980s with clinical imaging to assess cardiac morphology and function and to characterize myocardium (e.g., myocardial edema) using the proton (hydrogen) relaxation properties T1 and T2. Next, with the development of clinically applicable paramagnetic contrast agents, it was applied to the assessment of myocardial perfusion and the vasculature in the early 1990s and to the assessment of viability with the detection of myocardial scar in the 1990s and early 2000s. In addition, it was applied to the assessment of the vasculature, including the aorta and the peripheral and coronary arteries. Interestingly, it came full circle with the development and application of clinical methods to assess myocardial metabolism.

From the Keck School of Medicine; Viterbi School of Engineering, University of Southern Calfornia; and Loma Linda School of Medicine Loma Linda University, Los Angeles, California.

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It is the single technology that can be used to assess ventricular function, cardiac morphology, the vasculature, perfusion, viability, and metabolism, the so-called comprehensive cardiac examination—or, as I introduced in one of the initial talks to the Society of Magnetic Resonance in Medicine (SMRM) (which the author was instrumental in starting in 1982), the "one-stop-shop for cardiac imaging." All of this imaging was possible by using the principles of magnetic resonance without the need for ionizing radiation and with high resolution in 3 dimensions.

The NMR Phenomenon: Felix Bloch and Edwin Purcell (Nobel Laureates, 1946)

Magnetic resonance imaging (MRI), and the 5 Nobel Prize discoveries important in its development, evolved with the elucidation of the phenomenon in liquids and solids known as nuclear magnetic resonance (NMR), the development of NMR spectroscopy, and the discovery of the approaches that made it possible to image (NMR imaging, now known as MRI). Felix Bloch at Stanford on the west coast and Edwin Purcell at Harvard on the east coast discovered and independently reported the phenomenon of NMR in the same year—1946. For this discovery, both Bloch and Purcell received the Nobel Prize in Physics in 1952.

In brief, when a substance containing the nuclei of certain isotopes with magnetic polarity due to spin (examples of biologically rele-

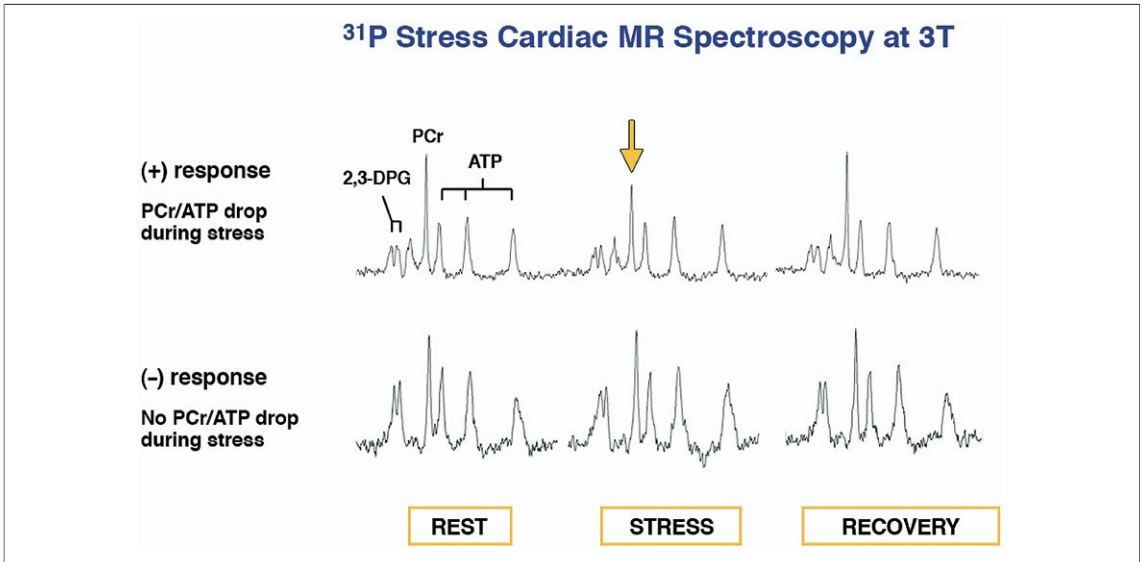

Figure 1. ^{31}P In Vivo Myocardial Spectra in Two Women With No Evidence of Significant Angiographic Coronary Disease

