Diagnostic Imaging 24(13):65-73 CARDIO IMAGING: December 2002

Faster speed, better spatial resolution lead 3T benefits

New pulse sequences and strategies for cardiac imaging and spectroscopy must be developed

By John R. Forder, Ph.D., Krishna Nayak, Ph.D., and Gerald M. Pohost, M.D.

The FDA has approved 3T MR scanners for whole-body, including cardiovascular, imaging, and multinuclear spectroscopy at this field strength is pending approval. The three main vendors of clinical MR scanners-GE, Philips, and Siemens-all have clinical 3T whole-body platforms available.

While 3T platforms have demonstrated a clear advantage over 1.5T and lower fields in many neuroimaging and neurospectroscopy applications, pulse sequences and strategies for cardiac imaging and spectroscopy at the higher field strength are under active development. Merely transporting sequences that were effective at lower fields will not be sufficient. Rather, pulse- and gradient-sequence design and implementation must take into account the characteristics and physics of the higher field.

Signal to noise improves at higher field, due to the increased polarization of the nuclear spins present in the magnetic field, and the transverse relaxation rates are increased. Unfortunately, motion, flow, and susceptibility effects also increase; these problems are intrinsic to cardiac imaging and spectroscopy. The interactions of the radio-frequency wavelengths that are required and the impact of the magnetohydrodynamic effects on electrocardiogram triggering, which has not been important at 1.5T, may need to be addressed. Standing waves due to body dielectric resonances pose new challenges for the design of receiver coils. And increased T1 relaxation times of blood, myocardium, and epicardial fat must be considered with black blood sequences or in fat-saturation schemes.

Despite the difficulties inherent in imaging at 3T, there are significant benefits. The higher field (greater than or equal to3T) scanners will improve a number of areas related to clinical cardiac studies: spatial resolution, fast imaging speed, myocardial tagging techniques, perfusion imaging, development of cardiac blood oxygen level-dependent (BOLD) imaging, MR-guided catheter placement, and cardiac spectroscopy.

ADVANTAGES OF 3T CARDIOVASCULAR IMAGING

The improved signal to noise can be used to increase either the speed of the imaging protocols or the spatial resolution. This has been done with extraordinary results in neuroimaging,[1] with brain structures identifiable at 3T that could not be identified at lower fields. Improvement in spatial resolution comes at the price of speed, however, and the specific goals of the study must be identified so that the improved signal can be used most effectively. In general, spatial resolution can be increased by up to 40% (compared with 1.5T using the same imaging time and signal-to-noise ratio). Areas in which additional spatial resolution may be useful in cardiac studies include perfusion imaging, viability imaging, coronary imaging (Figures 1 and 2), and cardiac spectroscopy (Figure 3).

With the introduction of variable density sampling methods, and generalized parallel imaging and reconstruction methods such as SENSE and SMASH, signal to noise can be freely traded off for imaging speed. This approach may be of particular benefit to ventricular function and wall motion imaging, especially under stress conditions requiring frame rates of at least 24 images per second.

Single breath-hold cardiac imaging has largely eliminated respiratory motion artifacts, producing high-quality images of the heart.[2] In order to achieve the short data acquisition times associated with fast imaging sequences at 1.5T, small flip angles are used. As a result, motion artifacts are reduced in the images, but this improvement in image quality also lowers the SNR. The shift to higher fields improves the SNR.[3] Increased speed reduces motion and flow artifacts,

allowing real-time acquisition and display of cardiac images. Studies for the analysis of wall motion abnormalities can be completed in a single breath-hold with excellent signal to noise. In addition, the longer longitudinal (T1) relaxation times seen at 3T are useful in measurements of regional myocardial wall motion analysis. Myocardial tagging relies on RF interference patterns that are generated to noninvasively label tissue position and allow point-tracking of the myocardial wall throughout the cardiac cycle.[4,5] The increased T1 relaxation rates result in increased RF tag line persistence at higher fields, simplifying the analysis of regional wall motion by ensuring that the tag lines continue throughout the cardiac cycle.

