R.W. de Boer[1])

Magnetization transfer contrast

Part 2: Clinical applications

The use of MTC in clinical scanning is based on the fact that different biological tissues show different sensitivities for magnetization transfer (MT). This is summarized in Tables 1 and 2.

Table 1 shows the biological tissues and fluids which do not show a measurable effect (quantified as < 5% signal attenuation), and Table 2 shows the tissues with significant signal reduction due to MT. These figures are compiled from the literature, and have been experimentally collected at different field strengths with a variety of MRI pulse sequences. Tissue types are listed in order of the amount of signal reduction with MT. Note that sub-maximal signal reduction can still be relevant (or sometimes even desirable) from a clinical point of view.

Table 1. Biological tissues and fluids not influenced by MT (experimentally defined as less than 5% signal attenuation.

adipose tissue (fat)
bone marrow
fluid
oedema
blood (fast flowing)
blood (in ventricle)
CSF
bile
synovial fluid
urine

Table 2. Signal attenuation in biological tissues with MT imaging (typical values reported for 1.5 T, measured with a variety of MRI pulse sequences).

skin	80%
skeletal muscle	60 - 80%
hyaline cartilage	70 - 75%
cardiac muscle	50 - 70%
white brain matter	42 - 69%
grey brain matter	39 - 52%
tendons/menisci/ligaments	50%
fibroglandular (breast)	30 - 40%
liver	35 - 40%
spleen	25 - 35%
pancreas	25 - 35%
kidney	25 - 35%
blood (in vitro)	15 - 25%
joint effusion	20 %

[1]) Philips Medical Systems, Best, the Netherlands.

From a practical perspective, any clinical situation where one wants to increase the contrast between tissues from Table 1 and tissues from Table 2 will benefit from MTC. More fundamentally, many investigators try to relate the characteristics of normal and pathological tissue to the underlying fundamental biophysical and biochemical properties. It is hoped that MTC in relation to tissue characterization will increase the diagnostic specificity.

Recently, Wolff and Balaban[1] summarized the present state of the art in MT imaging. Many of the potential clinical applications of MTC which appear to be very promising must, unfortunately, still be considered as works in progress. This paper discusses the successful current applications, as well as potentially attractive new clinical applications.

Successful MTC applications

Intracranial MR angiography

Time-of-flight (TOF) magnetic resonance angiography has proved to be an effective technique for imaging intracranial vessels. This technique is based on the flow-related enhancement phenomenon. Stationary brain tissue within the volume of excitation becomes partially saturated due to the multiple RF pulses. On the other hand, inflowing unsaturated blood maintains a high signal resulting in a good contrast between the vessels and the background brain tissue[7,8].

Typically, 3D volumes are measured with fast gradient-echo sequences and flow compensation schemes. Optimization of contrast is based on careful selection of the repetition time TR and excitation flip angle α, and is dependent on the flow velocity.

In order to further improve the vessel conspicuity in TOF MR angiography, Edelman[7] added an off-resonance MTC pulse to an RF-spoiled gradient-echo sequence for further saturation of background tissue. A total of 80 small-calibre vessels were blindly evaluated

from MIP (maximum intensity projection) images obtained without and with MTC. The results indicated that 71% of the vessels could be seen better with MTC. He concluded that the use of MTC pulses in conjunction with 2D and 3D flow-compensated gradient-echo sequences results in substantial improvement in small-vessel conspicuity. The only limitation of MTC was the increase in the minimum repetition time, necessitated by the application of the 16 ms off-resonance MTC pulse.

Pike et al.[8] used a 1 ms on-resonance pulse in combination with a velocity-compensated 3D time-of-flight pulse sequence. The addition of this pulse (plus the time for a spoiler gradient) increased the minimum TR by only 5 ms. It was shown that this technique also enhanced the blood-to-tissue contrast significantly. These initial results were reproduced by other groups[9-17]. It was generally concluded that for the small, tortuous intracranial vessels (relatively slow flow) MTC improved vascular visualization (Fig. 2).

For imaging systems with a whole-body RF transmitter system, care must be taken to minimize the effect of the RF pulses outside the imaging volume. Kouwenhoven et al.[11] proposed a subtle but important modification of the off-resonance MTC 3D TOF technique. The use of a small magnetic field gradient (400 μT/m), applied during the MTC RF pulse, will create a Spatially Varying Off-Resonance Frequency (SVORF - see Figure 1). Using this technique, arterial blood entering the imaging volume will have experienced MTC pulses with a larger frequency offset, so that the signal reduction will be less. Cranial to the imaging volume, the MTC pulses become on-resonance and will suppress the venous blood, which obviates the need for additional venous presaturation pulses (Fig. 1).

A similar technique was described by Miyazaki et al.[16]. In conclusion, MTC is a clinically useful technique for contrast augmentation in MR angiography. It is currently used routinely at many imaging sites to improve small vessel conspicuity[1].

