Cardiovascular Molecular Imaging

Imaging Techniques and Quantification

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Molecular Cardiovascular Imaging

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality in the western world and developing countries. Diseases affecting the cardiovascular system are expected to be the main cause of death globally within the next 20 years. This is due to the rising prevalence of CVD in the eastern parts of Europe, developing countries and an increasing incidence of obesity and diabetes in the western world [1].

Molecular imaging with targeted contrast agents using MRI refers to the noninvasive visualization of biological processes at the cellular and molecular level with MRI in vivo to improve characterization and detection of normal and diseased tissues. Compared to other molecular imaging modalities (e.g. SPECT, PET), MRI provides excellent spatial resolution, unique soft tissue contrast and has the ability to simultaneously assess anatomy, function and biological processes at the cellular and molecular level.[2] The disadvantage of MRI is its relatively low sensitivity for contrast agents (~50μ), which makes imaging of low abundance targets challenging.

Properties of Molecular MR Contrast Agents

Several classes of molecular MR contrast agent exist, which include small molecular weight contrast agents and nanoparticles. MR contrast agents can be used to shorten local T1 and T2 relaxation times. Gadolinium (Gd) based contrast agents cause an increase in the longitudinal relaxation rate (R1), due to their paramagnetic properties. The increase in R1 is found to be directly proportional to the contrast agent concentration and can be calculated by measuring the intrinsic relaxation rate R1 before and after contrast agent injection. Contrast agents, however, also influence and shorten the T2 relaxation time[3]. Due to the low abundance of certain molecular imaging targets, longitudinal and transverse relaxivity, r1 and r2, are essential for the design of target specific contrast agents and will be discussed later.

Detection of Targeted Contrast Agent

Signal intensity in MRI primarily depends on the local values of longitudinal and transverse relaxation rates of water protons. Gadolinium and iron oxide based MR contrast agents are therefore not directly detectable, but only indirectly by their effect on surrounding water protons. Usually a threshold for a local concentration of a contrast agent (typically μM to mM for agents having a r1 between 4-80 mM-1s-1) has to be reached to alter relaxation rate of water protons sufficiently for detectable signal effects.

MR Sequences for Molecular Imaging

MR imaging sequences can be divided into spin echo (SE) and gradient echo (GRE) sequences (Table 1). Several types of SE or GRE imaging sequences can be used for optimal contrast depending on the type of contrast agent, location, motion, etc.

Spin echo sequences

T1 and T2 weighted spin echo (SE) sequences belong to the standard sequence repertoire of every MR scanner. In the presence of a T1 lowering contrast agent, high-resolution images with excellent soft tissue contrast with concomitant T1 weighting can be achieved. If morphologic details in combination with visualization of contrast uptake are required with one single imaging sequence, spin echo approaches are often the method of choice. However, fast spin echo (FSE) sequences do not exhibit a linear relationship between contrast agent concentration and MR signal for higher concentrations (>1mM) for a typical contrast agent with a relaxivity (r1) of 4 (mM x s)-1. If the concentrations are higher, the T2 effect will increase and limit and decrease the maximum obtainable signal due to the finite achievable echo time (TE).[3]

T1 weighted gradient echo sequences

3D gradient echo sequences with RF spoiling (TE < 5ms, TR < 10ms, flip angle =30-60°) are heavily T1 weighted and exhibit a near linear relationship between contrast agent concentration and MR signal intensity.[3] Therefore, these sequences are well suited for higher contrast agent concentrations. Due to their short scan times (5-60s) and excellent background suppression, these sequences are applied for first pass contrast enhanced angiography of the large vessels and in molecular imaging of non-moving tissues. A disadvantage of this approach is the hyperintense appearance of blood (non-specific background signal). Prepulses can be used to saturate the magnetization of inflowing blood thereby minimizing the blood signal. This sequence was successfully used for imaging aortic thrombus using a fibrin-binding contrast agent.[4,5]

T1 weighted inversion recovery gradient echo sequences

The advantages of inversion recovery (IR) sequences compared to other approaches are the excellent background suppression and its insensitivity to blood flow and have been shown particularly useful for the visualization of small amounts of contrast uptake with excellent suppression of background tissue and blood.

