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Accelerating Cardiovascular Magnetic Resonance Imaging: Signal Processing Meets Nuclear Spins

Cardiovascular diseases are still the leading cause of death worldwide, accounting for an estimated 30% of all deaths across the globe, more than cancer, injury, and HIV/AIDS combined (Figure 1). Efforts to address cardiovascular disease with technology can be traced back nearly 200 years to the invention of the stethoscope in 1816. The many successful technological advances since then have significantly transformed the detection, diagnosis, and treatment of cardiovascular diseases over the last two centuries.

Cardiovascular imaging technology has enabled measurement and visualization of the structure and function of the beating heart and has become an indispensable part of cardiac health care. A number of cardiac imaging modalities are available to the new generation of cardiologists: cardiac ultrasound, known as echocardiography (ECHO), and X-ray computed tomography (CT) are typically used to image cardiac structure; positron emission tomography (PET) and single photon emission computed tomography (SPECT) are typically used to image cardiac function. Magnetic resonance imaging (MRI), the topic of this column, is suitable for both structural and functional imaging (Figure 2).

CARDIOVASCULAR MRI

Because of the particular properties of the magnetic resonance (MR) phenomenon, MRI has unique potential for cardiovascular imaging. MRI is already the gold standard modality for cardiac chamber anatomy and function, detection and assessment of myocardial infarction, evaluation of congenital heart disease, and more [1]. Further advances in myocardial perfusion imaging, blood flow velocity imaging, spectroscopic imaging, and other applications have brought MRI closer to achieving its potential as the premier all-around imaging modality for cardiologists, although technological challenges still exist for each of these applications.

The primary challenge facing cardiovascular MRI is imaging speed. There is a fundamental tradeoff between the temporal resolution and spatial resolution of MRI, both of which are major concerns when imaging the beating heart. Conventionally, the sampling requirements for MRI are governed by the Nyquist–Shannon theorem. The earliest methods to accelerate MRI were fast-scanning methods focused on manipulating nuclear spins for fast data acquisition, all within the Nyquist–Shannon framework. Fast-scanning technology is now a relatively mature area of research, giving way to solutions which leverage different signal processing frameworks for sub-Nyquist imaging within the sampling constraints of nuclear spin physics.

OVERCOMING THE NYQUIST BARRIER

In cardiovascular MRI, the desired spatiotemporal image $\rho(\mathbf{r},t)$ is related to the signal $\{d_q(\mathbf{k},t)\}_{q=1}^{Q}$ from an array of Q receive coils as

$$d_q(\mathbf{k},t)=\int_{-\infty}^{\infty}S_q(\mathbf{r})\rho(\mathbf{r},t)e^{-i2\pi\mathbf{k}\cdot\mathbf{r}}d\mathbf{r}, \quad (1)$$

where $S_q(\mathbf{r})$ represents the spatial sensitivity of the qth receive coil. For conventional image reconstruction, the coil sensitivities are absorbed into the desired image function for each coil, $\rho_q(\mathbf{r},t)=S_q(\mathbf{r})\rho(\mathbf{r},t)$, which are then independently reconstructed from the Nyquist-sampled $(\mathbf{k},t)$-space data via the inverse Fourier transform. The resulting coil images are combined to form the final reconstructed image.

