Advanced imaging and spectroscopy techniques for body magnetic resonance

Heer, P. de

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SUMMARY AND GENERAL DISCUSSION

SUMMARY

The aim of this thesis was to develop advanced body MR techniques that can contribute to the knowledge of the metabolic syndrome (MetS). Such techniques are important since the incidence of the metabolic syndrome is reaching pandemic proportions.
In the first part of this thesis, consisting of chapters 2, 3 and 4, new techniques for body MR were developed. Body MR is routinely conducted using MR scanners up to 1.5 T. However in the recent years, a substantial number of these 1.5 T scanners have been replaced by high field scanners (≥ 3 T). The main drive to switch to higher field scanners is that the higher magnetic field will result in a larger effective magnetization of the spins, thereby increasing the signal-to-noise ratio (SNR). Nevertheless, in body MR it is challenging to achieve this gain in SNR due to an increase in imaging artefacts. One of the causes for these artefacts is that due to decreasing wavelength of the RF signal resulting in constructive and deconstructive interference, it is more difficult to create a homogeneous transmit field. In **chapter two**, (Increasing Signal Homogeneity and Image Quality in Abdominal Imaging at 3 T with Very High Permittivity Materials) we addressed this problem by applying high dielectric pads which significantly reduce the coefficient of variance creating a more uniform transmit field for abdominal imaging using a 3 T MR scanner. Furthermore, the high dielectric pads decreased average power, thereby reducing the global specific absorption rate (SAR). This was the case for both the quadrature driven and the RF shimmed 3 T birdcage coil.
In **chapter three**, a similar approach (Improved Cardiac Proton Magnetic Resonance Spectroscopy at 3 T Using High Permittivity Pads) was used to increase the SNR of cardiac proton spectra. The pads were optimized using a finite time domain solver to obtain maximal RF field in the septum of the heart instead of a more homogeneous RF field over the whole heart region. In-vivo, the pads demonstrated an average increase in spectral SNR of 60%. If the SNR is high, this gain in SNR can be traded for a reduction in acquisition time by a factor of two and a half, addressing one of the biggest problems with MRS, namely the relatively long total acquisition time.
Even after optimizing the transmit field and receive sensitivity, MR spectroscopy remains technically challenging to perform reliably. This is partly due to the dynamic field fluctuations introduced by respiratory motion, and in the case of heart, cardiac motion. Furthermore, there is an inherent low SNR of the metabolites of interest as well as a great dependency on the homogeneity of the static magnetic field. For cardiac MR spectroscopy in particular, there are no standard (clinical) protocols offered by manufacturers. Since there are many parameters that significantly impact the spectral quality, designing such a scan protocol remains challenging. In **chapter four** (Parameter Optimization for Reproducible Cardiac ^{1}H-MR Spectroscopy at 3 Tesla) we described how cardiac proton MR spectroscopy can be optimized and measured the reproducibility of these measurements. The optimized protocol involves a local power optimization, pencil beam B_0 shimming, a cardiac trigger delay of 200 ms, pencil beam navigator-based respiratory compensation, and MOIST water suppression. Using this optimized protocol, a high intra- (C_v = 5%) and intersession (C_v = 6.5%) reproducibility of the myocardial triglyceride content was achieved.
In the second part of this thesis (chapters five, six and seven), the previously developed techniques were applied in clinical studies to gain additional insight in the development/treatment of the MetS. In **chapter five** (MR of Multi-Organ Involvement in the Metabolic Syndrome), a literature review of the MetS was provided, focussing on the primary organs affected including the brain, skeletal muscle, pancreas, heart, liver and kidney. Crucial symptoms of MetS pathophysiology, ranging from ectopic lipid accumulation to end-organ damage can be evaluated using multiple MR techniques. Therefore, MR could be of added value in attempts to unravel the MetS pathophysiology as well as monitoring of therapy efficacy.
At present, much remains unknown as to how MetS affects the kidneys. Subsequently, there is a strong need for non-invasive tools to measure renal fat content. Although spectroscopy in the heart and liver has become the non-invasive gold standard for metabolite quantification, it was not yet performed in the kidneys. As with heart and liver measurements breathing complicates the application of spectroscopy in the kidney, but more importantly the limited size of the spectroscopy voxel results in low SNR. In **chapter six** (Metabolic Imaging of Human Kidney Triglyceride Content: Reproducibility of Proton Magnetic Resonance Spectroscopy), we demonstrated that MR spectroscopy can be performed in the kidney. Furthermore, we showed that pencil beam navigator respiratory triggering significantly improves both spectral quality and reproducibility.
In liver and cardiac spectroscopy several studies have been performed to validate the technique to the criterion standard; biopsy. However, to our knowledge there has been no validation study performed to test the accuracy of renal MR spectroscopy. In **chapter seven** (Metabolic imaging of fatty kidney in diabesity: validation and dietary intervention), we validated this technique by comparing lipid measurements using renal proton MR spectroscopy with biopsies of porcine kidneys. The lipids measured by proton MR spectroscopy and the enzymatic assay (biopsy) correlated significantly ($r=0.86$, $p < 0.0001$). In addition, the effects of dietary intervention on the renal lipids were measured. One group was fed a regular diet (group A), one a high lipid diet (group B) and a third group followed the same high lipid diet combined with a low-dose of streptozocin (group C) to induce insulin-independent diabetes. After the 9-month diet, the renal lipids in group C (high lipid diet combined with streptozocin) were significantly higher compared to group A (regular diet). Renal lipids were not significantly different between group B (high lipid diet) and group A (regular diet).

