In vivo phase imaging of human epiphyseal cartilage at 7 T

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Abstract

Purpose: To assess the potential clinical utility of in vivo susceptibility-weighted imaging (SWI) and quantitative susceptibility mapping (QSM) of growth cartilage in the juvenile human knee at 7 T.

Methods: High resolution gradient echo images of the knees of 6 healthy children and adolescents aged 6 to 15 were acquired with a 28 channel coil at 7 T. Phase images from the coils were combined using a short echo-time reference scan method (COMPOSER).

Results: Veins oriented perpendicular to the static B_0 field appeared doubled in SWI but not QSM. Veins and layers in the cartilage were visible in all children up to the age of 13.

Conclusion: Phase imaging using SWI and QSM allows the in vivo visualization of veins and layers in human growth cartilage.

Keywords: Quantitative Susceptibility Mapping, Susceptibility-Weighted Imaging, phase, cartilage, epiphyseal cartilage, veins, layers

Introduction

Susceptibility-Weighted Imaging (SWI) and Quantitative Susceptibility Mapping (QSM) have recently been applied in the cartilage of synovial joints in anaesthetized animals and human cadaver samples at ultra-high field (1,2), with a view to better understanding the pathogenesis of cartilage disorders. The potential of ultra-high field SWI and QSM to provide insights into the normal and abnormal cartilage of children in vivo has yet to be explored.

The two main macromolecular constituents of cartilage are glycosaminoglycans and collagen. The organization of collagen fibrils in articular cartilage depends on the site and age. A quite homogeneous isotropic arrangement of fibers in neonatal cartilage develops to radial intermediate and transitional layers postnatally, evolving into a thinner trilaminar 'arcade' structure in adulthood (3). Radially oriented fibers in the deep cartilage zone close to the bone give way to a predominantly isotropic transitional zone. Each collagen fiber forms an arch such as that, in the superficial zone, the fibrils run parallel to the articular surface (4).

In children and adolescents, before the epiphyseal plate is closed, the shape of the distal end of long bones is formed by the chondroepiphysis. During pre and postnatal development the cartilage canals are formed by protrusions of mesenchymal stem cells from the periphery of chondroepiphysis. Eventually, these pluripotent mesenchymal cells differentiate to venules and arterioles (5). Disorders of the ossification process of the epiphyseal cartilage may lead to diseases such as Perthes disease in the hip and Osgood-Schlatter disease and osteochondrosis dissecans (OCD) in the knee (6). There is mounting evidence that these diseases have a common pathophysiological origin in the vessels in the growth cartilage (7,8). Studies of spontaneously occurring OCD in pigs, for instance, have indicated that the early (subclinical) lesions are characterized by areas of chondronecrosis that are closely associated with non-perfused vessels in cartilage canals (8).

Significant inroads towards establishing cartilage vessel imaging in the epiphysis of juvenile humans in vivo have been made recently in the animal work and in situ work by Nissi, Toth, Ellermann and colleagues (1,2,9,10). Taking advantage of the SNR and

sensitivity to susceptibility-based contrast at high field (3 T) and ultra-high field (7 T and 9.4 T), they have demonstrated that cartilage vessels can be visualized in the distal femur and humerus of ex vivo and in vivo anaesthetized piglets (2,10). With SWI at 9.4 T, they have shown that the vascular architecture at OCD predilection sites in human cadavers (aged 1 to 36 months) is similar to that in pigs (which are prone to OCD) but not goats (which are not) (9). The same group has applied QSM to a goat model of preclinical OCD (11) and has demonstrated ex vivo at 9.4 T and 7 T that visualization of cartilage vessels is improved using "true SWI" (tSWI) (1), where QSM (rather than filtered phase) is used to enhance the contrast present in magnitude images (12).