PARALLEL IMAGING

Parallel imaging utilizes the additional encoding power of the receive coil sensitivities $\{S_q(\mathbf{r})\}_{q=1}^{Q}$ to solve the reconstruction problem from the sub-Nyquist data. This approach is an ingenious application of Papoulis' multichannel sampling theorem to MRI [2]. It is well known that, under certain conditions, a signal that is bandlimited in either time or space can be exactly recovered from sub-Nyquist measurements of the signal from multiple sensors. More specifically, consider that $\rho(\mathbf{r},t)$ is spatially bandlimited to the region $[-B/2,B/2]$ and $\{d_q(\mathbf{k},t)\}_{q=1}^{Q}$ are the outputs from a bank of Q linear and $\mathbf{k}$-shift-invariant filters $\{S_q(\mathbf{r})\}_{q=1}^{Q}$. Papoulis' multichannel sampling theorem states that $d(\mathbf{k},t)=\int_{-\infty}^{\infty}\rho(\mathbf{r},t)e^{-i2\pi\mathbf{k}\cdot\mathbf{r}}d\mathbf{r}$, and therefore $\rho(\mathbf{r},t)$, can be recovered from complex samples of $\{d_q(\mathbf{k},t)\}_{q=1}^{Q}$ taken at rate $\Delta\hat{k}=Q/B$ (i.e., a factor of Q above the Nyquist rate $\Delta k=1/B$) using interpolation kernels $\{g_q(\mathbf{k})\}_{q=1}^{Q}$ derived from $\{S_q(\mathbf{r})\}_{q=1}^{Q}$.

In the situation with known $\{S_q(\mathbf{r})\}_{q=1}^{Q}$, $\rho(\mathbf{r},t)$ can be recovered in image space by inverting (1) (e.g., sensitivity encoding for fast MRI (SENSE) [3]). When $\{S_q(\mathbf{r})\}_{q=1}^{Q}$ are unknown, $\rho(\mathbf{r},t)$ can be recovered using $\mathbf{k}$-space interpolation kernels (analogous to the $\{g_q(\mathbf{k})\}_{q=1}^{Q}$ in Papoulis' sampling theorem), which are learned from auxiliary data (e.g., generalized autocalibrating partially parallel acquisitions (GRAPPA) [4]). Although Papoulis' multichannel sampling framework permits acceleration factors up to Q,

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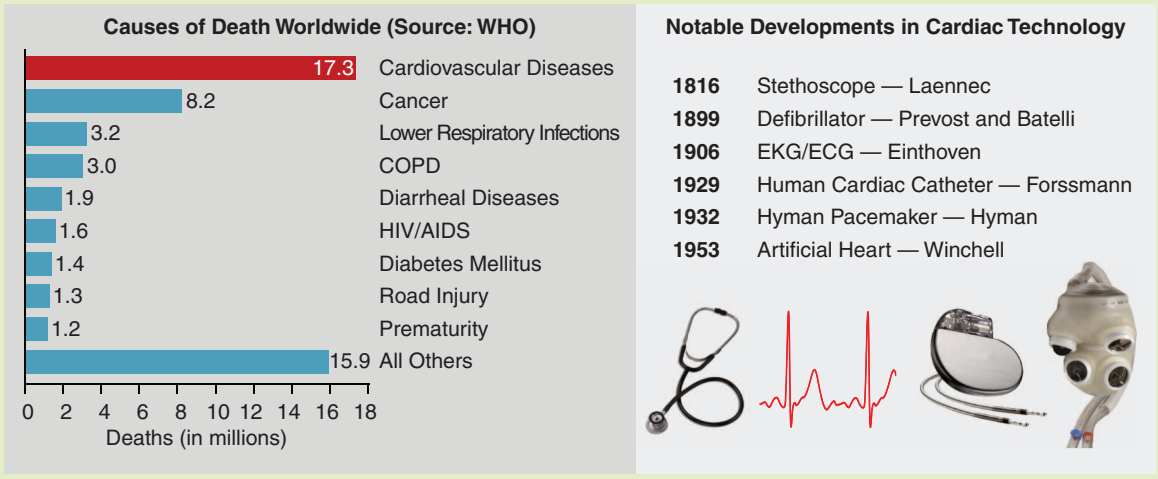
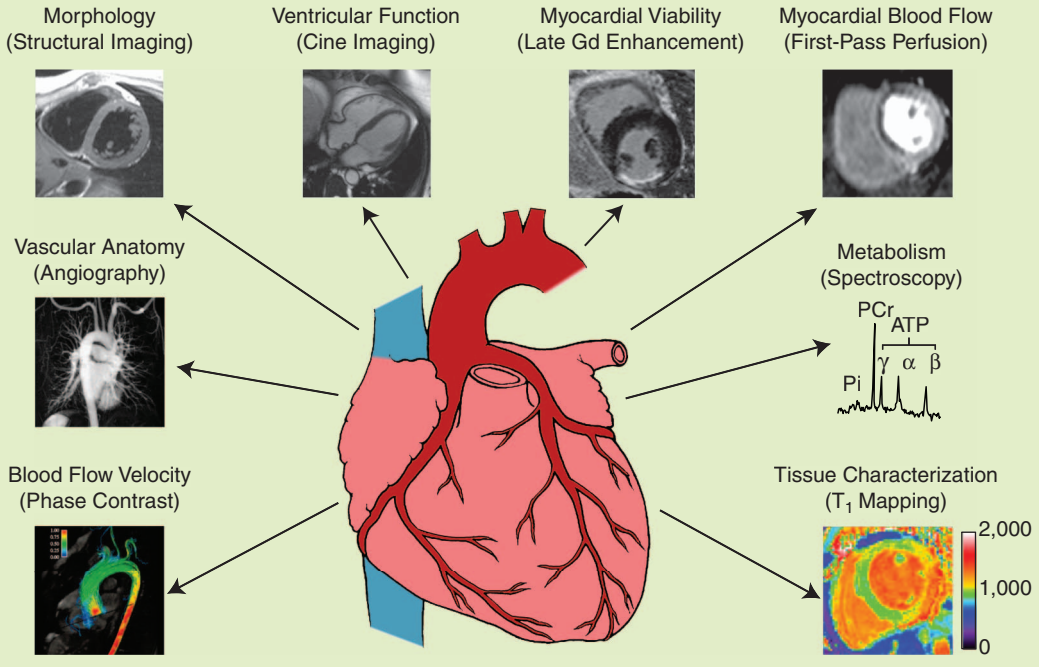