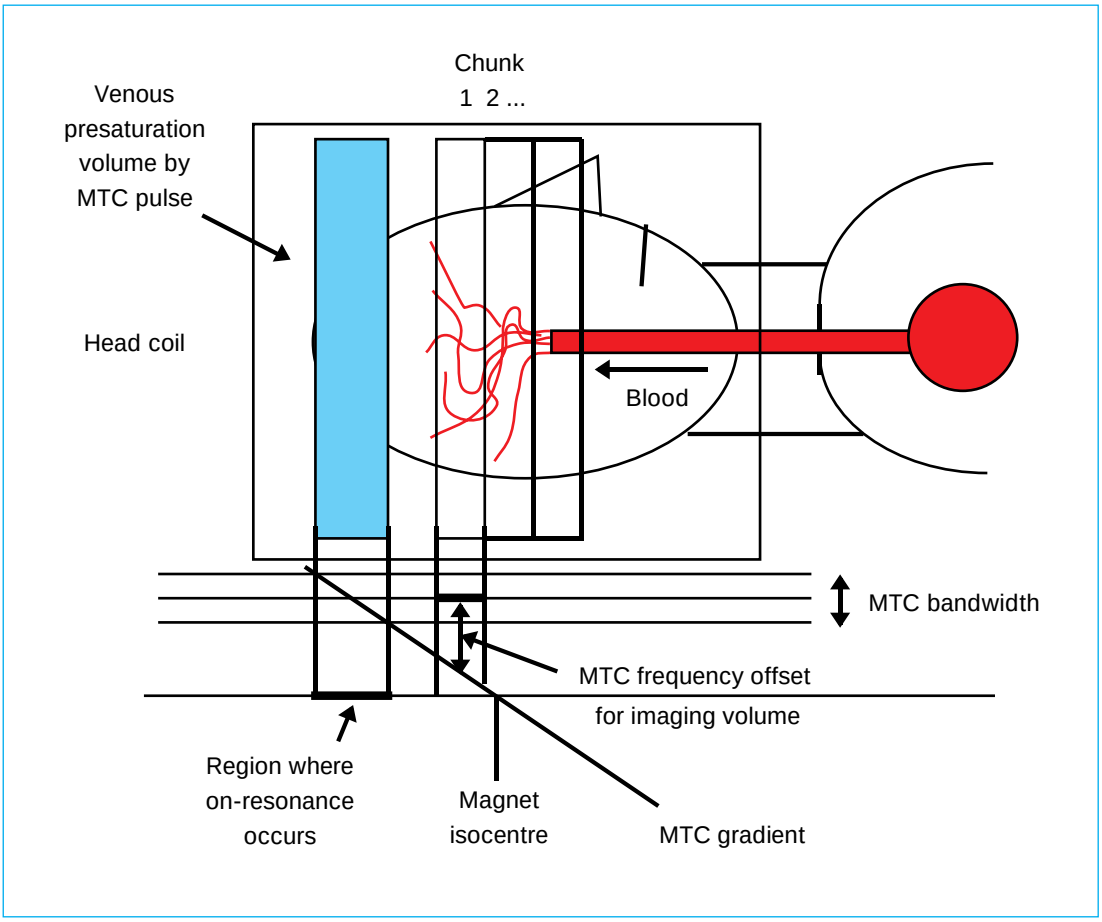


Fig. 1. Schematic diagram of the magnetic field gradient applied during the MTC pulse in order to create a Spatially Varying Off-Resonance Frequency (SVORF).

1

Multiple sclerosis classification

Multiple sclerosis (MS) is a disease in which there are patches of demyelination throughout the white matter of the central nervous system, sometimes extending into the grey matter. The course of the disease is usually prolonged with remissions and relapses over a period of many years. Magnetic resonance imaging has proved to be a sensitive method for detecting MS lesions

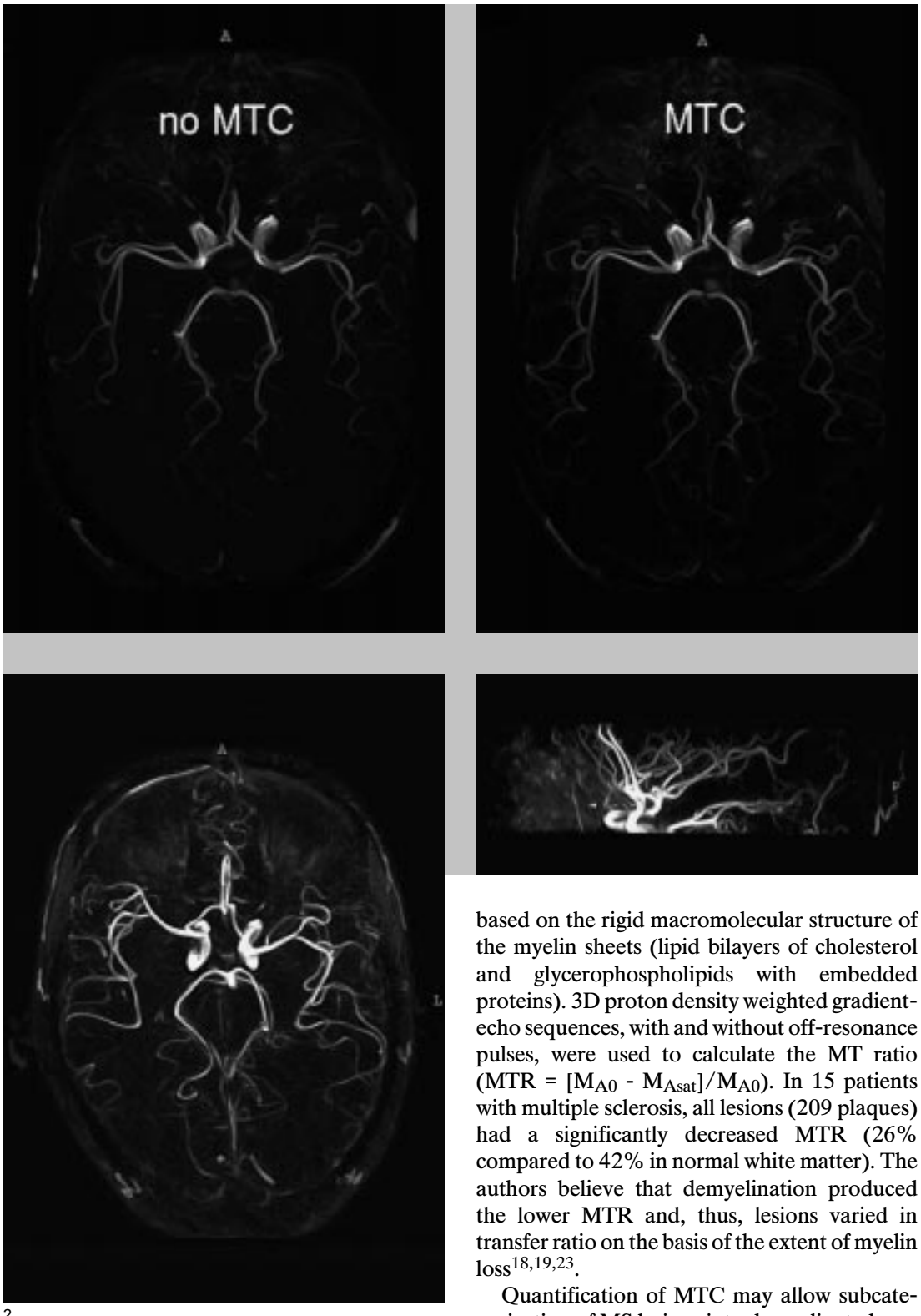


Fig. 2. Examples of intracranial MR angiography using MTC.

2

in vivo (Fig. 3), but lacks specificity to further characterize the stage of the disease process.

Although MRI with contrast agents helps to separate active from nonactive plaques, it is not specific with respect to the pathological substrate of the MS lesion (oedema, demyelination, gliosis).

Dousset et al.[18] were the first to use MT techniques to subcategorize the MS lesions, based on the rigid macromolecular structure of the myelin sheets (lipid bilayers of cholesterol and glycerophospholipids with embedded proteins). 3D proton density weighted gradient-echo sequences, with and without off-resonance pulses, were used to calculate the MT ratio (MTR = $[M_{A0} - M_{Asat}]/M_{A0}$). In 15 patients with multiple sclerosis, all lesions (209 plaques) had a significantly decreased MTR (26% compared to 42% in normal white matter). The authors believe that demyelination produced the lower MTR and, thus, lesions varied in transfer ratio on the basis of the extent of myelin loss[18,19,23].