GENERAL DISCUSSION

PART ONE: TECHNICAL DEVELOPMENTS - HIGH FIELD BODY MR

Body MR can benefit from higher field strengths (3 T and higher) but often acquisition protocols cannot directly be transferred from lower field scanners since the increase in field strength introduces new artefacts, in addition to exacerbating the existing ones. Therefore, it can be challenging to achieve the theoretical improvements in image and spectral quality. These artefacts are to a large extent caused by the shortening of the wavelength of the transmit (RF) field in comparison to the size of the imaging object. The RF field then constructively and destructively adds causing hyper and hypointense areas in the image.

This problem of decreased transmit homogeneity has been addressed by MR manufacturers by the introduction of multi-transmit systems. Alternatively, it has been shown that in neuro and cardiac imaging dielectric pads can be used to homogenize the transmit field.[29,59] In this thesis a new application of the pads in abdominal imaging was examined. When using the high dielectric pads for liver imaging, the shading artefacts (caused by the inhomogeneous transmit field) have been reduced resulting in higher image quality. In particular, the high dielectric pads may be of added value in patients with ascites or pregnant women, where effect of such shading artefacts is the highest. Application of these pads could be the difference between an unusable and an useful scan for the radiologist.

In this thesis, we have shown that the high dielectric materials used for passive shimming can also be applied in MR spectroscopy to increase the signal-to-noise ratio. When designing such pads for MRS, maximal transmit/receive sensitivity is a more important optimization parameter then transmit inhomogeneity since the MRS voxel is small in contrast to regular imaging. This results in pads that are of higher permittivity and thicker than the pads used when the main optimization parameter is the homogeneity of the transmit field. By applying these pads for cardiac spectroscopy, an increase of 60% in SNR was achieved. This effect was predominantly attributed to an increase in receive sensitivity. This effect will most likely also translate to spectroscopy of other organs, however, additional studies are needed. Furthermore, although passive radiofrequency shimming increases image and spectral quality, the dielectric pads have to be placed on the patient which is an extra step that limits implementation feasibility in the clinic. Moreover, correct placement of the dielectric pads requires the MR operator to have a basic knowledge about the methodology of the pads. A potential solution to this problem could be to incorporate the dielectric pads into phased array receive coils.