[FIG1] **Notable facts about cardiovascular diseases and cardiac technologies.**



[FIG2] **Applications of cardiovascular MRI.**

measurement noise, auxiliary data acquisition, and ill-conditioning of the reconstruction problem limit the practically achievable acceleration factor. As a result, acceleration factors well below Q are applied in practice. To achieve greater acceleration, parallel imaging is often applied jointly with complementary acceleration approaches such as compressed sensing (CS) and/or subspace imaging.

COMPRESSED SENSING

CS theory enables recovery of sparse signals from sub-Nyquist measurements and has found important application in MRI, especially cardiac MRI. After discretizing and vectorizing $\rho(\mathbf{r}, t)$ and $d(\mathbf{k}, t)$ as $\boldsymbol{\rho}$ and $\mathbf{d}$, respectively, the data acquisition equation (1) can be formulated as $\mathbf{A}\boldsymbol{\rho} = \mathbf{d}$. Under the CS theory, $\boldsymbol{\rho}$ can be recovered from $\mathbf{d}$ by minimizing $\|\mathbf{T}\boldsymbol{\rho}\|_1$ subject to $\mathbf{A}\boldsymbol{\rho} = \mathbf{d}$ or $\|\mathbf{d} - \mathbf{A}\boldsymbol{\rho}\|_2^2 < \epsilon$ (in the case with noise), where $\mathbf{T}$ is a sparsifying transform.

Cardiovascular images are sparse in a number of transform domains [5], including the $(\mathbf{r}, f)$-space (spatial-spectral), wavelet-spectral, or spatiotemporal finite-difference domains. $\mathbf{T}$ is commonly chosen to transform the image vector $\boldsymbol{\rho}$ into one of these domains. Randomly ordered $(\mathbf{k}, t)$-space sampling is also used for CS MRI, as it generally results in a

sampling basis $\mathbf{A}$ which is incoherent with any of the previously mentioned sparse bases. Image reconstruction can be performed by solving an unconstrained optimization problem:

$$\arg\min_{\boldsymbol{\rho}} \|\mathbf{d} - \mathbf{A}\boldsymbol{\rho}\|_2^2 + \lambda \|\mathbf{T}\boldsymbol{\rho}\|_1,$$

where λ is a regularization parameter.