Quantification of MTC may allow subcategorization of MS lesions into demyelinated versus oedematous lesions, which cannot be seen with standard spin-echo or gradient-echo MRI.

Grossman et al.[20,22] showed nice examples of images of MTC and gadolinium enhancement, where the centre of the lesion had the lowest MTR values, which would presumably correspond to regions of greatest myelin loss. The peripheral rim of enhancement, which had a higher MTR, and presumably more myelin, is

the region of active demyelination. The original findings were confirmed by Gass et al.[21] in a study with 43 patients. All MS subgroups showed significantly lower average MT ratios than age-matched controls and small-vessel disease patients. Secondary progressive MS patients showed significantly lower lesion MT ratios than those with benign disease, and there was an inverse correlation of disability with average lesion MTR. They concluded that the reduced MTR in multiple sclerosis patients may provide an indication of the degree of demyelination and axonal loss, both of which are likely to cause the functional deficits in MS. Thus, magnetization transfer imaging is a robust quantitative method which can differentiate demyelination in MS from less destructive pathological changes, and may be useful in monitoring drug treatment[21].

Gadolinium-enhanced MR imaging of the central nervous system

The use of gadolinium-based paramagnetic agents in MR imaging of the central nervous system (CNS) has been demonstrated in a variety of CNS lesions. Contrast agents are used to increase the signal intensity in regions where the agent accumulates by increasing its relaxation rate. By shortening the longitudinal relaxation time, these agents increase contrast in T_1-weighted images between normal (non-enhancing) brain and brain areas with a disrupted blood-brain barrier where contrast material accumulates (Fig. 4).

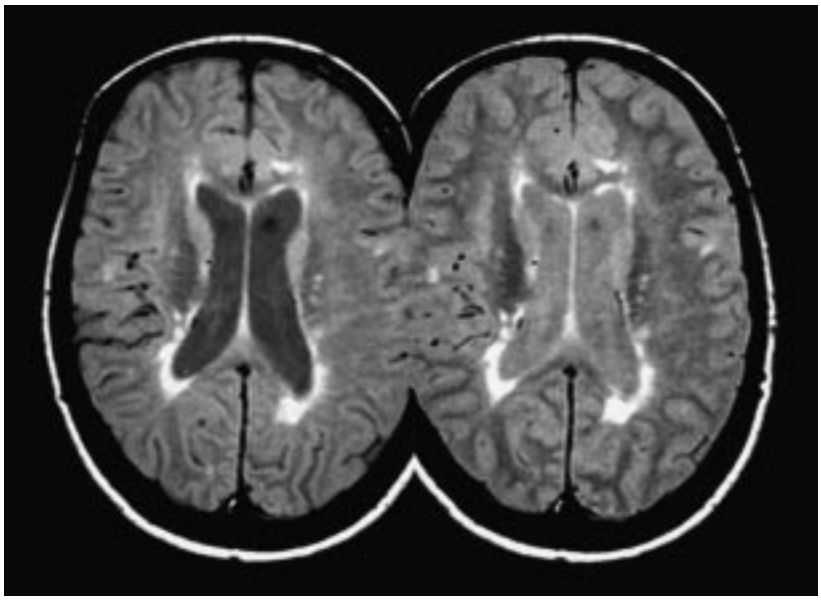
The purpose is to optimize the differences in signal between lesions and background brain tissue[29]. Any technique that will increase this contrast will increase the sensitivity of diagnosing tumours, infections and infarctions.

Tanttu et al.[24] were the first to combine magnetization transfer with gadolinium-enhanced MR imaging. They reported on three cases (multiple sclerosis, neuroma, and meningioma) imaged at 0.1 T, and studied the separate and combined effects of magnetization transfer and gadolinium-enhancement. In each case the best contrast was obtained when both techniques were combined. This synergistic effect was explained by the fact that the paramagnetic agents reduce the T_1 values and therefore, as discussed previously, also the magnitude of the magnetization transfer effect.

The signal of the enhancing lesions is actually reduced (12%-16%), but much less than the signal reduction of the background white matter (35%-37%), and therefore the contrast is increased.

The fact that MT amplifies the tissue contrast has been reported by many authors, both with on-resonance and off-resonance pulses[25-33]. Mehta[29] reported for example a contrast improvement factor of 1.6 - 2.1 for CNS tumours (metastases, glial tumours, lymphomas) when combining MT with gadolinium-enhanced MR imaging at 1.5 T. Similar synergistic effects were found in patients with recent infarctions[27], and a wide variety of enhancing brain lesions, including primary neoplasms, metastases, extra-axial lesions, cerebral infarctions, multiple sclerosis plaques, meningitis, vascular malformations, and contusions[38]. Of practical importance is the fact that the grey-white contrast can be reversed with MT. For these reasons, pre-contrast MT images are not used routinely. Conventional T_1-weighted images are used as the pre-contrast comparison to detect low-signal intensity lesions[65]. Finelli reported that one can achieve the same relative contrast improvement as that provided by triple-dose gadolinium, by using single-dose gadolinium in combination with magnetization transfer T_1-weighted imaging[28].

Because the MT technique quantitatively improves contrast enhancement with gadolinium-based agents, it allows the use of a reduced dose of paramagnetic contrast agent. If the current recommended dose of 0.1 mmol/kg can be reduced without clinical drawbacks, this can have important economic ramifications[1]. The optimum balance between lesion contrast, gadolinium dose, SAR, time and money is an intriguing problem that remains to be solved[28].



3

Fig. 3. Magnetic resonance imaging has proved to be a sensitive method for detecting multiple sclerosis lesions, but lacks the specificity to further characterize the stage of the disease process.

Intra-articular cartilage evaluation (osteoarthritis)

Magnetic resonance imaging of joints plays an important role in the evaluation of soft-tissue

structures in patients with arthritis. It is the only non-invasive method with any potential for directly depicting articular cartilage and synovial tissue.

An important drawback of conventional imaging sequences is the relatively poor image contrast between articular cartilage, joint effusion, and inflamed synovial tissue.

In one of the very first clinical papers on magnetization transfer, Wollf et al.[34] studied the cartilage-synovial fluid contrast in the knees of human volunteers. He was able to show significant increase in contrast on high-resolution 3D gradient-echo images (Fig. 5). He concluded that MTC not only provides better structural information about the knee, but may also provide non-invasive insight into the structure and biochemical composition of cartilage *in vivo*.

The latter idea was studied in detail by Kim et al.[62]. Articular cartilage is a three dimensional helical matrix of collagen fibres (type II collagen which is highly hydrophilic) and proteoglycans. *In vitro* data demonstrate that the structure and concentration of the collagen matrix are the predominant determinants of the magnetization transfer process in articular cartilage, with little or no contribution from proteoglycans.