^{31}P in vivo myocardial spectra in 2 women with no evidence of significant angiographic coronary artery disease yet one **(upper row)** has an abnormal reduction in PCr/ATP with handgrip stress testing and the other **(lower row)** has a normal response in PCr/ATP with handgrip stress. Such findings suggestive of myocardial ischemia might indicate the presence of microvascular dysfunction within the myocardium (4). Spectroscopy performed in the year 2000, Heewon Kim, PhD, Keck School of Medicine, University of Southern California. PCr/ATP = phosphocreatine/adenosine triphosphate.

vant nuclei are hydrogen, hydrogen-1 or ^{1}H; carbon-13; fluorine-19; sodium-23; and phosphorus-31) was placed in a relatively high magnetic field (B) the Larmor equation indicated the frequency of the radio waves (ω) that were absorbed by the nuclei to induce resonance:

$$\omega = \gamma B$$

The gyromagnetic ratio (γ) is constant for each specific nucleus. The resultant resonance frequency allowed determination of the specific nucleus.

The Basis for NMR Spectroscopy: Richard Ernst (Nobel Laureate, 1966)

In 1991, Richard Ernst, PhD, received the Nobel Prize for his 1966 work in which he demonstrated that it was possible to substantially improve the sensitivity for generating NMR spectra from samples of inorganic, organic, and ultimately biological materials by applying the mathematical operation, the Fourier transformation to NMR. With these discoveries, Ernst provided the platform for development, the higher speed, and more efficient performance of NMR spectroscopy.

NMR Spectroscopy Applied to the Heart

Among the earliest NMR studies applied to the heart was ^{31}P NMR spectroscopy. Unfortunately, the term "NMR" has been truncated to the less-precise term, that of magnetic resonance (MR). In brief, at a given high magnetic field (e.g., 8.4T), the radiofrequency energy at the Larmor frequency is absorbed and released to and from the hydrogen nuclei of an isolated perfused rat heart. Resultant radiofrequency signal output is subjected to the mathematical operation—Fourier transformation as per the approach of Ernst. This step converts the released energy in the time domain (K space) into the spatial domain (a spectrum) (Fig. 1) (4). The peaks contained in the spectrum represent different nuclear species within a molecule. In this case, there are 3 peaks for ATP (one each for the gamma, alpha, and beta phosphates of ATP), for phosphocreatine (PCr), and for several phosphorus-containing molecules in the inorganic phosphate region of the spectrum (including 2, 3 diphosphoglycerate in red blood cells and inorganic phosphate within muscle and other tissues).

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NMR Imaging: Paul Lauterbur and Peter Mansfield (Nobel Laureates, 2003)

In the early 1970s, both Paul Lauterbur, PhD, and Peter Mansfield, PhD, discovered the basis for NMR imaging. When one adds an additional, small magnetic field spatial gradient to the spectrometer, the variations in resonance induced within the sample interrogated were different from point to point. This addition provided a means to generate an image. Lauterbur called this approach the imaginative term "zeugmatography." Zeugma is a Greek-derived term, meaning to combine 2 components. In this case, he was referring to the generation of images by combining 2 energy sources, magnetic fields and radiofrequency. The addition of orthogonal magnetic field gradients allowed images (i.e., "...tography") to be generated. Mansfield provided the basis for the generation of images at high-speed imaging, which he termed "echo-planar" imaging. Accordingly, Mansfield had a profound impact on the utility of NMR imaging (zeugmatography) for cardiovascular applications. Lauterbur and Mansfield received the Nobel Prize in Medicine and Physiology in 2003.