Measurements of myocardial tissue perfusion can be classified into two broad categories: those that require administration of an exogenous contrast agent and those that rely on noninvasive, or spin, labeling. Administration of contrast relies on examination of the upslope of the tissue intensity during the first pass of the contrast agent.[6-8] Higher magnetic field may result in a greater dynamic range in the tissue intensity enhancement and, combined with reduced scan times for the fast imaging sequences, greater temporal resolution in quantitating the increase in tissue intensity.

In addition to perfusion imaging performed with contrast agents, noninvasive perfusion measurements made using spin-labeling techniques have been applied with some success in the heart.[9-12] The increase in signal to noise at higher field, coupled with the increased transverse (T1) relaxation times of the tissue, benefit quantitative perfusion imaging. This technique relies on inversion of the spins within the imaging plane, followed by a delay equal to the T1 relaxation time of the tissue and subsequent imaging.[10,12] Images are acquired with and without the inversion pulse, and regional perfusion maps are constructed from the data.

Viability testing in the myocardium using delayed contrast enhancement has been exploited at 1.5T.[13-16] Gadolinium chelates persist in the border areas of myocardial infarcts, and testing in these regions agrees well with viability measurements made in animals using triphenyl tetrazolium chloride staining. Since the contrast-based enhancement is based on the shortening of the T1 relaxation rates of the surrounding tissue, the prolongation of T1 relaxation rates at higher field promises to deliver an increase in the dynamic range that can be measured. Further investigations into the mechanism of delayed contrast enhancement at 3T are warranted.

MRI-guided placement of intravascular catheters relies on real-time imaging and sufficient dynamic range in the image sensitivity to spin-spin relaxation to visualize the catheter. Low flip angle, short repetition times (TR), and increased sensitivity to susceptibility suggest that these applications will benefit from the shift to 3T. Catheter-based MR receiving coils will also benefit from higher field, as the increase in signal to noise will aid in both the high-resolution imaging of the vessel wall and attempts to characterize atherosclerotic plaque by spectroscopic means.

Measurements of regional oxygen concentration performed at high field strength offer an increase in sensitivity by exploiting the BOLD effect, which has been used in the brain to yield new information regarding neuronal activation.[17-22] The relationship between deoxyhemoglobin content and image intensity also exists in the heart.[10,12,23-28] BOLD imaging is based on the observation that while oxyhemoglobin is diamagnetic, deoxyhemoglobin is paramagnetic.[29] The heme groups in deoxyhemoglobin act like tiny bar magnets, disrupting the magnetic field of nearby nuclei, which then do not align as well with the external magnetic field, and the net magnetization of the tissue decreases. This translates into a decrease in image intensity that is proportional to the amount of deoxyhemoglobin present. Susceptibility effects are more pronounced at higher fields, and therefore susceptibility-based imaging sequences acquire increased sensitivity to oxygenation changes. Several groups are working to quantitate the deoxyhemoglobin effect. This work will be aided by a shift to higher fields and may make imaging of the regional oxygenation status of the myocardium possible.[12,27,28]

DISADVANTAGES OF 3T CARDIOVASCULAR IMAGING

Literature values[30] of tissue dielectric constants allow calculation of the RF wavelength within the body to be about 25 to 30 cm at 3T; this is approaching the size of the receiver coil and human body dimensions. Besides the B1 field pattern of the RF transmit coil, body dielectric resonances or standing wave phenomena may influence the electromagnetic field distribution inside the body,30 making receiver coil design more difficult than at lower field strengths. For cardiac imaging, phased-array coils consisting of two to four elements have strongly improved

image quality from surface coils.[31-35] Bottomley et al[32] reported an optimum design of phased-array coils for cardiac imaging at 1.5T. Similar optimization will be needed for phased-array coils at 3T, due to the shorter RF wavelength.

RF penetration decreases at higher fields, and RF power deposition increases for pulse sequences, since the amount of energy required to tilt the nuclear spins out of alignment with the magnetic field increases. This precludes the use of some sequences, such as multislice fast spin-echo-the power required for the sequence of 180 degrees refocusing pulses would effectively cook the tissue under study. Refocused steady-state free precession (SSFP) sequences, also known as true fast imaging with steady-state precession (TrueFISP), or fast imaging employing steady-state acquisition (FIESTA), which often use high flip angles and short TR, will also require careful design so as to not exceed specific absorption rate (SAR) limits. SSFP sequences that are highly sensitive to off-resonance frequencies will require shorter TRs to avoid banding artifacts.