Other groups studied MTC as a method to increase specificity of low-grade chondromalacia[34,35,47]. Fine tuning of the MT pulse sequences revealed that it is not always necessary to suppress cartilage maximally, as long as it is not iso-intense with fluid. A blind comparison between MTC and conventional gradient-echo images by six musculoskeletal radiologists in 40 cases, however, did not show a diagnostic advantage for osteochondral abnormalities.

Peterfy[36,37] showed that magnetization transfer can not only be used to distinguish cartilage from joint fluid, but can also differentiate synovial pannus from adjacent fluid. In patients with inflammatory arthritis and osteoarthritis, MT was combined with gadolinium enhancement. When MT-enhanced images were subtracted from conventional gradient-echo images, articular cartilage and synovial pannus showed large contrast with adjacent joint fluid, fat and bone tissue. Because pannus enhances with gadolinium, subtracting post-gadolinium from pre-gadolinium MT images revealed the

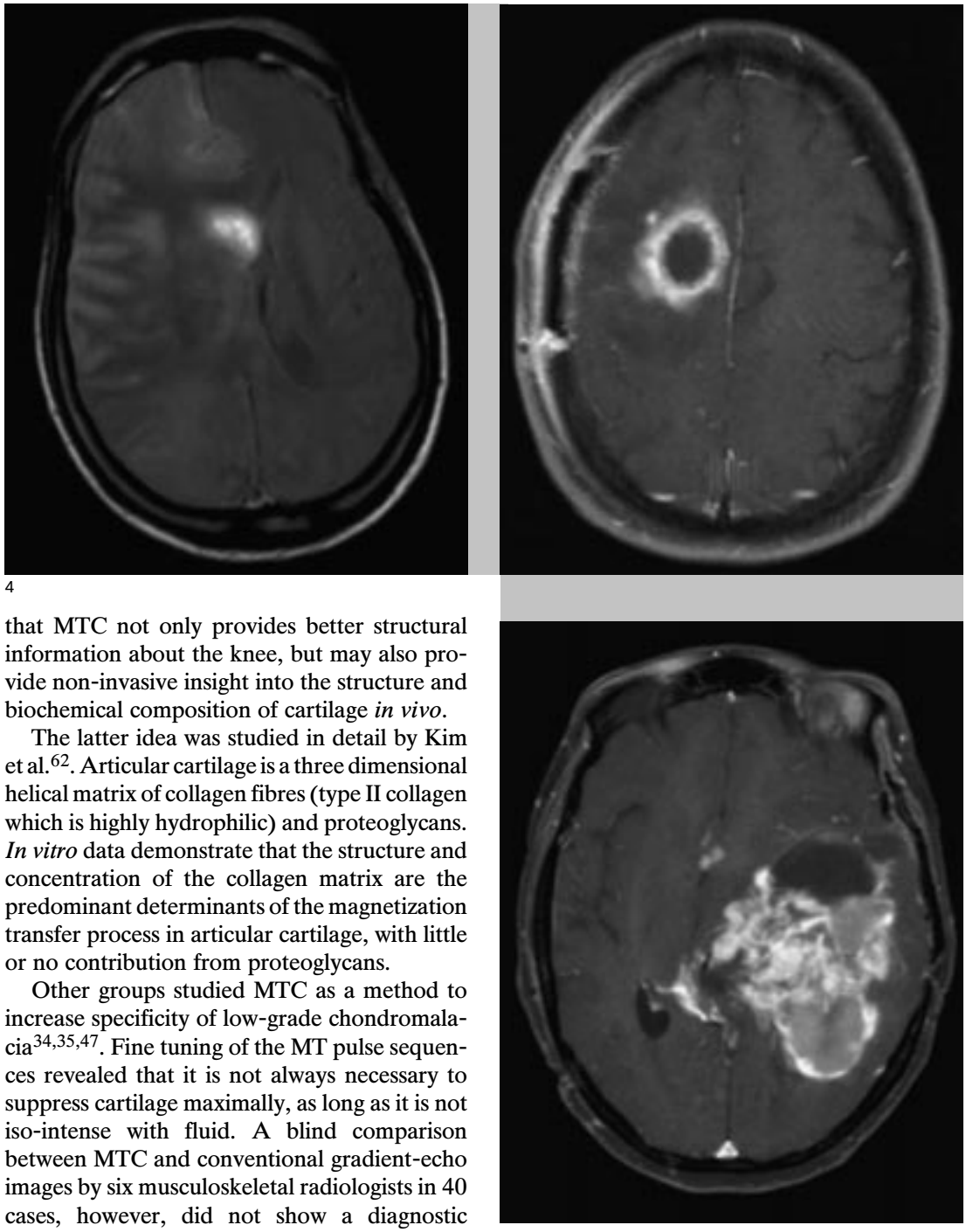


Fig. 4. The combination of magnetization transfer with gadolinium-enhanced MR imaging amplifies the tumour-brain contrast.

difference between hypertrophic synovial tissue and articular cartilage.

Due to the high contrast with these pulse sequences, semi-automated segmentation is possible. This makes volumetric quantification of cartilage feasible, and may improve monitoring of arthritic disease progression and efficacy of medical treatment[37].

Work in progress

Cardiac (work in progress)

Cardiovascular applications were first mentioned by Balaban in 1991[38]. Cardiac muscle tissue shows a strong MT effect and when off-resonance pulses are used MT is insensitive to motion. Based on the large MTC between myocardium and blood, volumetric studies and coronary angiography may prove to be useful[5].

The latter idea was pursued by Li et al.[41] using a non-breath-hold 3D technique. The contrast was optimized by applying fat saturation and magnetization transfer contrast techniques to suppress the signals of fat and myocardium surrounding the coronary arteries. An example of such an approach at 0.5 T using 3D echo planar imaging (EPI) by the Philips research laboratories is shown in Figure 6.

Hypertensive cardiomyopathy was studied using an animal model[39]. However, hypertrophic cardiomyopathy does not alter M_{Asat}/M_{A0}, although the accompanying change in tissue water content influences water proton relaxation. Myocardial ischaemia was also studied using MT[40,42,43].