MR spectroscopy is known to be a challenging technique to perform in the body and the reproducibility is often a major concern. As shown in this thesis, many variables can affect the reproducibility of MR spectroscopy. For example, respiratory triggering is an important factor that should be addressed carefully. At present, most studies use breath holds or a pencil beam navigator at the lung-liver interface to address this problem. When using breath holds, it is known that the amount of air in the lungs varies between subsequent breath holds resulting in variation of the location of the volume of interest between the breath holds and thus decreases the reproducibility. Furthermore, a breath hold scan is not ideal for body scans in clinical populations since patients often have reduced breath-holding capability. Application of a pencil beam navigator is better suited for MRS acquisitions since it triggers the spectroscopy sequence consistently in the same respiratory state without the need for breath-holds. Unfortunately even though such a pencil beam navigator is standard practice for body imaging the MR manufacturers do not offer this function for spectroscopy. The navigator can be made available by adapting the scanner software but not all research groups have access to the scanner software. Secondly, a pencil beam navigator can only track the lung liver interface in one dimension (lung-liver interface in feet-head direction). This may be sufficient when measuring the liver, but the movement of other organs like the heart and kidneys have to be estimated from this indirect respiratory measurement. Nonetheless, in this thesis we have shown that the current 1D implementation of the navigator allows for reproducible cardiac spectra, although it would be more optimal if the navigator could track the 3D displacement of the organ of interest. Such a 3D navigator would also decrease the need for the subject to lie perfectly still in the scanner since it is often challenging for patients to lay completely still throughout an entire scan session (from the acquisition of the spectroscopy planning scan until the end of the spectroscopy acquisition). When a patient has moved substantially, it can lead to incorrect lipid quantification when peri-organ adipose tissue becomes included in the MRS voxel due to the movement. This can be confirmed by acquiring an additional post-MRS plan scan or in the post processing of the separate averages of the spectroscopy data.

Another variable of great importance for the reproducibility of MRS is the power optimization. If the power of the excitation is over or underestimated, the desired flip angle will not be reached which will result in a signal loss. This signal loss in single voxel spectroscopy (eg. PRESS, STEAM) is, due to the multiple refocussing pulses, much higher than most imaging sequences. When looking solely to the signal dependence on the flip angle for the STEAM it can be described by,

$$S(\theta)_{STEAM} = S_0 \sin\theta_1 \sin\theta_2 \sin\theta_3 \qquad \text{(Equation 1)}$$

where S_0 is the signal when flip angles $\theta_{1\text{-}3} = \pi/2$.[60-61] For the PRESS sequence the signal dependence to the flip angle is even greater due to the two 180 degree refocusing pulses. Here the signal equation becomes,

$$S(\theta)_{PRESS} = S_0 \sin\theta_1 \sin^2(\theta_2/2) \sin^2(\theta_3/2) \qquad \text{(Equation 2)}$$

where S_0 is the signal when flip angle $\theta_1 = \pi/2$ and $\theta_{2\text{-}3} = \pi$.[62-64] For example, when the deviation of the flip angle is 20% when using the PRESS sequence, this will result in a signal loss of approximately 22%. This loss in signal will have a strong impact on the reproducibility stressing the need for a good power optimization. In this thesis we compared the standard system "global" power optimization with "local" power optimization. Global in this case refers to the fact that power optimization is performed by integrating the signal intensity over an entire transverse slice through the heart, whereas local applies only to the spectroscopic VOI. Local power optimization method was performed by monitoring the intensity of the water peak and incrementing the tip angles of the excitation pulse and the two refocusing pulses in the PRESS sequence in steps of 5% (range, 90%–150% of the global power optimization result), and choosing the power which produced the maximum signal intensity. In terms of SNR, using local rather than global power optimization showed a significant increase. Local power optimization requires no changes to the system software, and so is easy to implement in a clinical setting. We observed that the power underestimation from a global power measurement was