Fast imaging techniques such as interleaved spiral scans [36-39] and interleaved echo-planar imaging [40-43] are commonly used for real-time cardiac imaging at lower magnetic field strengths. These techniques are particularly sensitive to susceptibility artifacts, especially near the heart-lung boundary; field inhomogeneities; and low T2* values within the heart, especially adjacent to the coronary sinus (the posterior vein of the left ventricle).[44] These may lead to signal losses and image distortions that are more pronounced at higher field strengths.

Increased T1s will also require timing adjustments in inversion recovery-based imaging sequences such as double-inversion black blood imaging and inversion recovery fat suppression. Both techniques will require longer inversion times to achieve the desired contrast. The longer T1s will be beneficial in other cases, such as selective inversion recovery and myocardial tagging sequences, which depend on an RF saturation or inversion tag that persists for some time. Longer T1s allow a significantly longer imaging period after initial contrast preparation.

Gradient switching to accommodate fast imaging sequences at 3T also poses a problem: The magnitude of the gradients and the ramp times required may cause peripheral nerve stimulation. GE, Philips, and Siemens have addressed this by incorporating shorter gradient sets, thereby decreasing the power requirements and minimizing peripheral nerve stimulation.

3T CARDIOVASCULAR SPECTROSCOPY

Higher fields in spectroscopy offer major benefits that are important for the cardiologist. Increased signal to noise allows signals that could not be observed at 1.5T to be reliably detected at 3T. This has important implications for cardiac phosphorus-31 nuclear MR spectroscopy, in which routine identification of the intracellular inorganic phosphate peak is not possible at 1.5T. The ratio of inorganic phosphate (Pi) to phosphocreatine (PCr) is a more sensitive indicator of myocardial ischemia than the ratio of PCr to adenosine triphosphate (ATP).

The higher field increases our ability to distinguish between adjacent peaks in the NMR spectrum. Improvement in spectral resolution allows peaks that overlap at 1.5T to be resolved at the higher field, which would assist, for example, in the separation of 2,3 diphosphoglycerate from Pi. The narrower line widths in higher fields also improve resolution of the frequency of peaks that can be observed. Improved frequency assignment of the Pi peak, for example, should lead to higher resolution in the measurement of intracellular pH, calculated from the frequency shift of the Pi peak relative to PCr.

Increased field strength leads to stronger coupling between nuclei, and techniques that improve the detection of relatively weak nuclei, such as carbon-13, will benefit from the shift to the higher field. One such technique, cross-polarization transfer, transfers the signal from the C-13 nuclei to adjacent protons for detection.45-48 Higher field increases the signal to noise of the proton nuclei directly, but the coupling between the proton and the carbon is also increased at higher field, resulting in additional benefit.

As with imaging, the higher SNR can be used to increase the speed with which spectroscopic data are acquired or to decrease the area from which the data are acquired. A decrease in the area that is queried is of paramount importance to cardiovascular spectroscopy, since issues regarding signal contamination from adjacent tissue (ventricular blood pool, skeletal muscle, or liver) are real concerns. Combination of 3D chemical shift imaging and spatial

localization with optimal pointspread function (SLOOP) should permit localization of spectra from the ventricular wall with minimum contamination.

Traditional spectroscopic localization methods do not use gradients during the data acquisition, due to the risk of contamination from signals outside the volume of interest. Even commonly used spectroscopic volume selection methods such as ISIS and DRESS that employ gradients do so only to select the region from which spectra are acquired. Gradients are turned off for the data acquisition. Additional acquisition speed can be gained, however, by more closely linking spectroscopic and fast imaging methods. By relaxing the requirement not to employ gradients during the acquisition, rapid imaging strategies such as echo-planar imaging can be incorporated to increase the speed of data acquisition for spectroscopic imaging. Advances in scanner hardware have made such strategies possible.

Clinical spectroscopic studies have used several isotopes to examine energetic status, lipid content,[49-51] lactate concentrations,[52-65] and ionic homeostasis.[66] Reports using P-31 NMR spectroscopy combined with handgrip stress suggest this technique may have clinical utility in the diagnosis of myocardial ischemia.