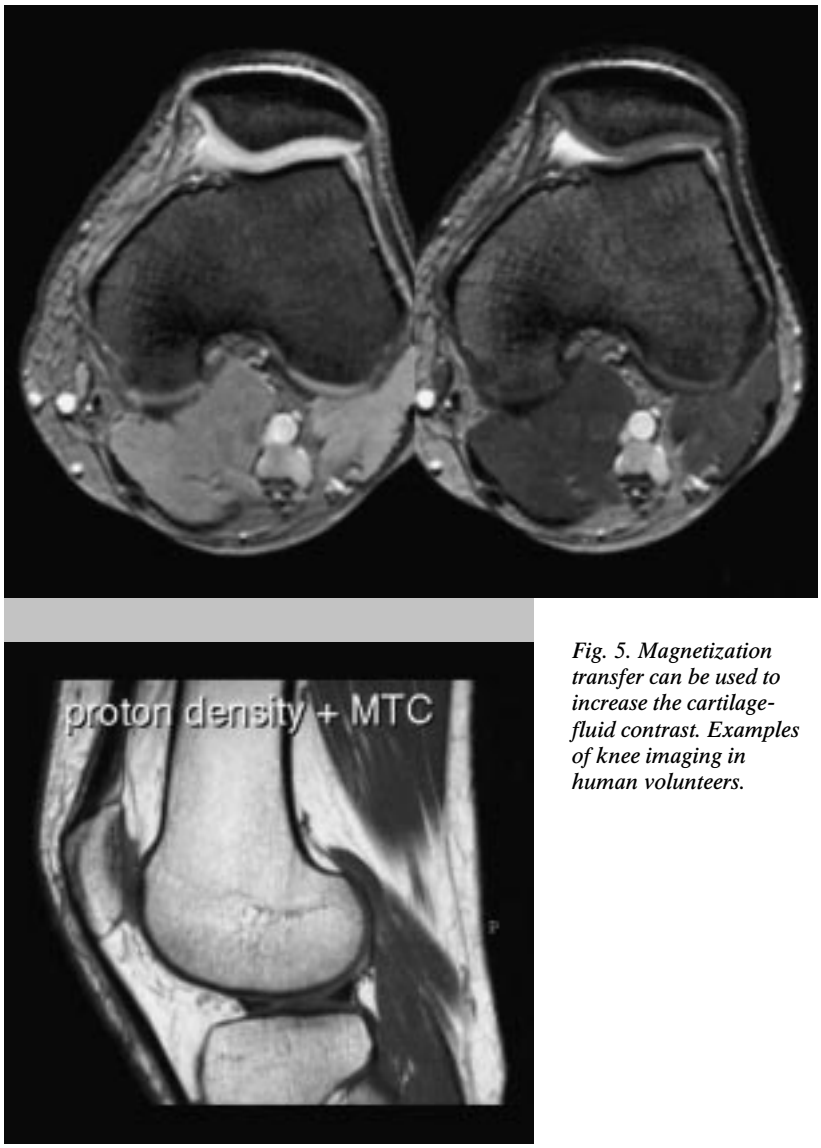
A potentially very attractive method to evaluate myocardial perfusion without a contrast agent was published by Prasad[40]. Experiments with an isolated heart model demonstrate increase of MT-weighted signal intensity and T_{1sat} with flow. From studies with an ex vivo piglet heart it was concluded that contrast between ischaemic and non-ischaemic tissue improved when MT was combined with low doses of Gd-DTPA-BMA[42,43]. Moreover, MT is related to the distribution of cellular water (intracellular oedema) which is known to be associated with the acute phase of myocardial ischaemia.

Musculoskeletal (work in progress)

The effect of exercise on muscles is of great scientific interest. First observations showed that MT increased contrast between active and less active muscles. This phenomenon was explained by an increase in extracellular water content[44].

Further studies provided better insight in muscle physiology and flow[45,46] but did not open new clinical opportunities.

A very interesting result of a clinical study with patients suffering from amyotrophic lateral sclerosis (ALS or Gehrig's disease) is shown in Figure 7. Using an approach similar to that described by Hajnal[6], the changes in longitudinal relaxation time were exploited. MT results



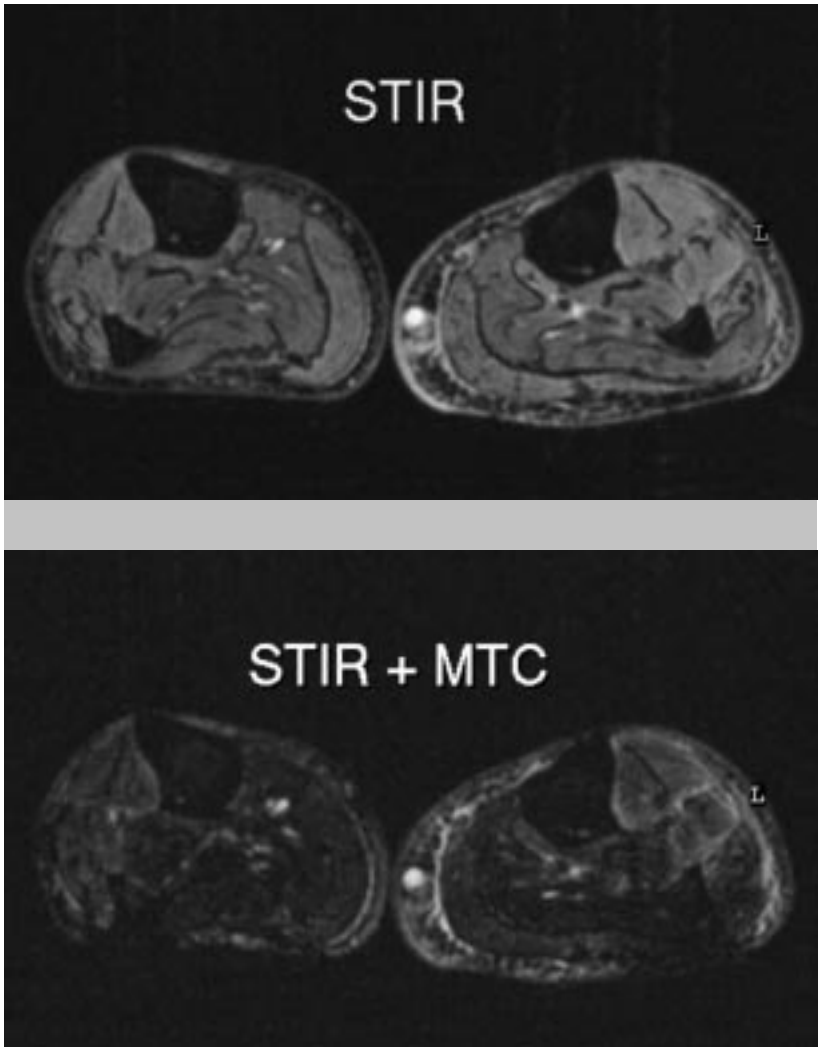
5

Fig. 5. Magnetization transfer can be used to increase the cartilage-fluid contrast. Examples of knee imaging in human volunteers.