The challenges of applying SWI and QSM in vivo in children to study cartilage vessels and layers are manifold. Prior work has focussed on very young animals and in situ human samples in which cartilage is more densely vascularized than in children and adolescents, who typically do not present with suspected OCD before the age of 10 (13). In order to make SWI and QSM viable in children, measurement times also need to be radically reduced, from 11-98 min (1,2) to a few minutes.

This study gives an insight into the clinical potential of imaging the vessels and growth cartilage using SWI and QSM at ultra-high field in a group of children and adolescents aged 6 to 15 years old.

Methods

Six healthy subjects, who were all minors, had the purpose of the research explained to them in non-technical language and participated with written informed consent and the written informed consent of their legal guardians. The study was approved by the Ethics Committee of the Medical University of Vienna. The subjects are identified by the labels C1-6 in the rest of the manuscript. Their genders and ages were as follows: C1 (m, 6 y.o.), C2 (m, 10 y.o.), C3 (m, 10 y.o.), C4 (m, 10 y.o.), C5 (m, 13 y.o.), C6 (f, 15 y.o.).

Measurements were made with a 7 Tesla Siemens MAGNETOM scanner (Siemens Healthcare, Erlangen, Germany) and a 28 channel knee coil (QED, Mayfield Village, OH, USA). The following measurements were performed:

SWI scan

The scan to be reconstructed was a high resolution, sagittal, 3D gradient-echo acquisition with TE = 10.3 ms and repetition time (TR) = 23 ms, GRAPPA factor 3 in anterior-posterior direction, receiver bandwidth of 140 Hz/pixel, with subject-dependent matrix sizes of 448×[308,308,406,322,392,434]×88 (where the matrix size in the phase encoding direction was adjusted to a subject-specific field of view), 0.3 mm in-plane resolution and between 1.0 mm and 1.4 mm thick slices, acquisition time (TA) between 3 min 8 sec and 4 min 14 sec.

Short Echo time Reference (SER) scan

The SER scan for the phase combination with COMPOSER method (14) was a 3D gradient-echo sequence (15,16). The following parameters were used: TE/TR = 0.8/14 ms, GRAPPA factor 2 in anterior-posterior direction, receiver bandwidth = 400 Hz/pixel, matrix size 128×64×40, 1.8×1.8×2.3 mm^3 resolution, and TA = 25 s.

Multi-echo acquisition

For T_2*-mapping, a 3D multi-echo gradient-echo scan was acquired with a monopolar-readout and TEs/TR = [3.7, 8.0, 12.3, 16.6, 20.9, 25.2, 29.6, 33.9, 38.2, 42.5]/113 ms, GRAPPA factor 2, receiver bandwidth of 338 Hz/pixel, 192×132×32 matrix size, 0.78×0.78×3.0 mm^3 resolution, and TA = 2 min 58 sec. For the youngest subject (C1) the acquisition time was shortened to TA = 1 min 1 sec and the parameters were adjusted accordingly: TEs/TR = [2.9, 6.3, 9.8, 13.2, 16.7, 20.2, 23.6]/38 ms, GRAPPA factor 2, receiver bandwidth of 501 Hz/pixel, 192×150×32 matrix size, 0.78×0.78×3.0 mm^3 resolution.

Analysis

Phase images from the phase array coil were combined offline using the COMPOSER method (14) implemented in MATLAB (Mathworks Inc, Natick, MA). For the generation of SWI, combined phase images were Laplacian unwrapped and high-pass filtered prior to the generation of positive phase masks in which values were set to 1 for negative phase and decreased linearly to zero for phase values between 0 and the maximum present. These masks were raised to the power of 4 and multiplied by the corresponding magnitude images.

For tSWI, binary masks of signal-yielding regions were generated by setting all voxels that had values in magnitude images equal to or greater than an empirically derived threshold to 1 and those below to 0. These masks were then edited by hand using mricro (http://www.cabiatl.com/mricro/mricro/mricro.html). QSMs were generated with single-step Total Generalized Variation (17), using combined, wrapped phase images and image masks. QSMs were high-pass filtered using a 20x20 voxel 2D Gaussian kernel with a standard deviation σ=4 (2D instead of 3D kernel was used due to relatively large slice thickness). Positive QSM masks were generated, raised to the power of 4 and multiplied by the corresponding magnitude images.