Although the sensitivity of the carbon nucleus is much lower than that of phosphorus, the relatively low natural abundance (~1.1%) makes this atom ideal for the study of intermediary energy metabolism. Infusion of C-13-enriched substrates facilitates assessing incorporation into metabolite pools with very little background signal. With a few exceptions, this nucleus has not yet been used in clinical MR studies. With the introduction of higher fields for clinical magnets, carbon spectroscopy may become feasible as a clinical tool.

Clinical phosphorus spectra from heart muscle can show up to seven peaks: the three phosphates associated with ATP (a, b, and g), PCr, Pi, phosphomonoesters, and phosphodiesters (Figure 3). The ATP and PCr have been used for clinical studies of myocardium on conventional 1.5T clinical magnets. With the wider availability of clinical 3T magnets and FDA approval for their application to body imaging, the visualization of Pi will become possible, allowing improved assessment of changes in PCr and of intracellular pH.

The b-phosphate peak is used to estimate ATP concentration because this peak position does not experience contamination by signals from adenosine monophosphate and adenosine diphosphate. The myocardium exhibits tight control over the production and utilization of ATP, with synthesis carefully matched to metabolic demand. Since the coronary circulation extracts a high percentage of the oxygen that is present in the blood, increases in metabolic demand are usually accompanied by increases in coronary blood flow.

Under normal conditions, more than 80% of the ATP produced is used for mechanical contraction. Increased heart rate or left ventricular contractility is usually accompanied by an increase in coronary blood flow. In the presence of a critical stenosis, however, the coronary vasculature may already be maximally vasodilated. Only under conditions of increased workload-either through mechanical activity or by pharmacologic means-does the PCr decrease to maintain the ATP pool. It is this paradigm, the P-31 NMR stress test, that is employed in spectroscopy to diagnose myocardial ischemia.

The ratio of PCr to the b-ATP peak is commonly used to provide insight into myocardial energetics and to assess the severity of an ischemic event. It has been used to diagnose myocardial ischemia in the absence of overt epicardial coronary artery disease,[67] suggesting the potential for noninvasively assessing microvascular disease in the heart.

Pi also increases during ischemia, due to increased ATP hydrolysis that is not matched by an increased ATP synthesis. Although the resonance position of the Pi relative to PCr can be used to calculate pH, the magnetic fields used by most clinical platforms do not afford the sensitivity to reliably detect this peak.

The increasing availability of higher field magnets for clinical use will allow a decrease in the myocardial volume that is being interrogated. This will minimize the contribution of 2,3 diphosphoglycerate, which is present in red blood cells, from the left ventricular blood pool and increase the likelihood of routine detection of Pi. These changes are summarized in the accompanying table. The ratio of Pi to PCr may serve as a more sensitive index of myocardial ischemia, since Pi should increase while PCr decreases.

The increase in field strength from 1.5T to 3T will require development of sequences that have been tailored for the higher field, taking into account susceptibility, motion artifacts,

relaxation times, and SAR. The benefits of the higher field are readily apparent, with increased signal to noise that can be used to increase spatial or temporal resolution. Areas of research that depend on susceptibility for measurements, such as contrast-based and oxygen-sensitive techniques, will gain from the higher field, as will techniques such as myocardial tagging and spin-labeling perfusion measurements that can take advantage of the increased T1 relaxation. It will not be long before 3T becomes the standard for cardiac MR studies.

Dr. Forder is an associate professor of medicine and director of NMR science in cardiovascular medicine and Dr. Pohost is a professor of medicine and chief of cardiovascular medicine, both at Keck School of Medicine at the University of Southern California in Los Angeles, CA. Dr. Nayak is a lecturer and research associate in the Department of Electrical Engineering at Stanford University in Stanford, CA.