Early NMR Imaging

Nuclear MRI was performed in several physics laboratories, including those of Lauterbur, Mansfield, and Raymond Andrew. Interestingly, substantial independent imaging development took place in both the Mansfield and Andrew laboratories at the University of Nottingham in the United Kingdom. The first laboratories for medical NMR imaging included the laboratories at the University of California in San Francisco; in the Department of Radiology headed by Alexander Margulis, MD. The principal group of scientists included Leon Kaufman and Lawrence E. Crookes, at the University of Aberdeen in Scotland in the laboratory of John Mallard, PhD; and at the Massachusetts General Hospital in a multidepartimental laboratory under the aegis of this author. Clinical MRI were in part outgrowths of the activities of this laboratory.

NMR Imaging in Boston

Among the earliest seeds for the development of the field of CMR occurred at the Massachusetts General Hospital (MGH) in approximately 1980. Here a collaboration was initiated between Joanne S. Ingwall, PhD, and Gerald M. Pohost, MD. Ingwall, a widely recognized and highly respected cardiac cell biologist, was recruited to set up a laboratory at the Peter Bent Brigham Hospital in the late 1970s. The collaboration started with the assessment of Thallium-201, the radionuclide myocardial perfusion imaging agent. Ionic thallium chloride had interesting and clinically relevant properties. They were awarded a National Institutes of Health (NIH) research grant (R01) to study the mechanism of thallium redistribution. A key component was to determine the relationship between thallium uptake and viability. Ingwall used perfusion independent isolated fetal mouse hearts in cell culture to assess the relationship between thallium uptake and cell death. The results as published in a manuscript (5) suggested that thallium uptake was related to the amount of viable myocardium. The amount of lactic dehydrogenase (LDH) released into the culture medium was used as the marker to quantify the amount of myocardial cell death. Virtually simultaneously, Ingwall was working at the Francis Bitter National Magnet Laboratory at the Massachusetts Institute of Technology using a 270-MHz NMR spectrometer to study myocardial phosphate metabolism in an isolated perfused Langendorff rat heart model. Coupled with the work of Lauterbur, Ingwall predicted a potential clinical future in the imaging of the distribution of ATP and phosphocreatine in the myocardium to determine the distribution and extent of myocardial ischemia and viability. Ingwall's enthusiasm for NMR spectroscopy and her studies of myocardial phosphate metabolism were among the most important factors influencing the author's early interest in NMR. Subsequently, a collaboration was initiated in the late 1970s to include Eric Fossel, PhD, an NMR spectroscopist, and Mark Goldman, MD, a cardiologist at the MGH, Ingwall and Pohost. This collaboration resulted in an initial article predicting many of the present day clinical applications of NMR to the study of cardiovascular disease (6).

It was clear that an essential component to the development of a program in NMR imaging was the recruitment of an expert NMR physicist, as well as new instrumentation and funding. We went to the UK and visited the laboratories of Andrew and one of his principal students, Waldo Hinshaw, PhD. Ultimately, we attended the British Society of NMR meeting in York, England. Hinshaw, Ingwall, Fossel, Goldman, and Pohost presented their perspective on the future clinical applications of NMR at the headquarters of Johnson and Johnson.

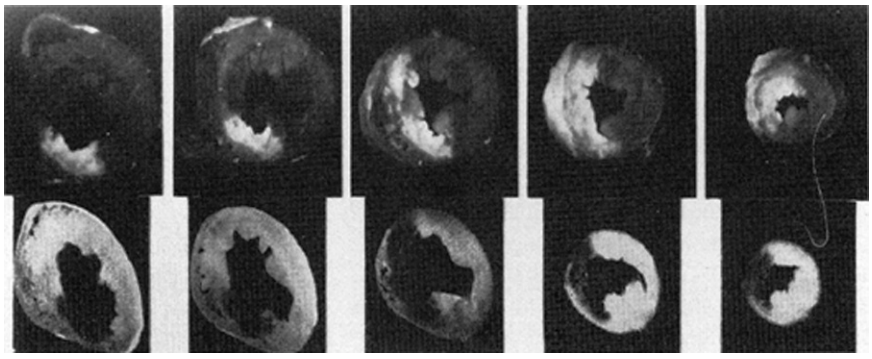

Figure 2. In Vitro NMR Perfusion Images of Canine Heart With LAD Occlusion at 1.44T (Lower Row of Short-Axis Images)