Furthermore, IR techniques can be easily combined with ECG triggering and respiratory gating thereby allowing for high-resolution cardiac imaging.

A limitation of this approach is the limited morphologic information, which can be ameliorated by the acquisition and fusion of with a morphologic scan. Due to the excellent blood suppression this approach is particularly useful for imaging of biological processes in the myocardium and the vessel wall.

The choice of the repetition time TR_{IR} of the inversion prepulse determines the optimum inversion delay TI ($TI = \ln 2 \times T1 - T1 \times \ln(\exp(-TR_{IR}/T1) + 1)$) and thus the maximum achievable signal intensity of the administered contrast agent.

T2* weighted GE sequences

Iron based contrast agents can be visualized as signal loss in T2 and T2*-weighted MRI images.[6] The resulting hypo-intense signal can be detected at nanomolar local concentrations, yielding a significantly higher sensitivity compared with the detection threshold of gadolinium based contrast agents.[7]

Iron oxide particle detection can be ambiguous, because signal loss may be mimicked by artifacts, resulting from cardiac motion, interfaces between the trachea/lung and surrounding tissue, local hemorrhage or calcification.[8] Additionally, if tissues adjacent to iron oxide accumulations do not yield high signal to noise ratios (SNR), like the thoracic vessels, it can be difficult to localize, delineate and quantify the exact area of signal void.[7]

Positive contrast techniques

A drawback of negative contrast techniques like T2* weighted sequences is the difficulty to discriminate signal attenuation or void from the typically used iron oxides from other sources of signal loss such as air, hemorrhage, motion artifacts, signal cancellations at water-fat interfaces or calcifications.[9-11]

In particular much of the thoracic aorta and the inferior wall of the myocardium are prone to susceptibility artifacts due to their proximity to lung tissue.

To overcome this limitation and allow for easier quantification of iron oxide uptake positive contrast techniques have been developed. These include techniques that selectively excite off-resonance spins,[12] sequences that modulate the slice rephasing gradient to fully rephase only spins that experience additional rephasing from the dipole field generated by the iron oxide[13] and sequences that use either inversion recovery or chemical saturation techniques to suppress on-resonance protons.[14,15] Most of these methods require

dedicated imaging sequences, precise knowledge about the anticipated frequency shifts and are prone to large-scale field inhomogeneities and local alternations due to chemical shift.[16-18]

An alternative method, susceptibility gradient mapping (SGM), can be applied by post-processing. This technique has been demonstrated to allow positive contrast visualization of iron oxide on MR gradient echo data sets.[19] SGM utilizes the local shift in k-space due to local field distortions (susceptibility gradients), resulting from the presence of iron oxide particles.[20]

T1 Quantification

Measurements of the T1 relaxation time are usually performed with inversion recovery sequences. By changing the inversion delay TI between the non-selective inversion prepulse and data acquisition, signal from tissue A (T1 = $T1_A$) will be nulled if the inversion delay TI fulfills the condition TI = $T1_A$ x ln2. Most T1 measurements approaches are based on the Look and Locker sequence, which acquires multiple images (6-10) along the T1 relaxation curve after an initial inversion prepulse[21]. Several new approaches have been proposed to reduce imaging time[22] and to enable T1 measurements in moving organs such as the heart[23].

T2* Quantification

T2* maps are acquired by sampling the signal along the free induction decay (FID) curve using multiple echo times (TE) at a constant repetition time (TR). The most common approaches are based on gradient echo sequences with signal sampling along Cartesian trajectories[24,25]. The drawback is the relatively long scanning time with this approach. In a recent study, Schaeffter et al. proposed a faster approach by taking advantage of the undersampling properties of radial imaging[26]. Undersampled radial sub-images with differing echo times (TE) were reconstructed from a complete radial data set that was acquired with multiple TEs. An exponential pixel-by-pixel fit of the FID as derived from the undersampled sub-images then allows generation of T2* maps[27].

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