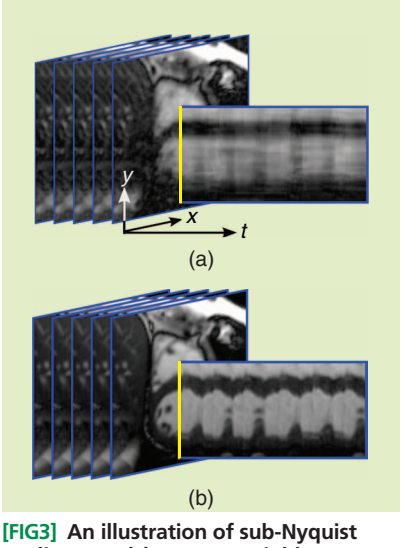
Like parallel imaging, CS is an effective strategy to accelerate cardiovascular MRI and is most effective when jointly used with parallel imaging and/or subspace imaging.

SUBSPACE IMAGING

Subspace imaging exploits the fact that cardiovascular signals have a high degree of spatiotemporal correlation (or reside in a low-dimensional subspace). More specifically, the spatiotemporal changes of cardiac MR data can be expressed as $d(\mathbf{k}, t) = \sum_{\ell=1}^{L} u_\ell(\mathbf{k}) v_\ell(t)$ [6]. In other words, $d(\mathbf{k}, t)$ is Lth-order partially separable. It can be shown that the Casorati matrix $\mathbf{C}$ formed with elements $C_{ij} = d(\mathbf{k}_i, t_j)$ has a rank no more than L. This property enables recovery of $d(\mathbf{k}, t)$ (or the missing entries of $\mathbf{C}$) from highly undersampled measurements by imposing a rank or subspace constraint.

MR cardiac signals are highly correlated and as a result, the separation rank L is rather low (around 32). In addition, special data acquisition schemes can be implemented, which acquire at least L rows of $\mathbf{C}$ in full and sparsely sample the remaining rows of $\mathbf{C}$. This allows the temporal subspace to be predetermined and the rank-constrained matrix completion problem to be solved with this known subspace, which significantly simplifies the subspace imaging reconstruction problem.

Subspace imaging provides a powerful tool to accelerate cardiovascular MRI. It produces best results when jointly imposed alongside parallel imaging and/or CS, as demonstrated in Figure 3.



[FIG3] An illustration of sub-Nyquist cardiac MRI. (a) Nearest-neighbor temporal interpolation of the (*k*,*t*)-space data demonstrates the low temporal sampling rate of MRI as well as the resulting spatiotemporal artifacts and blurring. (b) Reconstruction of the same data using parallel imaging, CS, and subspace imaging shows the power of accelerated imaging. Images are shown stacked along the time dimension, and spatiotemporal slices show the temporal profiles over the yellow lines.