Paramagnetic $MnCl_2$ was administered in vivo soon after the occlusion. For comparison, TTC staining was used to identify the territory of infarction. This is among the first cardiac NMR studies to be published. Reproduced with permission from Goldman et al. (11). LAD = left anterior descending artery; NMR = nuclear magnetic resonance; TTC = triphenyltetrazolium chloride.

Johnson and Johnson soon acquired the imaging instrumentation company Technicare (Solon, Ohio)—subsequently, Dr. Hinshaw moved to Technicare; Johnson and Johnson funded the MGH team; and Technicare provided the group with 2 new NMR imaging devices: one with a 1.44T, ~8-cm bore, superconducting magnet, and the second with a 0.15T, 40-cm bore resistive magnet. The small-bore system was to be used for laboratory-type studies, whereas the larger-bore system was used for both laboratory and clinical neuroimaging.

The team at the MGH continued to expand with the development of a multidisciplinary group including Ian Pykett, PhD, an imaging physicist from the Peter Mansfield group in Nottingham, UK; J. Phillip Kistler, MD, a neurologist who specialized in stroke; Jeffrey Newhouse, MD, a radiologist with interest in x-ray computed tomography; Thomas Brady, MD, a nuclear medicine physician, recruited as a fellow from the University of Michigan; C. Tyler Burt, PhD, an established NMR spectroscopist; Ferdi Buonano, MD, a neurologist with an interest in imaging; and Bruce Rosen, MD, a student and then resident in radiology. The earliest studies from the MGH NMR imaging laboratory demonstrated that cerebral infarction could be clearly delineated in laboratory animal models of ischemic stroke using the 0.15T (restive magnet) platform (7,8). In another study the remarkable tugging effects of NMR imaging on a ferromagnetic aneurysm clip in a laboratory animal was demonstrated (9).

Early cardiac imaging studies emphasized the interest of the author in myocardial perfusion imaging (10). The first cardiac high resolution NMR imaging study to be published used the intravenous administration of paramagnetic $MnCl_2$ (as originally suggested by Lauterbur) intravenously injected in a laboratory animal with a left anterior descending coronary ligation (Fig. 2). It was known from radionuclide studies with ^{52m}Mn that manganese ion was deposited in the myocardium. The hearts were imaged in the small-bore, higher-field magnet with an SSFP pulse sequence. The time of repetition was 7.3 m; slice thickness was 3 mm; slice acquisition time was 2.3 min; images were acquired using a 256 × 256 matrix interpolated to 512 × 512. Images demonstrated myocardial perfusion deficits with exquisite detail. The heart was then stained with the supravital dye triphenyltetrazolium chloride. When we considered the volume of infarction, the correlation between NMR and triphenyltetrazolium chloride was $r = 0.94$. On a slice-by-slice basis, the correlation was $r = 0.93$.

NMR was clearly gaining scientific momentum, as it was highlighted in a *Disease-a-Month* volume on NMR imaging (11). A review group for the American Medical Association (AMA) chaired by the author wrote a series of articles on NMR for the various organ systems imaging for the *Journal of the American Medical Association* (12).

Imaging and Spectroscopy Between Boston and Birmingham

One of the interesting aspects of NMR is the biophysical properties that one could image. They included the relaxation properties T1 (spin lattice relaxation) and T2 (spin spin relaxation). The Sarnoff Foundation provided funding to

engage medical students in a personalized research experience with respected cardiovascular scientists. Adam Ratner and Robert Canby were 2 such highly productive fellows.