Results

The problem of "vessel doubling" in SWI is depicted in Figure 1. The dipole phase distribution around veins that run perpendicular to B_0 is visible in the phase image in the top row of the figure. These veins were resolved in the QSM. Vessels which were poorly visualized in the magnitude were enhanced in the SWI, but vessel doubling was also introduced (see arrows). This artifact did not occur in tSWI.

Figure 1 about here.

Examples of the appearance of veins in the SWI of the cartilage are presented in Figure 2. Dot-like structures represent vessels perpendicular to the imaging plane, linear structures correspond to veins and cartilage canals parallel to the imaging plane (see arrows). There was considerable variability in the cartilage thickness and the amount of vessels between the three subjects who were aged 10 (C2, C3 and C4); the structure of the vessel network and the cartilage appearance in subject C3 is more similar to that of C1 (age 6) and in subject C2 more akin to that in C5 (age 13). Despite this variation, the global expected trend of diminishing vessel network with age is apparent from the youngest child (C1, age 6) to the oldest (C6, age 15), in whom no vessels could be seen.

Figure 2 about here.

In addition to the vessels, a hyperintense layer in phase and corresponding hypointense layer in SWI were apparent in the transitional zone of all subjects other than the oldest (C6) (see Figure 3). This was most apparent in the tibia but also visible in the femoral cartilage, as is clear from the enlargements in Figure 3. In the femoral cartilage it was constrained to the weight-bearing region. The hypointense layer in SWI was mostly poorly or not visible in magnitude images and did not correspond well to T_2* values, although direct comparison is difficult as T_2* data were acquired at a lower resolution.

Figure 3 about here.

Discussion

In vivo SWI of the epiphyseal cartilage of the knee at ultra-high field shows venous vessels and layers in the cartilage in all subjects other than the oldest, in whom only mature (hyaline) cartilage was present.

The dipole distribution of phase around veins which run perpendicular to B_0 led to vessel doubling in SWI in the coronal and sagittal planes. This effect was not present in tSWI, as has been previously reported both in neuroimaging (12,18) and prior cartilage work (1). The use of tSWI may be worthwhile for quantification of vessel density or in vivo oxygen saturation (SvO_2) (19), but seems to be unnecessary in the investigation of the layer structure of cartilage, as this appears broadly similar in SWI and tSWI. A disadvantage of tSWI is that it requires tissue segmentation in order to create the masks which are required to generate QSMs. Segmentation is more complex in the joints than in neuroimaging, and tools are less well developed, especially for use in children. As such, mask generation is still a time-consuming semi-automated procedure. The recent iterative methods of Buch et al. and others, which allow the susceptibility of short T_2* species to be estimated, offer a solution to the segmentation problem which would certainly benefit future studies in this field (20).

The accuracy of QSM values was not assessed in this study, but it has been shown that it is adversely affected by the presence of fat. The problem can be remedied by the use of fat-

water separation (21,22) but the need for multiple acquisitions with incrementally shifted echo times makes this too long and prone to motion for pediatric investigations.