References

1. Thulborn KR. Clinical rationale for very-high-field (3.0 Tesla) functional magnetic resonance imaging. Top Magn Reson Imaging 1999;10:37-50.
2. Atkinson DJ, Edelman RR. Cineangiography of the heart in a single breath hold with a segmented turboFLASH sequence. Radiology 1991;178:357-360.
3. Noeske R, Seifert F, Rhein KH, Rinneberg H. Human cardiac imaging at 3 Teslausing phased array coils. Magn Reson Med 2000;44:978-982.
4. Zerhouni EA, Parish DM, Rogers WJ, et al. Human heart: tagging with MR imaging-a method for noninvasive assessment of myocardial motion. Radiology 1988;169:59-63.
5. Zerhouni EA. Myocardial tagging by magnetic resonance imaging. Coron Artery Dis 1993;4:334-339.
6. Wilke N, Simm C, Zhang J, et al. Contrast-enhanced first pass myocardial perfusion imaging: correlation between myocardial blood flow in dogs at rest and during hyperemia. Magn Reson Med 1993;29:485-497.
7. Wilke N, Kroll K, Merkle H, et al. Regional myocardial blood volume and flow: first-pass MR imaging with polylysine-Gd-DTPA. J Magn Reson Imaging 1995;5:227-237.
8. Machnig T, Koroneos A, Engels G, et al. [Quantitative evaluation of myocardial perfusion with ultrafast magnetic resonance tomography]. Z Kardiol 1994;83:840-850.
9. Detre JA, Zhang W, Roberts DA, et al. Tissue specific perfusion imaging using arterial spin labeling. NMR Biomed 1994;7:75-82.
10. Reeder SB, Atalay MK, McVeigh ER, et al. Quantitative cardiac perfusion: a noninvasive spin-labeling method that exploits coronary vessel geometry. Radiology 1996;200:177-184.
11. Belle V, Kahler E, Waller C, et al. In vivo quantitative mapping of cardiac perfusion in rats using a noninvasive MR spin-labeling method. J Magn Reson Imaging 1998;8:1240-1245.
12. Reeder SB, Holmes AA, McVeigh ER, Forder JR. Simultaneous noninvasive determination of regional myocardial perfusion and oxygen content in rabbits: toward direct measurement of myocardial oxygen consumption at MR imaging. Radiology 1999;212:739-747.
13. Kim RJ, Hillenbrand HB, Judd RM. Evaluation of myocardial viability by MRI. Herz 2000;25:417-430.
14. Mazur W, Nagueh SF. Myocardial viability: recent developments in detection and clinical significance. Curr Opin Cardiol 2001;16:277-281.
15. Smith HJ. Contrast-enhanced MR imaging in the diagnosis and preservation of cardiac viability. Acta Radiol 2001;42:539.
16. Sandstede JJ, Beer M, Lipke C, et al. Time course of contrast enhancement patterns after Gd-BOPTA in correlation to myocardial infarction and viability: a feasibility study. J Magn Reson Imaging 2001;14:789-794.
17. Ogawa S, Tank DW, Menon R, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci U S A 1992;89:5951-5955.
18. Duyn JH, Moonen CT, van Yperen GH, et al. Inflow versus deoxyhemoglobin effects in BOLD functional MRI using gradient echoes at 1.5 T. NMR Biomed 1994;7:83-88.
19. Folkers P, Luyten P. From morphology to function: new neuro applications in functional magnetic resonance. Ital J Neurol Sci 1997;18:367-372.
20. Booth JR, Macwhinney B, Thulborn KR, et al. Functional organization of activation patterns in children: whole brain fMRI imaging during three different cognitive tasks. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:669-682.