Adam Ratner was involved in studies in which imaging of T1 and T2 was used to assess the severity of a myocardial ischemic insult. It appeared that these parameters would increase when the laboratory animal was subjected to a myocardial ischemic insult and that this increase was in part due to myocardial edema. In one such study, published in *Circulation* (13), changes in TI and T2 were compared with myocardial perfusion in dogs both with and after coronary artery occlusion. In the occlusion model, there was an inverse relationship between the relaxation times and flow. In the reperfusion model, there was a relationship between T1 and T2 and flow during the period of reperfusion. The results suggested that the proton relaxation times corresponded to the severity of an ischemic insult. It was concluded that because the use of NMR imaging could display differences in relaxation times, imaging could provide a means to assess noninvasively the severity of the myocardial ischemic insult.

Canby et al. (14) were responsible for a study published in the *Journal of the American College of Cardiology* in which they demonstrated that the ^{31}P NMR spectroscopy-determined phosphocreatine/adenosine triphosphate ratio was inversely related to the severity of histologically demonstrated cardiac allograft rejection in a rat model. This relationship suggested that in vivo^{31}P NMR spectroscopy might be useful for detecting and assessing the severity of cardiac rejection. There were many distinguished collaborators in my NMR program at the University of Alabama at Birmingham. They included (in alphabetical order): Alain Bouchard, MD (cardiologist); James Balschi, PhD (spectroscopist); Halima Benjelloun, MD (cardiologist); Vera Bittner, MD (cardiologist); John Chatham, PhD (spectroscopist); Greg Cranney, MD (cardiologist); Mark Doyle (physicist); Lou Dell'Italia, MD (cardiologist); Gabriel Elgavish, PhD (lanthanide chemist); Bill Evanochko, PhD (spectroscopist); John Forder, PhD; Hoby Hetherington, PhD; Jan den Hollander, PhD; Lynne Johnson, MD (nuclear cardiologist); Ruben Kuzniecky, MD (neurologist); YT Lim, MD (cardiologist); Chaim Lotan, MD (cardiologist); Tetsuya Matsuda (cardiologist); Jeannie McMillin, PhD (cardiac biochemist); Julie Pan, MD, PhD (neurologist); Martin Pike, PhD (spectroscopist); Russell Reeves, MD (cardiologist); Don Twieg, PhD (biomedical engineer); and Paul Wolkowicz, PhD (cardiac biochemist).

The New Societies: SMRM Then International Society for Magnetic Resonance in Medicine (ISMRM), the Society of Cardiovascular Magnetic Resonance

The Society of Magnetic Resonance in Medicine. It was clear that NMR was going to become an important research and clinical tool. I thought that it would be useful to start a multidisciplinary scientific/clinical society dedicated to new developments in NMR and to education. Dr. Ingwall was also very much in favor of such a society. Although she did not participate in the Society's organization at that time, she became its president at a later date. The first step was to organize an Executive Committee. Accordingly, we created a 5-person Executive Committee. Tom Budinger, MD, PhD, was an ideal person to catalyze the formation and growth of this new Society. He was a professor in the Department of Electrical Engineering and Computer Sciences, University of California, Berkeley, and, a key member of the Lawrence Berkeley National Laboratory. He had a great interest in NMR and had made substantial contributions to the field of positron emission tomography and NMR. Tom enthusiastically agreed with the formation of this Society and with the other members of the Executive Committee. Dr. Lauterbur also thought it was a great idea and we thought it most appropriate that he be the Society's first President. I agreed to take the position of Secretary/Treasurer.