6

Fig. 6. Combined fat saturation and magnetization transfer contrast techniques were used to suppress the signals of fat and myocardium surrounding the coronary arteries, resulting in this 3D surface rendered reconstruction of the coronary artery tree.

Fig. 7. Patient suffering from amyotrophic lateral sclerosis. The STIR (Short Tau Inversion Recovery) technique was combined with MTC such that muscle and fat signals were suppressed simultaneously. The signal from muscle oedema is clearly visualized.



7

in a significant decrease in T_{1sat} of muscles and, based on the STIR (Short Tau Inversion Recovery) technique, muscles and fat are suppressed simultaneously. Signal from muscle oedema is now clearly visualized using this approach.

Liver (work in progress)

Outwater et al.[48] applied magnetization transfer techniques to optimize contrast in the abdomen. They demonstrated that MT can increase the lesion-to-liver contrast of haemangiomas and cysts over that in gradient-echo imaging without off-resonance MTC pulses. MT does not increase the contrast between metastases and liver parenchyma. Haemangiomas tend to transfer magnetization considerably more than fluids but less than malignant lesions. Part of this can be explained by the blood content. *In vitro* studies showed a significant inverse relationship between haematocrit and signal reduction due to MT. At 0.1 T, MT-increased contrast between hepatic neoplasms and normal liver parenchyma was found[49]. Li et al.[50], however, concluded that at 1.5 T MTC was inferior to T_2-weighted sequences in distinguishing necrotic from viable tumours. Other MTC studies did not find significant improvements in detecting hepatic neoplasms[51,52] and liver fibrosis[54]. However, the presence of fat in the liver will affect MT parameters[53].

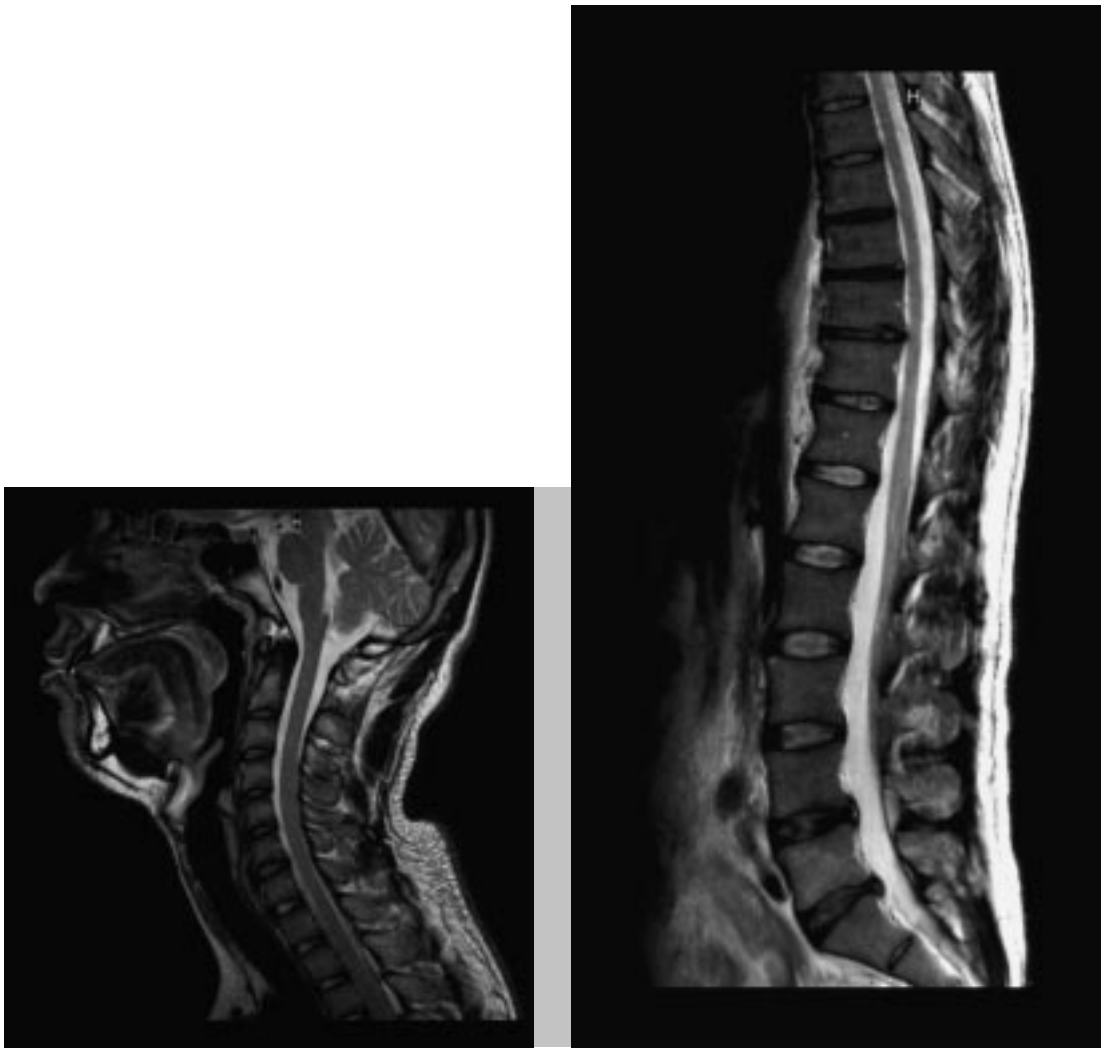
Spine (work in progress)

Finelli et al.[55] studied the use of magnetization transfer for improved contrast on gradient-echo MR images of the cervical spine in 103 patients with degenerative disc disease or intrinsic cord lesions. MT provided an average 2.2 to 2.4-fold improvement in spinal cord-CSF contrast.

The increase in spinal cord-CSF contrast and lesion-spinal cord contrast improved image quality and allowed higher resolution imaging, which translated into superior clinical performance of this sequence (Fig. 8).

Clinically, the technique has proved to be helpful for the delineation of lateral disc herniations and foraminal stenosis, and the detection of intrinsic spinal cord lesions such as multiple sclerosis plaques.

A potential drawback compared to the T_2-weighted SE sequence is the decreased sensitivity to disc degeneration and loss of disc hydration. Similar results were found by Yoshioka[56], who also demonstrated that MTC provided clearer visualization of syringomyelia.



8

Fig. 8. The increase in spinal cord-CSF contrast due to magnetization transfer with TSE improves image quality and allows higher resolution imaging.

Breast (work in progress)
There are surprisingly few publications of MTC in mammography. The original work of Pierce et al.[57] showed a combination of fat suppression and magnetization transfer to be very useful in evaluating multi-focal and inflammatory carcinomas.