APPLICATIONS

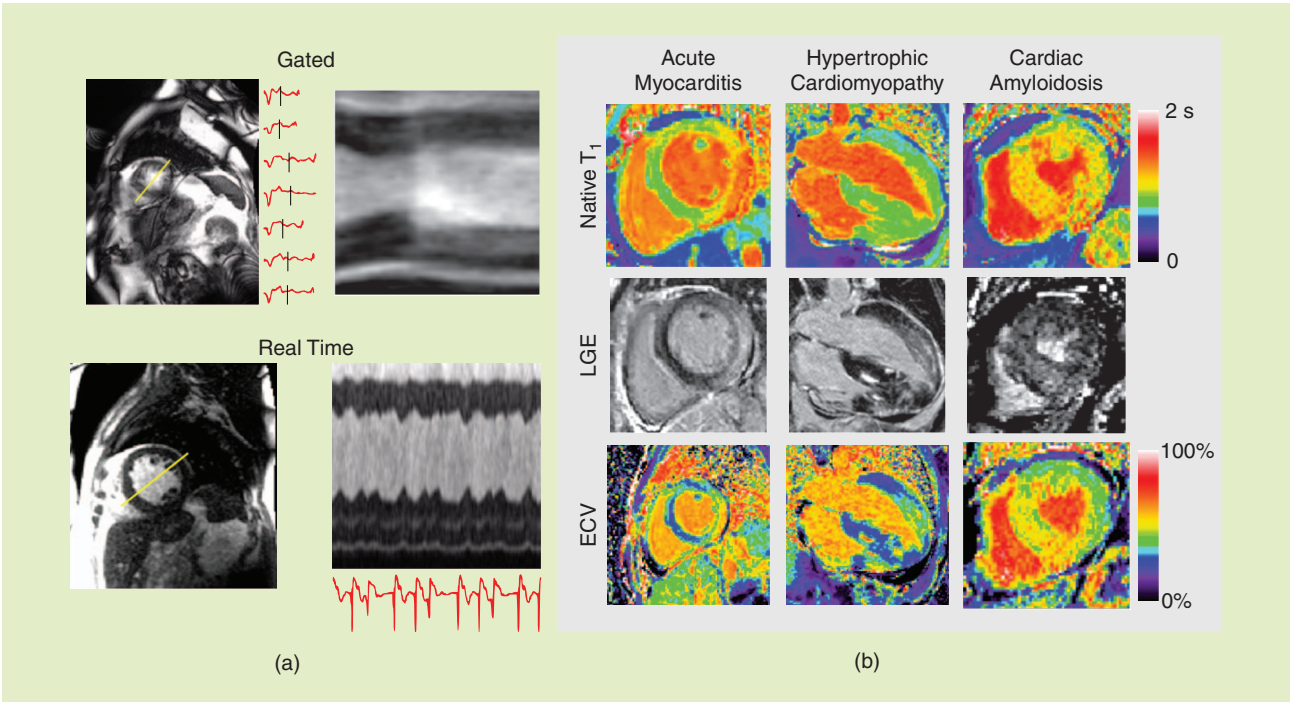
CINE IMAGING

Dynamic cine image sequences depict the structure and function of the heart, including the mechanical contraction, timing, and extent of wall motion and thickening, as well as the function of valves. From these images, it is possible to perform a multitude of cardiac assessments. Global measures such as cardiac mass, blood volume, and ejection fraction can be measured from time-resolved images at different cardiac phases. Regional wall motion may be used to determine and localize abnormal tissue function: akinetic regions of the myocardium (i.e., the cardiac wall) can be well visualized, helping to determine the extent of injury to the myocardium. Functional cine imaging may augment morphological imaging to better assess complex structural abnormalities and congenital heart defects by visualizing the motion of the blood and valves. Cine imaging may also be used to assess the mechanical activation of the heart, which may be important in understanding arrhythmias and in guiding treatment. When used in conjunction with contrast enhanced viability imaging, it may further be used to distinguish irreversibly damaged myocardium from stunned myocardium after ischemia.

The cornerstone of cine imaging is cardiac motion; however, it is challenging to acquire high spatial resolution images quickly enough to resolve the motion of the heart. For this reason, "gated" methods are commonly employed to utilize data acquired across multiple heartbeats, with the underlying assumption that each heartbeat is the same, i.e., that $\rho(\mathbf{r}, t)$ is periodic. This is achieved by using the electrocardiogram (ECG) as a reference signal and instructing the subject to hold his or her breath; the data from multiple heartbeats are then combined to reconstruct a single representative heartbeat. However, many patients are unable to hold their breath adequately or may have variations in their heart rhythms that violate the assumption of a stationary (i.e., periodic) heart, leading to poor image quality using gated methods. For this reason, it is often preferable to use accelerated methods that can produce high spatial-resolution images quickly enough to resolve cardiac and respiratory motions without resorting to ECG triggering or breath-holding. These accelerated methods are referred to as *real-time* imaging methods. Figure 4(a) shows a comparison between gated and real-time imaging on patients with atrial fibrillation.