The other 2 members of the Executive Committee included Britton Chance, PhD, a pioneer in biophysical science at the University of Pennsylvania and Alex Margulies, MD, the head of one of the most advanced radiology departments in the world—the University of California at San Francisco. The first job of the Executive Committee was to determine how many and who should be members of the initial Board of Trustees. Finally, the *Journal*, the *Journal of Magnetic Resonance in Medicine*, needed to be started. In addition to Mansfield, who we recruited, the rest of the Board included: David Hoult, PhD, (NMR physicist); Seymour Koenig, PhD (NMR

physicist, paramagnetics); John Mallard, PhD; George Radda, PhD (in vivo NMR spectroscopist); Robert Schulman, PhD (Yale spectroscopist); Katherine Scott, PhD (NMR spectroscopist); Harold Swartz, PhD (electron spin resonance); and several other notables in the field. It is important to note the diversity of the fields represented by the members of the Board. They were not all physicians; they were not all radiologists, cardiologists, or neurologists; they were not all spectroscopists, physicists, or engineers. They represented scientists and physicians spanning virtually every aspect of magnetic resonance.

The first job was to plan the first annual meeting. It took place in Boston. We planned for an attendance of 250 but, by the end of the first day of the meeting, the room at the Park Plaza Hotel had to be expanded to accommodate more than 800 attendees. Subsequently, the annual meetings increased in attendance and were an important source for support and growth of the Society. What happened to the SMRM? After almost 10 years of existence, it merged with the newer and considerably smaller Society comprised largely of radiologists—SMRM; its name was changed to ISMRM and its multidisciplinary composition diminished.

The Society of Cardiovascular Magnetic Resonance. There was so much potential for the application of MR approaches to the cardiovascular system that I organized several annual meetings sponsored by the American Heart Association in collaboration with Charlie Higgins, MD, a pioneer in cardiovascular radiology at the University of California at San Francisco. These meetings became increasingly more popular and after several years I brought up the concept of establishing another Society focused on cardiovascular magnetic resonance. The response was mixed. Some were very much against it, but the majority was for it. Professor Donald Longmore, MD, a highly respected surgeon and MRI physician from the Royal Brompton Hospital in London was the most supportive. Accordingly, we proceeded to organize a new Society similar to the way in which we had organized the original SMRM. We developed a Board, an Executive Committee, a Journal (the *Journal of Cardiovascular Magnetic Resonance,* or JCMR), an annual meeting and several committees. That Society is growing and has been instrumental in providing an educational and scientific mission. It has an annual meeting every winter and it is truly international. It has chapters in most continents including the latest chapter in Latin America. Although there aren't any Nobel Laureates in key Society positions yet, Mansfield, Lauterbur and Ernst have been honorary members of the editorial board of the *JCMR*.

Conclusions

There have been many changes since those early days. The old and remarkable SMRM is now the ISMRM. It remains an excellent society. Yet nothing could replace the excitement and enthusiasm observed at the meetings of the more disciplinarily diverse SMRM with so many pioneers in attendance. Cardiovascular imaging has substantially progressed. Echocardiography and nuclear cardiology remain the basics of cardiac imaging and can be found in many cardiologists' offices. Some larger practices have computed tomography angiographic equipment and others even have CMR. Since 1986, the official name for the discipline has become MRI rather than the more precise NMR imaging. In fact, NMR is no longer used in the context of imaging. Why was the name changed? It was supposed to be changed to prevent lay people from being concerned that they were being exposed to a nuclear process during their imaging study. Yet, patients don't generally complain when they undergo a nuclear medicine study. Nevertheless, even the 2003 Nobel Committee used the term CMR. Magnetic field strength for cardiovascular imaging has increased from 0.1 to 0.2T to 1.5T, and some are using platforms of 3.0T. Magnets are now being built for commercial use at field strengths as high as 7.0T. CMR continues to evolve technically while the other imaging technologies are changing at a slower pace. Like echocardiography, CMR has no ionization properties. Contrast agents generally are safe, with the exception of studies in patients with end-stage renal disease and new contrast agents are being developed as nanotechnology and molecular imaging approaches continue to develop. In fact, many of us believe that CMR will ultimately provide the "one-stop-shop" for cardiovascular imaging.

Reprint requests and correspondence: Dr. Gerald M. Pohost, 9777 Wilshire Boulevard, 4th Floor, Beverly Hills, California 90212. *E-mail: gerry2710@yahoo.com.*

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