Editorial

Extending the Frontiers of Cardiac Magnetic Resonance

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Inflammation is a common reaction in biological systems, which develops, for example, to defend the body against infectious agents, to repair tissue, and to respond to ischemic insults. It can also be a disease process in itself, as in autoimmune diseases. Flögel et al describe a novel, elegant, and noninvasive approach to inflammatory mechanisms at a cellular level. The noninvasive nature of their strategy is of paramount importance. In particular, it allows for a series of repetitive measurements to be obtained from the same animal and thus yields information on the evolution of the inflammatory process without destruction of the system under investigation. This is almost impossible to achieve with invasive techniques.

Flögel et al elegantly exploit a primary mode of action of inflammatory cells (ie, phagocytosis of potentially harmful agents), which in this case happens to be a magnetic resonance (MR)–active contrast medium. Another remarkable aspect of their work is the use of the naturally occurring stable fluorine isotope 19F as the MR-active nucleus for imaging. Why is this unique? This 19F-MR imaging strategy takes advantage of the fact that after administration of 19F-containing compounds, any signal detected in the body via MR imaging (MRI) is emanating from the injected contrast medium (ie, an extraordinary contrast-to-noise ratio [CNR] is present, because no background signal from the body is detected by 19F-MR imaging). If the MR scanner is thereafter tuned to the 1H resonance frequency, conventional MRI occurs, and all morphological and functional information on the organ can be acquired. Because this imaging is performed in the same location and with the same equipment, registration is ideal; this allows “fusion imaging” to be used to combine specific signals of inflammatory cells (19F imaging) with organ function and anatomy (conventional 1H imaging).

The performance of the authors’ imaging approach is impressive. In addition to an excellent CNR, the signals are received from voxels as small as 0.5×0.5×2 mm³, and the 19F-containing contrast medium consisting of nanoparticles loaded with perfluorocarbons is biologically inert. Moreover, in the study, these perfluorocarbons were monitored in the body for up to 6 days and were detected not only in the ischemic territories undergoing repair but also in the postoperative sutures and in the liver, where the signals persisted for several months. Considering these features and the high sensitivity of this technique in detecting populations as small as a few hundred macrophages, this approach is a promising candidate for future research. It will likely provide new insight into inflammatory processes in the cardiovascular system and may also be applicable in clinical situations.

Translation of Animal Multinuclei MRI to Humans: General Considerations

An average perfluorocarbon loading per cell of <1 pmol was detectable by the presented 19F-MRI technique in vitro using a 9.4-T system. Because the MR detection system adds noise to any signal from the body, the signal-to-noise ratio (SNR) is a crucial characteristic of imaging-system performance. As shown in Figure 1, SNR, spatial resolution, and time for signal acquisition are inversely related. Rapid imaging typically occurs with lower SNR, reduced spatial resolution (large voxel volume), or both. In other words, the SNR is directly proportional to voxel size and the square root of the acquisition time and is inversely proportional to the square root of the receiver bandwidth. Thus, the required spatial resolution and the available imaging acquisition time dictate the SNR, which relates to the sensitivity to detect excited 19F and 1H nuclei. Because noise is added from the volume of the receiver coil, noise increases substantially when small-animal imaging techniques are applied to humans. As indicated by Figure 1, a sufficiently high concentration of 19F isotope must be brought into the target voxel to generate adequate signal. Although 19F-MRI in mice detects concentrations of ~0.2 μmol per voxel of 0.5×0.5×2 mm³ at 9.4 T, in humans at 3 T and employing a voxel size of 5×5×5 mm³ in a head coil, ~4 mmol would be detected with the same SNR of 20 after the same acquisition duration of 20 minutes. The 19F technique with excellent CNR can measure slow processes, which do not require high temporal resolution, and hence it allows for long acquisition times and thereby increases SNR. Accordingly, this 19F technique represents a powerful application of MR at one end of the MRI spectrum, where slow processes are to be probed (see Figure 2).

On the other end of the spectrum, another nucleus, 13C, is present, which allows for very fast MRI of specific processes with high temporal and spatial resolution (Figure 2). For fast processes, long signal acquisition is not feasible. The 13C techniques exploit the hyperpolarization of these 13C compounds, which yield SNRs that are up to 10 000 times higher than can be obtained with conventional 1H MRI. Although 19F nuclei in perfluorocarbons remain in the body for weeks

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and allow (in principle) for very long acquisition times, ¹³C-labeled compounds “lose” their hyperpolarized state with short half-lives (for [¹³C]pyruvate, ~25 seconds), and imaging can only be performed for 1 to 2 minutes. This means that the sensitivity of the measurements obtained using [¹³C]pyruvate cannot be increased by increasing the signal acquisition time, and the technique is ideal to study short-lived processes with extremely high sensitivity. Assuming 5% polarization of [¹³C]pyruvate at the time of imaging in the target voxel of 5×5×5 mm³ in a 3-T scanner using a head coil and measuring for 400 milliseconds (!), ~100 µmol of the [¹³C] compound per voxel would be detected. In a recent canine study performed with hyperpolarized [¹³C]pyruvate in a 3-T scanner, an estimated 5 µmol of [¹³C]pyruvate was detected per voxel of 5×5×5 mm³ (assuming a homogeneous distribution of the injected [¹³C]pyruvate in the body =30 seconds after administration).³ Accordingly, this hyperpolarized [¹³C] approach allows for near-real-time noninvasive metabolic imaging at resolutions in the millimeter dimension.⁴ Not only is the initial SNR enormous as generated by the hyperpolarization, it also allows monitoring of the metabolic fate of, eg, injected [¹³C]pyruvate metabolized into [¹³C]lactate, [¹³C]alanine, and others by means of the serially acquired spectra. This unique feature was recently exploited to invasively monitor pH in tumor tissue.⁵ As for [¹⁹F] imaging, this hyperpolarized [¹³C] imaging yields excellent CNRs, as any signal detected in the body is uniquely emanating from the compound injected and its metabolic products. In pig experiments, this technique was used to probe the citric acid cycle in mitochondria after subjecting the animals to short episodes of ischemia.⁶ In this setting, a “metabolic memory” was identified, which is a potentially adaptive mechanism to preserve function in the