Advanced image reconstruction methods that use signal processing to permit rapid imaging and fill in the missing data from undersampled acquisitions are routinely applied to cardiac functional cine. These methods are used to reduce the breath-hold duration for gated, segmented scans to several heartbeats, as well as for real-time imaging. Indeed, cine imaging has advanced to the point where it is now possible to image two-dimensional (2-D) slices of the heart at 1.0 mm in-plane spatial resolution and 20 frames per second (fps), using hybrid fast-scanning, parallel imaging, CS, and subspace imaging methods [7].

Methods that can acquire time-resolved three-dimensional (3-D) volumes have potential to greatly simplify the workflow and improve the analysis of cardiac function. Three-dimensional methods require an even higher degree of acceleration and



[FIG4] Example images from different applications of cardiac MRI. (a) Examples of gated and real-time imaging of patients with irregular heartbeats. Individual heartbeats do not match up when "stacked" as in gated imaging, producing artifacts. Real-time imaging is fast enough to image each heartbeat individually, avoiding these artifacts. (b) Examples of both qualitative (LGE) and quantitative [Native T_1 and extracellular volume (ECV) fraction] cardiovascular MR images. Quantitative imaging has advantages over qualitative imaging when the disease is globally diffuse, which is more difficult to discern using qualitative imaging (as in the cardiac amyloidosis example).

are a subject of active investigation. There is also demand for even higher spatiotemporal resolution: submillimeter resolution to capture detail of small structures such as atria, coronary arteries, or thin walls such as the right ventricle, and temporal resolution on the order of 10–20 ms for the assessment of diastolic function [8]. Validating the fidelity of advanced image reconstruction methods is an important area of research.

VIABILITY IMAGING

Late gadolinium enhancement (LGE) imaging (also known as *delayed enhancement imaging*) is used to assess the viability of myocardial tissue (i.e., whether the tissue is dead or alive). The heart is typically imaged 10–20 min after the administration of gadolinium-based contrast agent into the blood stream. Gadolinium contrast agents shorten the spin-lattice relaxation time constant T_1 (a key mechanism in the contrast of ρ), boosting the signal when using T_1-weighted imaging and therefore brightening voxels in which the contrast agent is concentrated. After a period of time following the administration of the gadolinium based contrast agent, concentration is higher in fibrous scar tissue than in normal myocardium, since the contrast agent in that tissue washes out at a slower rate. With T_1-weighted sequences such as inversion recovery, the normal myocardium appears dark and scar tissue appears bright, leading to positive contrast. LGE has become the gold standard for viability imaging.

MRI IS ALREADY THE GOLD STANDARD MODALITY FOR CARDIAC CHAMBER ANATOMY AND FUNCTION, DETECTION AND ASSESSMENT OF MYOCARDIAL INFARCTION, EVALUATION OF CONGENITAL HEART DISEASE, AND MORE.

To measure enough data (lines of k-space) to achieve the desired spatial resolution, it is customary to acquire data over multiple heartbeats in a gated, segmented fashion. This approach presumes that the subject has a stable heart period and is able to reliably hold their breath, but it is difficult (or for sicker subjects, impossible) to fulfill this requirement. Accelerated parallel imaging may be used to acquire LGE images in a single heartbeat [9]. Using this approach, the patients may breathe freely, and imaging is not sensitive to arrhythmias.

TISSUE CHARACTERIZATION

The physics of MR provides a rich set of contrasts useful in characterizing tissue and answering a number of clinical questions. Various contrasts such as T_1, T_2, or T_2* may be achieved by varying the pulse sequence used in data acquisition, revealing characteristics of the local chemical environment. For instance, it is possible to image and quantify water, fat, and iron content, which can be used to diagnose

and differentiate disease. While qualitative T_1-weighted imaging may reveal regional differences in the T_1 of tissue (such as the elevated T_1 due to edema in acute myocarditis), it is more challenging to detect when there is a global shift in T_1. In this instance, there will be no regional differences or spatial contrast observed. To detect diseases that result in a global abnormality (i.e., a uniform contrast change), it is required to quantify the actual value of T_1 or other parameters (e.g., T_2 or T_2*).