Others[58,59] further studied the effects of lesion-enhancing contrast agents. Similar to applications in the central nervous system, the synergistic effect of MT and contrast agents can be exploited to increase sensitivity in MR mammography[5].

Tissue characterization (work in progress)
Based on the different relaxation mechanisms, it is to be expected that MT imaging can provide information that may be more specific than that obtained from T_1 or T_2. Since the original publications of Wolff and Balaban[2,3,4] scientists have been using magnetization transfer techniques to pursue the unique biophysical and biochemical properties of biological tissues[60,61].

Studies have been performed on multiple sclerosis plaques[18], meningiomas[25], intracranial haemorrhage[64], wallerian degeneration in the feline visual system[65], lipids[66, 67], articular cartilage[62], myocardial tissue[38, 39], and haematomas[63].

Most studies attempted to quantify MT by means of the dynamics described in Part 1 of this article[68]. Experimentally, the ability to completely saturate the 'bound pool' without direct saturation of the 'free pool' (non-magnetization transfer mediated) is problematic, and reported magnetization transfer rate calculations should be regarded with great care.

Clinically, no definite advantages of tissue characterization have yet been published. Still, many authors conceive this as a useful and attractive approach, especially since changes on a macromolecular level most probably precede cellular changes as associated with subsequent disease development[69].

Acknowledgements
The author gratefully acknowledges the contributions of M.K. Kouwenhoven MSc, L.H. Hofland MSc, S. Sheppard MSc, J.A. den Boer PhD, M.S. Silver PhD, A.R. Gillams MD,

M. Vahlensieck MD, D.J. Jensen PhD, H.J. Kooijman PhD and M. Beese MD, in understanding the MR physics and applications of MTC.

References

1. Wolff SD, Balaban RS. Magnetization Transfer Imaging: Practical Aspects and Clinical Applications. Radiology 1994; 192: 593-599.
2. Wolff SD, Balaban RS. Magnetization Transfer Contrast (MTC) and Tissue Water Proton Relaxation In Vivo. Magn Reson Med 1989; 10: 135-144.
3. Eng J, Ceckler TL, Balaban RS. Quantitative 1H Magnetization Transfer Imaging in vivo. Magn Reson Med 1991; 17: 304-314.
4. Wolff SD, Eng J, Balaban RS. Magnetization Transfer Contrast: Method for improving Contrast in Gradient-Recalled-Echo Images. Radiology 1991; 179: 133-137.
5. Balaban RS, Ceckler TL. Magnetization Transfer Contrast in Magnetic Resonance Imaging. Magn Reson Q 1992; 8(2): 116-137.
6. Hajnal JV, Baudouin CJ, Oatridge A, Young IR, Bydder GM. Design and Implementation of Magnetization Transfer Pulse Sequences for Clinical Use. J Comput Assist Tomogr 1992; 16(1): 7-18.

MR angiography:

7. Edelman RE, Ahn SS, Chien D, Wei Li, Goldman A, Mantello M, Kramer J, Kleefield J. Improved Time-of-Flight MR Angiography of the Brain with Magnetization Transfer Contrast. Radiology 1992; 184: 395-399.
8. Pike GB, Hu BS, Glover GH, Enzmann DR. Magnetization Transfer Time-of-Flight Magnetic Resonance Angiography. Magn Reson Med 1992; 25: 372-379.
9. Lin W, Tkach JA, Haacke EM, Masaryk TJ. Intracranial MR Angiography: Application of Magnetization Transfer Contrast and Fat Saturation to Short Gradient-Echo, Velocity-Compensated Sequences. Radiology 1993; 186: 753-761.
10. Tkach JA, Ruggieri PM, Ross JS, Modic MT, Dillinger JJ, Masaryk TJ. Pulse Sequence Strategies for Vascular Contrast in Time-of-Flight Carotid MR Angiography. Magn Reson Imaging 1993; 3(6): 811-820.
11. Kouwenhoven M, Hofland L, Boer RW de, Vaals JJ van. Improved MTC Angiography with Spatially Varying Off-Resonance Frequency. Proceedings of The SMRM, 12th Annual Meeting New York, 1993; 1: 383.
12. Elster AD, King JC, Mathews VP, Hamilton CA . Cranial Tissues: Appearance at Gadolinium-Enhanced and Nonenhanced MR Imaging with Magnetization Transfer Contrast. Radiology 1994; 190: 541-546.
13. Atkinson D, Brant-Zawadzki MN, Gillan GD, Purdy D, Laub G. Improved MR Angiography: Magnetization Transfer Suppression with Variable Flip Angle excitation and Increased Resolution. Radiology 1994; 190: 890.
14. Dousset V, Franconi JM, Degrèze P. Use of Magnetization Transfer Contrast To Improve Cerebral 3D MR Angiography. Neuroradiol 1994; 36: 188.
15. Tkach JA, Lin W, Duda JJ, Haacke EM, Masaryk TJ. Optimizing Three-Dimensional Time-of-Flight MR Angiography with Variable Repetition Time. Radiology 1994; 191(3): 805-811.
16. Miyazaki M, Kojima F, Ichinose N, Onozato Y, Igarashi H. A Novel Saturation Transfer Contrast Method for 3D Time-of-flight MR Angiography: a Slice Selective Off-Resonance Sync Pulse (SORS) Technique. Magn Reson Med 1994; 32: 52-59.
17. Mathews VP, Elster AD, King JC, Ulmer JL, Hamilton CA, Strottmann JM. Combined Effects of Magnetization Transfer and Gadolinium in Cranial MR Imaging and MR Angiography. AJR 1995; 164(1): 169-172.

Multiple Sclerosis:

18. Dousset V, Grossman RI, Ramer KN et al. Experimental Allergic Encephalomyelitis and Multiple Sclerosis: Lesion Characterization with Magnetization Transfer Imaging. Radiology 1992; 182: 483.
19. Dousset V. Magnetization Transfer Imaging In Vivo Study of Normal Brain Tissues and Characterization of Multiple Sclerosis and Experimental Allergic Encephalomyelitis Lesions (letter). J Neuroradiol 1993; 20(4): 297.
20. Grossman RI, Gomori JM, Ramer KN, Lexa FJ, Schnall MD. Magnetization Transfer: Theory and Clinical Applications in Neuroradiology. Radiographics 1994; 14: 279-290.
21. Gass A, Barker GJ, Kidd D et al. Correlation of Magnetization Transfer Ratio with Clinical Disability in Multiple Sclerosis. Ann Neurol 1994; 36(1): 62-67.
22. Grossman RI. Magnetization Transfer in Multiple Sclerosis. Ann Neurol 1994; 36 Suppl: S97-99.
23. Dousset V. Magnetization Transfer Imaging In Vivo Study of Normal Brain Tissues and Characterization of Multiple Sclerosis and Experimental Allergic Encephalomyelitis Lesions (letter). J Neuroradiol 1993; 20(4): 297.