21. Ugurbil K, Adriany G, Andersen P, et al. Magnetic resonance studies of brain function and neurochemistry. Annu Rev Biomed Eng 2000;2:633-660.
22. Kim SG, Ashe J, Georgopoulos AP, et al. Functional imaging of human motor cortex at high magnetic field. J Neurophysiol 1993;69:297-302.
23. Niemi P, Poncelet BP, Kwong KK, et al. Myocardial intensity changes associated with flow stimulation in blood oxygenation sensitive magnetic resonance imaging. Magn Reson Med 1996;36:78-82.
24. Wacker CM, Bock M, Hartlep AW, et al. BOLD-MRI in ten patients with coronary artery disease: evidence for imaging of capillary recruitment in myocardium supplied by the stenotic artery. Magma 1999;8:48-54.
25. Bache RJ, Zhang J, Murakami Y, et al. Myocardial oxygenation at high workstates in hearts with left ventricular hypertrophy. Cardiovasc Res 1999;42:616-626.
26. Bauer WR, Nadler W, Bock M, et al. The relationship between the BOLD-induced T(2) and T(2)(*): a theoretical approach for the vasculature of myocardium. Magn Reson Med 1999;42:1004-1010.
27. Atalay MK, Reeder SB, Zerhouni EA, Forder JR. Blood oxygenation dependence of T1 and T2 in the isolated, perfused rabbit heart at 4.7T. Magn Reson Med 1995;34:623-627.
28. Atalay MK, Forder JR, Chacko VP, et al. Oxygenation in the rabbit myocardium: assessment with susceptibility-dependent MR imaging. Radiology 1993;189:759-764.
29. Thulborn KR, Waterton JC, Matthews PM, Radda GK. Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. Biochim Biophys Acta 1982;714:265-270.
30. Singerman RW, Denison TJ, Wen H, Balaban RS. Simulation of B1 field distribution and intrinsic signal-to-noise in cardiac MRI as a function of static magnetic field. J Magn Reson 1997;125:72-83.
31. Fayad ZA, Connick TJ, Axel L. An improved quadrature or phased array coil for MR cardiac imaging. Magn Reson Med 1995;34:186-193.
32. Bottomley PA, Lugo Olivieri CH, Giaquinto R. What is the optimum phased array coil design for cardiac and torso magnetic resonance? Magn Reson Med 1997;37:591-599.
33. Hardy CJ, Bottomley PA, Rohling KW, Roemer PB. An NMR phased array for human cardiac 31P spectroscopy. Magn Reson Med 1992;28:54-64.
34. Sakuma H, Globits S, Bourne MW, et al. Improved reproducibility in measuring LV volumes and mass using multicoil breath-hold cine MR imaging. J Magn Reson Imaging 1996;6:124-127.
35. Constantinidis CD, Westgate CR, O'Dell WG, et al. A phased array coil for human cardiac imaging. Magn Reson Med 1995;34:92-98.
36. Oesterle C, Hennel F, Hennig J. Quiet imaging with interleaved spiral read-out. Magn Reson Imaging 2001;19:1333-1337.
37. Block W, Pauly J, Nishimura D. RARE spiral T2-weighted imaging. Magn Reson Med 1997;37:582-590.
38. Liao JR, Sommer FG, Herfkens RJ, Pelc NJ. Cine spiral imaging. Magn Reson Med 1995;34:490-493.
39. Glover GH. Simple analytic spiral K-space algorithm. Magn Reson Med 1999;42:412-415.
40. Botnar RM, Stuber M, Kissinger KV, Manning WJ. Free-breathing 3D coronary MRA: the impact of "isotropic" image resolution. J Magn Reson Imaging 2000;11:389-393.
41. Botnar RM, Stuber M, Danias PG, et al. A fast 3D approach for coronary MRA. J Magn Reson Imaging 1999;10:821-825.
42. Davis CP, McKinnon GC, Debatin JF, et al. Single-shot versus interleaved echo-planar MR imaging: application to visualization of cardiac valve leaflets. J Magn Reson Imaging 1995;5:107-112.
43. Reeder SB, Atalar E, Bolster BD Jr., McVeigh ER. Quantification and reduction of ghosting artifacts in interleaved echo-planar imaging. Magn Reson Med 1997;38:429-439.
44. Reeder SB, Faranesh AZ, Boxerman JL, McVeigh ER. In vivo measurement of T*2 and field inhomogeneity maps in the human heart at 1.5 T. Magn Reson Med 1998;39:988-998.
45. Artemov D, Bhujwalla ZM, Glickson JD. In vivo selective measurement of (1-13C)-glucose metabolism in tumors by heteronuclear cross polarization. Magn Reson Med 1995;33:151-155.
46. Artemov D, Bhujwalla ZM, Glickson JD. Band-selective heteronuclear cross polarization in liquids. J Magn Reson B 1995;107:286-288.
47. Pilatus U, Shim H, Artemov D, et al. Intracellular volume and apparent diffusion constants of perfused cancer cell cultures, as measured by NMR. Magn Reson Med 1997;37:825-832.
48. Artemov D, Bhujwalla ZM, Maxwell RJ, et al. Pharmacokinetics of the 13C labeled anticancer agent temozolomide detected in vivo by selective cross-polarization transfer. Magn Reson Med 1995;34:338-342.
49. Balschi JA, Hetherington HP, Bradley EL Jr., Pohost GM. Water-suppressed one-dimensional 1H NMR chemical shift imaging of the heart before and after regional ischemia. NMR Biomed 1995;8:79-86.
50. Balschi JA, Hetherington HP, Pohost GM. Water-suppressed one-dimensional 1H NMR spectroscopic imaging of myocardial metabolites in vivo. Magn Reson Med 1992;25:180-186.
51. Balschi JA, Hai JO, Wolkowicz PE, et al. 1H NMR measurement of triacylglycerol accumulation in the post-ischemic canine heart after transient increase of plasma lipids. J Mol Cell Cardiol 1997;29:471-480.