It is possible to quantify these parameters by collecting multiple images with different parameter weightings to generate parametric maps. These maps have proven useful in cases of globally diffuse disease processes such as fibrosis and edema [10]. Figure 4(b) shows some of the advantages of quantitative imaging over qualitative imaging, particularly for the cardiac amyloidosis example, wherein amyloids have globally infiltrated the myocardium and therefore do not exhibit the local enhancements required to allow detection via qualitative imaging. Quantitative MRI is more objective and provides a means to perform serial measurements which may be used to evaluate the effectiveness of therapies in the long term.

Parametric mapping places additional demands on accelerated imaging to achieve the desired image quality and spatiotemporal resolution in the presence of motion. For example, in creating a pixelwise map of the time constant T_1, images are acquired at varying delays following an inversion or saturation of the magnetization, and measurements of the signal at each pixel are fit to an exponential recovery curve. Quantitative measurements have great potential for disease detection but increase the demand for reliable and validated image reconstruction methods to achieve the desired accuracy and precision.

MYOCARDIAL PERFUSION IMAGING

Myocardial perfusion imaging measures blood flow through the myocardium to detect coronary artery disease. Imaging is performed to measure the wash-in and wash-out during the first passage of a bolus of gadolinium-based contrast agent. Regions with normal flow will appear brighter than regions with reduced flow (signal intensity is proportional to the concentration of contrast agent on a T_1-weighted image). Perfusion measurements can then be extracted from the signal intensity curve $\rho(\mathbf{r}_0, t)$ for any voxel $\mathbf{r}_0$ inside the myocardium. Myocardial perfusion contrast dynamics are transient,

METHODS THAT CAN ACQUIRE TIME-RESOLVED THREE-DIMENSIONAL VOLUMES HAVE POTENTIAL TO GREATLY SIMPLIFY THE WORKFLOW AND IMPROVE THE ANALYSIS OF CARDIAC FUNCTION.

so real-time imaging must be performed with adequate temporal resolution to freeze cardiac motion. Spatial coverage of the heart is achieved by imaging several 2-D slices in rapid succession or by a highly accelerated 3-D volumetric acquisition. Myocardial perfusion imaging is commonly performed under both stress (wherein the patient is generally administered a pharmacological stress agent) and at rest. Imaging during stress presents additional challenges due to increased heart rates and the subsequent requirement for even faster imaging. Myocardial perfusion imaging after exercise-induced stress (such as after a treadmill session) is even more challenging due to the need to image within seconds of reaching peak stress.

Research in myocardial perfusion imaging is largely focused on increased speed and spatial coverage using highly undersampled acquisitions and advanced reconstruction. Although MR images are conventionally acquired by sampling $\mathbf{k}$-space on a Cartesian grid, new approaches to highly accelerated myocardial perfusion imaging have explored non-Cartesian sampling patterns such as radial or spiral $\mathbf{k}$-space trajectories [11]. Non-Cartesian trajectories also have the potential to achieve full 3-D coverage using CS reconstruction [12]. Respiratory motion correction via image registration allows for free breathing during the acquisition of first-pass contrast-enhanced images, and advanced image reconstruction methods that incorporate motion correction directly into the image reconstruction problem have been demonstrated. Myocardial perfusion is an active area of research with goals of achieving reliable, artifact free, high spatial resolution imaging and providing fully quantitative measurement of myocardial blood flow and flow reserve.