It is well known that vessels in growth cartilage decrease in number with age (23). With maturation, the cartilage canals containing vessels become incorporated into the ossification center or degenerate (24). Osteochondrosis, defined as a focal disturbance of enchondral ossification, is a common and clinically important joint disorder that occurs in children, adolescents and young adults. Classical examples in humans are Perthes disease, osteochondrosis dissecans and Osgood Schlatter disease (25). Recent literature strongly supports failure of blood supply to growth cartilage as being the first step in the pathogenesis of osteochondroses (7). The question arises whether SWI and tSWI images such as those presented here will allow these disorders to be further investigated. The image quality certainly falls short of the animal and in situ human work of Carlson and colleagues (1,2,9-11,26), which has demonstrated dense networks of well resolved veins. This discrepancy relates partly to imaging factors - shorter imaging times, low-level motion and physiological fluctuations encountered in vivo - but mostly to the low density of the vessels in the chondroepiphysis of the children and adolescents examined. Prior human cadaver work has focused on a sample of 1 month old baby (1) and specimens from children aged between 1 and 36 months (9). Based on the results presented here, it seems unlikely that the analysis of the density and local distribution of vessels in their cartilage canals will provide insight into the pathogenesis of OCD and other cartilage disorders which are thought to have a vascular origin, because most of these diseases occur after the age of 10. At this age the focal enchondral ossification disturbance is, at least in part, already surrounded by the ossification center. SWI and tSWI images only allow the evaluation of the cartilage - vessels at the ossification front and in the bone cannot be differentiated. One may speculate as to whether Perthes disease, which mainly occurs between the ages of 5 and 6, may be a more suitable area of application of UHF SWI. A further potential use may be to monitor the vascular supply of the unossified femoral epiphysis in the follow-up of abduction therapy for developmental dysplasia of the hip in the newborn (23).

An unexpected finding in this study was that SWI shows clear layers within the cartilage that are poorly visualized in the magnitude. These seem to reflect the multilaminar zones of radially, tangentially and isotropically oriented collagen fibers present in growth

cartilage (e.g. (4)) prior to evolution of the adult arcade structure. The visibility of these layers was restricted to the weight-bearing region, where radial collagen fibers are parallel to the main magnetic field. It is, thus, most probably an orientation-dependent effect. The appearance of layers in phase images of growth cartilage has not been noted in prior work, presumably because of the concentration on the vasculature. A recent study in adults showed a QSM contrast pattern which may be evoked by the arcade structure of the mature cartilage (22), which we also observed in the oldest subject, C6 (15 y.o.). The orientation of collagen fibers in the superficial zone is critical to the integrity of the cartilage, being disrupted in early osteoarthritis (27), for instance, so could potentially constitute a biomarker for the quality and integrity of cartilage, in fully developed as well as juvenile cartilage. In the follow-up of patients with cartilage repair surgeries it is important to be able to image the reorganization of the collagen fiber network noninvasively. Phase-based MRI may contribute to the assessment that is currently typically performed with zonal T_2 variation analysis, as it has been shown to do in patients with chondral damage (28).

The question arises as to what complementary information is offered by phase imaging of the cartilage which is not available using other contrast mechanisms. Transverse relaxation rates are dependent on both the water content in the cartilage (which increases in the early stages of degeneration (29)) and the interaction between water molecules and collagen fibers in cartilage (30), which is subject to the 'magic angle' factor (31). T_2 maps have been used to assess repair cartilage quality (32), but have to be interpreted with caution due to the orientation dependence. The magic angle effect has been used to visualize the layers present in juvenile pig femoral condyles (33) and collagen defects (4) but is of limited usefulness in vivo due to rotation constraints. T_2* mapping provides information about collagen structure (34) but its sensitivity to fiber orientation with respect to B_0 appears to be much weaker than in SWI or QSM (22). Wei et al. explain the weaker R_2* anisotropy with the fact that the anisotropies of the two constituents of this relaxation rate, R_2 and R_2', have opposing signs and may cancel each other. We have also shown here that T_2* maps and SWI present different, perhaps complementary, information. A comprehensive comparison of these methods regarding the appearance of layers within the cartilage was not envisaged in the study design. As a result, the T_2* and SWI data sets acquired – which are of different resolution, and could not accurately be coregistered – are

not ideal for this purpose. This poses an interesting topic for a future investigation in which higher resolution T_2* mapping with field inhomogeneity correction (35) may be needed in order to draw sound conclusions.