52. Weiss RG, Chacko VP, Glickson JD, Gerstenblith G. Comparative 13C and 31P NMR assessment of altered metabolism during graded reductions in coronary flow in intact rat hearts. Proc Natl Acad Sci U S A 1989;86:6426-6430.
53. Rath DP, Zhu H, Tong X, et al. Dynamic 13C NMR analysis of pyruvate and lactate oxidation in the in vivo canine myocardium: evidence of reduced utilization with increased work. Magn Reson Med 1997;38:896-906.
54. Jeffrey FM, Diczku V, Sherry AD, Malloy CR. Substrate selection in the isolated working rat heart: effects of reperfusion, afterload, and concentration. Basic Res Cardiol 1995;90:388-396.
55. Sherry AD, Sumegi B, Miller B, et al. Orientation-conserved transfer of symmetric Krebs cycle intermediates in mammalian tissue. Biochemistry 1994;33:6268-6275.
56. Kanamatsu T, Tsukada Y. Measurement of amino acid metabolism derived from [1-13C]glucose in the rat brain using 13C magnetic resonance spectroscopy. Neurochem Res 1994;19:603-612.
57. Malloy CR, Thompson JR, Jeffrey FM, Sherry AD. Contribution of exogenous substrates to acetyl coenzyme A: measurement by 13C NMR under non-steady-state conditions. Biochemistry 1990;29:6756-6761.
58. Sherry AD, Nunnally RL, Peshock RM. Metabolic studies of pyruvate- and lactate-perfused guinea pig hearts by 13C NMR. Determination of substrate preference by glutamate isotopomer distribution. J Biol Chem 1985;260:9272-9279.
59. Neurohr KJ, Shulman RG. Carbon-13 and phosphorus-31 nuclear magnetic resonance studies of myocardial metabolism in live guinea pigs. Adv Myocardiol 1985;6:185-193.
60. Ziegler A, Zaugg CE, Buser PT, et al. Non-invasive measurements of myocardial carbon metabolism using in vivo 13C NMR spectroscopy. NMR Biomed 2002;15:222-234.
61. Chatham JC, Forder JR. Relationship between cardiac function and substrate oxidation in hearts of diabetic rats. Am J Physiol 1997;273:H52-58.
62. Carvalho RA, Zhao P, Wiegers CB, et al. TCA cycle kinetics in the rat heart by analysis of (13)C isotopomers using indirect (1)H. Am J Physiol Heart Circ Physiol 2001;281:H1413-1421.
63. Weiss RG, Gloth ST, Kalil-Filho R, et al. Indexing tricarboxylic acid cycle flux in intact hearts by carbon-13 nuclear magnetic resonance. Circulation Research 1992;70:392-408.
64. Malloy CR, Sherry AD, Jeffrey FM. Carbon flux through citric acid cycle pathways in perfused heart by 13C NMR spectroscopy. FEBS Lett 1987;212:58-62.
65. Sherry AD, Malloy CR, Roby RE, et al. Propionate metabolism in the rat heart by 13C n.m.r. spectroscopy. Biochem J 1988;254:593-598.
66. Clarke K, Cross HR, Keon CA, et al. Cation MR spectroscopy (7Li, 23Na, 39K and 87Rb). Magma 1998;6:105-106.
67. Buchthal SD, den Hollander JA, Merz CN, et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. NEJM 2000;342:829-835.