PHASE CONTRAST VELOCITY MAPPING

Magnetic field gradients can also manipulate nuclear spins to encode the blood flow velocity in the phase of the complex image $\rho(\mathbf{r}, t)$. Velocity encoding in a single carefully chosen direction can provide flow measurements for targeted areas; velocity encoding in three directions can provide a vector field showing the path and speed of blood flow through all of the imaged chambers and vessels. This vector field can then be used to identify forward, regurgitant, and shunt flows and potentially be used to measure flow pressure as well as shear stress on the vessel wall.

Velocity encoding in multiple directions cannot be performed simultaneously; the data from each velocity encoding direction are collected separately, resulting in a threefold loss of temporal resolution. Phase contrast (PC) velocity mapping has been performed in 2-D without the use of ECG gating through a combination of fast-scanning, parallel imaging, and sparse sampling, achieving 1.8 mm in-plane spatial resolution at 23 fps [13], but the additional acceleration requirements of PC MRI have ensured that 3-D PC MRI is still solidly dominated by gated techniques [14]. Opportunities exist to accelerate 3-D PC MRI to the point where ECG gating is no longer required.

SPECTROSCOPIC IMAGING

MR spectroscopic imaging (MRSI) collects a nuclear MR (NMR) chemical spectrum for each voxel, adding yet another

image dimension. For example, ^{1}H spectroscopic imaging separates the hydrogen signals in water, fat, creatine, lactate, etc., from each other, generating images for each molecule. Phosphorus (^{31}P) imaging is even more useful, allowing monitoring of cardiac metabolism by isolating phosphocreatine (PCr), inorganic phosphate (Pi), and the phosphate groups in adenosine diphosphate (ADP) and adenosine triphosphate (ATP). Sodium (^{23}Na) imaging also has potential to assess extracellular volume (ECV) without the need for contrast agents due to the elevated sodium levels in myocardial scars.

The low abundance of spins in metabolites ensures that MRSI is extremely signal starved. Coupled with the sampling difficulties brought on by the additional imaging dimension, real-time dynamic cardiac MRSI has yet to be demonstrated. Static cardiac MRSI methods have addressed the signal-to-noise ratio problem by using large voxel sizes on the order of 20 mm and by averaging the signal from many different acquisitions over the course of 30 min or more [15]. The ability to perform high-resolution cine MRSI would represent a major step forward in cardiac imaging.

OUTLOOK

Cardiovascular MRI has come a long way since its inception and has had important clinical impact. Technological advancements based on signal processing for reconstruction of sparsely sampled data are making important impacts in many areas, including cardiovascular stress imaging, pediatric imaging of congenital heart disease, quantitative tissue characterization, vessel wall imaging, and image-guided therapeutic procedures. Quantitative imaging has the potential for earlier and more reliable detection of diseases. Advances in spectroscopic imaging could allow myocardial viability and ECV assessments without the use of contrast agents. Improvements in rapid imaging may be used to streamline the imaging workflow and reduce the cost of studies. Rapid 3-D whole-heart imaging will streamline the workflow even further by eliminating the need for scout scans and scan plane localization. These advances are quickly moving us toward an all-free-breathing paradigm for whole-heart cardiac MRI, allowing shorter scans with increased patient comfort.

Comprehensive physiological imaging is also an exciting possibility, which would provide metabolic and biochemical information about cardiac tissues in a wide number of conditions: hypertensive, valvular, and ischemic heart diseases, heart failure, cardiac transplantation, and cardiomyopathies. The fusion of MRI with other imaging modalities such as PET can leverage the various strengths of different modalities to provide even more physiological information.

Tracking and fully utilizing this physiological information will require advances in cardiovascular health informatics, a hugely important topic related to cardiac MRI as well as the broader signal processing community. Leveraging MRI's capability to acquire structural, functional, and physiological information of the heart may allow development of personalized computational models of the cardiovascular system. When combined with advances in health informatics, longitudinal personalized models could be retrieved and updated from any properly equipped clinical facility. These models, coupled with other real-time sensory data such as ECG signals, would not only quantitatively assess the current state of the heart, but could also be used to design personalized treatment (e.g., cardiac implants, pharmacotherapy) or even to predict future cardiac events.

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