The 3D gradient-echo images in this study were acquired with 0.3 mm in-plane resolution and between 1.0 mm and 1.4 mm thick slices. For optimum QSM reconstruction, reduction of partial volume effects and flexibility in visualisation, resolution should be chosen to be isotropic. The necessity to keep acquisition times short (maximum circa 3 – 4 minutes), in this group of minors, led to the decision to use thicker slices.

Phase-based imaging is prone to coil combination and unwrapping artefacts, particularly at very high field. Adaptive phase combination (36) can lead to low CNR and open-ended fringe lines at 7 T, while the strong high-pass filtering using in homodyne filtered combination (37) can lead to the erroneous appearance of contrast variation parallel to signal boundaries. Given the relative novelty of phase-based imaging in cartilage, particular care was taken to ensure that phase data were processed with effective methods. A preliminary report on the data acquired in this study showed that the COMPOSER phase combination method led to near-perfect phase matching over channels throughout the knee (38), reflected in high Q values (>99%) (39). Phase images showed no signs of phase artifacts, and those of the oldest subject (C6, Figure 3) are consistent with that reported recently by Wei et al. (22), leading us to be confident that the contrast variation observed across the cartilage reflects variation in tissue microstructure.

Although no measurements were made in this study at clinical field strength, prior comparative 3 T – 7 T SWI work by Springer et al. in the field of neuroimaging (40) suggests that ultra-high field MRI may be necessary for visualization of the vasculature of growing knee cartilage. It may be possible, however, to image cartilage layers at 3 T using longer echo times and other protocol modifications. However, pending regulatory authority approval for 7 T for neuroimaging and musculoskeletal diagnostics offers the prospect that UHF phase-based assessment of growth tissue vasculature may soon be available to clinical populations.

Phase contrast in GRE-based images is, like magnitude contrast, dependent on the orientation of susceptibility structures (41-44). QSM removes orientation dependence for scalar susceptibilities, but anisotropic tissues are known to have tensor values, which can

be elucidated with multi-orientation susceptibility tensor imaging (STI) (45). The tensor properties of white matter in the brain (46), the tubules in the kidney (47), muscle fibers in the heart (48) and the liver (49) have recently been investigated. Early reports suggest that the cartilage in the knee also has tensor susceptibility (50). As in the brain, however, that should not prohibit the exploration of phase imaging, SWI and QSM to provide new insights into the vascularization, structure and integrity of cartilage.

Conclusions

SWI and QSM allowed the visualization of veins and layers of growth cartilage in vivo. The clinical relevance of the ability to image the vasculature of growth cartilage in young children with a higher vascular component compared to older children and adolescents requires further studies of relevant pathologies. The unexpected finding in this study is that SWI shows clear layers within the cartilage probably reflecting multilaminar zones of radially, tangentially and isotropically oriented collagen fibers. Future work might compare phase-based contrast with existing approaches to the assessment of mature cartilage integrity.

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Fig. Captions

Figure 1: A comparison of the features of filtered phase images and QSMs (top row) and magnitude, SWI and tSWI images (bottom row), illustrated in subject C1. The arrows mark veins perpendicular to B_0 and the image plane, which are poorly visible in the magnitude image. These create dipole-like distributions in phase images, causing a vein doubling artifact in the SWI. QSM resolves these veins making each vein appear as a single well visible spot in tSWI.

Figure 2: Examples of vein appearance in the cartilage in SWI. Arrows point to the most evident examples of veins. The number of dot-like (perpendicular to image plane) and linear (parallel to image plane) vessels generally decreased with age, with no apparent vasculature in the oldest subject C6 (age 15).

Figure 3: Examples of cartilage fiber orientation appearance in SWI in comparison with magnitude-only images and T2*-maps for all the subjects. Layer-like contrast, visible in the filtered phase (fPhase), is mostly absent in the magnitude but appears in SWI via the phase mask. T2*-maps and SWI show different contrast pattern.