Multi-Parametric Magnetic Resonance Imaging – „Image Fusion“

Figure 1. The determinants of SNR and additional factors that influence image quality.

Figure 2. The MRI spectrum is illustrated, exploiting various nuclei ([¹⁹F], [¹H], [¹³C]) as signal sources. The [¹H] nucleus refers to conventional MRI, where the protons in the tissue, primarily water, generate the signal. Gadolinium-based contrast media facilitate the relaxation of the protons, thereby increasing SNR for a given MR pulse sequence. Unlike [¹H], the [¹⁹F] and [¹³C] techniques yield “uncontaminated” signals, because no background signal from the body is received, which generates specific information with extraordinary CNR. All 3 approaches can be combined, thereby opening the spectrum of possible targets in a single examination. Such a multiparametric MRI strategy will deliver quantitative biological information localized in space and time to describe complex biological systems. Moreover, its noninvasive nature and its lack of radiation will allow for serial examinations to track biological processes over time. *Calculated for a field strength of 3 Tesla, a voxel size of 5×5×5 mm³, with a head coil to obtain an SNR of 20. Effective concentration is quantity per voxel. Imaging time for [¹⁹F] is 20 minutes, for [¹³C] it is 400 ms.
postischemic period. During congestive heart failure, metabolic adaptations occur that can initiate a vicious cycle (eg, those that occur during diabetic congestive heart failure). This $^{13}$C technique “fused” with conventional $^1$H cardiac MRI could yield unique information in congestive heart failure on cardiac energetics, metabolic alterations, myocardial function and perfusion, as well as viability.

In conventional $^1$H imaging, where no hyperpolarization is applied, only 4 to 5 spins out of 1 million ($\approx 0.0005\%$) are contributing to the MR signal at the thermal equilibrium at 1.5 T (fully relaxed state), for which the abundance of water ($\approx 80$ mol/L concentration) in biological tissue is compensating. In addition, conventional gadolinium-based contrast media can facilitate recovery of magnetization after excitation, thereby allowing for faster relaxation (ie, faster imaging). Gadolinium chelates coupled to specific targeting molecules are used for molecular imaging, which is covered in detail elsewhere, whereas this editorial focuses on cardiac magnetic resonance exploiting nuclei other than $^1$H. Unfortunately, in $^1$H imaging, the magnetization cannot be increased beyond full relaxation by any contrast medium, and hence, an additional increase in signal (and thus an increase in sensitivity for $^1$H nuclei) can only be achieved by prolongation of signal acquisition. As a consequence, spatially restricted processes of a certain duration that require a minimum temporal and/or spatial resolution of imaging inherently limit the amount of available signal in $^1$H imaging. Here, $^{13}$C imaging can extend the capability of MR through hyperpolarization ($20\%$ to $30\%$ of spins at injection deliver signal). At this end of the spectrum, involving fast processes in the micromolar concentration range, $^{13}$C imaging can be used. At the opposite end of the spectrum, the $^{19}$F imaging is complementary, allowing for excellent CNR with high sensitivity for long-lasting processes such as inflammation, cell migration, differentiation, and others. All of this highly specific information of $^{19}$F and $^{13}$C imaging can be combined with conventional $^1$H imaging to yield information on such matters as tissue and organ morphology, function, perfusion, viability, flows, endothelial function, targeted imaging, and cell tracking (see Figure 2). Fusion of these different modalities (ie, a multiparametric MRI approach) will have a major impact in research and perhaps in clinical cardiology as well.

**Multiparametric MRI: Future Perspectives**

Our knowledge of the human genome has increased rapidly in recent years, and many signaling pathways involved in disease evolution and progression are now under intensive investigation. However, it is also frequently recognized that well-defined genotypes cannot always unambiguously predict specific phenotypes. In most cases, the complex interplay of a variety of genes and a large number of signaling molecules and metabolic reactions determine the development of a disease state. How can we identify key signals in such complex systems and differentiate them from less-important “bystanders,” which would only become relevant in some rare (ie, experimental) conditions? It appears highly desirable to develop a research tool that would allow us to monitor and quantify biological processes and to localize them in space and time to understand the complex interactions and to isolate key processes, which would become the target for interventions. Noninvasive imaging is this tool, as it describes and quantifies biological processes, and it localizes them within cells, tissues, and organs. By adding $^{19}$F and $^{13}$C imaging to conventional $^1$H imaging, we expect an extraordinary improvement in our capabilities to investigate complex biological systems by extending the spectrum into specific imaging of long-lasting and short-lived processes with a sensitivity and specificity never before obtained.

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**References**


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