greatest in subjects with either high body mass index or athletic subjects with high lung volume, but further study would be required to confirm this observation.
Even though MR spectroscopy has been used for several decades in organs like the liver and heart, little research has been conducted examining whether this technique can be applied in the kidney as well. This thesis showed that MR spectroscopy of the human kidney for detection of cortical triglyceride content is feasible. However, it remains challenging to apply renal MR spectroscopy since the limited maximum size of the spectroscopy voxel as well as very low lipid levels in the kidney cortex result in a low SNR with a subsequent need for many signal averages to get sufficient SNR. Secondly, kidney tissue is not homogenous with substantial anatomical and functional variation between cortex and medulla as well as glomeruli and tubuli. Finally, due to the close proximity of lipid contamination sources such as sinus and perirenal lipids, accurate voxel placement and reliable respiratory triggering are of great importance. To improve voxel planning, a fat image from a water-fat acquisition can be used since the contaminating sources are clearly visible. For respiratory triggering, a pencil beam navigator is preferred, although a 3D navigator might prove even more valuable since the kidney is relatively far from the lung liver interface. However, with kidney spectroscopy, small motion artefacts can still remain. Therefore, in post processing, averages should be analysed separately to confirm that none of the averages are contaminated by perirenal or sinus lipids.
At present, clinical application of MRS is mostly limited to neurology and the prostate.[65,66] In this thesis, a main challenge of implementation of the technique was overcome; the reproducibility. It was shown that both in the heart, as well as the kidney it is possible to acquire good quality and reliable spectra. Furthermore, it was shown that in porcine kidneys, the MR spectroscopy triglyceride levels strongly correlated with 'criterion standard' enzymatic assessment of triglyceride content. This opens up new possibilities to extend the (clinical) application of body MR spectroscopy.
However, the complexity of the acquisition and post-processing also contribute to the difficulties in the application of body MR spectroscopy. At present, the acquisition and reconstruction of MR spectroscopy requires extensive knowledge about the technique to obtain reliable results. In order to achieve a broader implementation of body MR spectroscopy, MR manufacturers need to play an important role since apart from the liver spectroscopy, no protocols are offered by the MR manufacturers for body MR spectroscopy. Moreover, on-scanner reconstruction and post-processing methods for spectroscopy data are limited and in most cases, off-line post-processing and analysis of the spectra is required.[67,68] Finally, the aforementioned 3D navigator that can track the separate organs could contribute to further improvement of reproducibility and support a wider application of body MR in general.

PART TWO: CLINICAL APPLICATIONS - METABOLIC SYNDROME
MetS is a systemic disease with a complex pathophysiology including insulin resistance, atherogenic dyslipidemia, hypertension, ectopic lipid accumulation, low-grade inflammation, prothrombotic state, and fibrosis resulting in end-organ damage.[48] Application of the techniques and optimizations described in this thesis, functional and structural consequences of MetS can be evaluated with MR throughout the entire body.
Using a porcine model, we demonstrated that renal triglyceride content increased over the metabolic spectrum in conjunction with hepatic triglycerides. Previous studies have shown a correlation between increased bodyweight and increased hepatic and renal triglyceride content in both animals and humans.[53,56] We observed similar trends, with increasing triglyceride content in the diabetic type 2 group. Using Oil Red O staining it was shown that renal lipid accumulation was most prominent in renal tubuli, albeit some lipid staining was also observed in the glomeruli. This is in accordance with a recent study of human nephrectomies, where lipid droplets were predominantly found in tubule cells and to a lesser extent in the glomeruli.[56]

OVERALL CONCLUSION OF THIS THESIS

As part of the present thesis advanced MR techniques were developed, including development and application of high dielectric materials for body MR imaging and spectroscopy, resulting in improved signal-to-noise ratio and reproducibility. These technical advances were used to study the metabolic syndrome, showing dietary effects on renal fat content.

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