Gadolinium enhancement:

24. Tanttu JI, Sepponen RE, Lipton MJ, Kuusela T. Synergistic Enhancement of MRI with Gd-DTPA and Magnetization Transfer. J Comput Assist Tomogr 1992; 16(1): 19-24.
25. Lundbom N. Determination of Magnetization Transfer Contrast in Tissue: MR Imaging Study of Brain Tumors. AJR 1992; 159: 1279.
26. Kurki TJI, Niemi PT, Lundbom N. Gadolinium-Enhanced Magnetization Transfer Contrast Imaging of Intracranial Tumors. Magn Reson Imaging 1992; 2: 401.
27. Mathews VP, King JC, Elster AD, Hamilton CA. Cerebral infarction: Effects of Dose and Magnetization Transfer Saturation at Gadolinium-Enhanced MRI. Radiology 1994; 190: 547-552.
28. Finelli DA, Hurst GC, Gullapali RP, Bellon EM. Improved Contrast of Enhancing Brain Lesions on Post-Gadolinium, T1W SE Images with use of Magnetization Transfer. Radiology 1994; 190: 553-559.
29. Mehta RC, Pike GB, Harros SP, Enzmann DR. Central Nervous System Tumor, Infection, and Infarction: Detection with Gadolinium-Enhanced Magnetization Transfer MRI. Radiology 1995; 195: 41-46.
30. Yousem DM, Montone KT, Sheppard LM, Rao VM, Weinstein GS, Hayden RE. Head and Neck Neoplasms: Magnetization Transfer Analysis. Radiology 1994; 192: 703.
31. Yousem DM, Schnall MD, Dougherty L. Magnetization Transfer Imaging of the Head and Neck: Normative Data. AJNR 1994; 15: 1117.
32. Boorstein JM, Wong KT, Grossman RI, Bolinger L, McGowan JC. Metastatic Lesions of the Brain: Imaging with Magnetization Transfer. Radiology 1994; 191: 799.
33. Elster AD, Mathews VP, King JC, Hamilton CA. Improved Detection of Gadolinium Enhancement using Magnetization Transfer Imaging. Neuroimaging Clin N Am 1994; 4(1): 185-192.

Cartilage evaluation:

34. Wolff SD, Chesnick S, Frank JA, Lim KO, Balaban RS. Magnetization Transfer Contrast: MR Imaging of the Knee. Radiology 1991; 179: 623-628.
35. Koskinen SK, Komu MES. Low-Field Strength Magnetization Transfer Contrast Imaging of Patellar Cartilage. Acta Radiol 1993; 34: 124.
36. Peterfy CG, Majumdar S, Lang P, van Dijke CF, Sack

K, Genant HK. MR Imaging of the Arthritic Knee: Improved Discrimination of Cartilage, Synovium, and Effusion with Pulsed Saturation Transfer and Fat-Suppressed T1-Weighted Sequences. Radiology 1994; 191: 413.
37. Peterfy CG, van Dijke CF, Janzen DL et al. Quantification of Articular Cartilage in the Knee with Pulsed Saturation Transfer Subtraction and Fat-Suppressed MR Imaging: Optimization and Validation. Radiology 1994; 192: 485.

Cardiac applications:
38. Balaban RS, Chesnick S, Hedges K, Samaha F, Heineman FW. Magnetization Transfer Contrast in MR Imaging of the Heart. Radiology 1991; 180: 671-675.
39. Scholz TS, Ceckler TL, Balaban RS. Magnetization Transfer Characterization of Hypertensive Cardiomyopathy: Significance of Tissue Water Content. Magn Reson Med 1993; 29(3): 352-358.
40. Prasad PV, Burstein D, Edelman RR. MRI Evaluation of Myocardial Perfusion without a Contrast Agent using Magnetization Transfer. Magn Reson Med 1993; 30: 650-653.
41. Li D, Paschal CB, Haacke EM, Adler LP. Coronary Arteries: Three-Dimensional MR Imaging with Fat Saturation and Magnetization Transfer Contrast. Radiology 1993; 187: 401-406.
42. Jones RA, Haraldseth O, Schjott J et al. Effect of Gd-DTPA-BMA on Magnetization Transfer: Application To Rapid Imaging of Cardiac Ischemia. Magn Reson Imaging 1993; 3(1): 31-39.
43. Haraldseth O, Jones RA, Schjott J, Rinck PA, Jynge P, Oksendal AN. Early Detection of Regional Myocardial Ischemia in Ex Vivo Piglet Hearts: MR Imaging with Magnetization Transfer. Magn Reson Imaging 1994; 4(4): 603-608.

Other musculoskeletal applications:
44. Zhu XP, Zhao S, Isherwood I. Magnetization Transfer Contrast (MTC) Imaging of Skeletal Muscle at 0.26 Tesla- Changes in Signal Intensity Following Exercise. Br J Radiol 1992; 65: 39-43.
45. Mattilla KT, Komu MES, Koskinen, SK. Exercise-induced Changes in Magnetization Transfer Contrast of Muscles. Acta Radiol 1993; 34: 559.
46. Yoshioko H, Takahashi H, Onaya H, Anno I, Niitsu M, Itai Y. Acute Change of Exercised Muscle using Magnetization Transfer Contrast MR Imaging. Magn Reson Imaging 1994; 12: 991-997.
47. Vahlensieck M, Dombrowski F, Leutner C, Wagner U, Reiser M. Magnetization Transfer Contrast (MTC) and MTC-Subtraction: Enhancement of Cartilage Lesions and Intracartilaginous Degeneration In Vitro. Skeletal Radiol 1994; 23(7): 535-539.

Liver:
48. Outwater E, Schnall MD, Braitman LE, Dinsmore BJ, Kressel HY. Magnetization Transfer of Hepatic Lesions: Evaluation of a Novel Contrast Technique in the Abdomen. Radiology 1992; 182: 535.
49. Kahn CE, Perera SD, Sepponen RE, Tanttu JI, Tierala EK, Lipton MJ. Magnetization Transfer imaging of the Abdomen at 0.1 T: Detection of Hepatic Neoplasms. Magn Reson Imaging 1993; 11: 67-71.
50. Li KCP, Jeffry RB, Ning S-C et al. Experimental Hepatic Tumor Necrosis: Comparison of Spin-echo and Pulsed Magnetization Transfer Contrast MRI. Invest Radiol 1993; 28: 896.
51. Loesberg AC, Kormano M, Lipton MJ. Magnetization Transfer Imaging of Normal and Abnormal Liver at 0.1 T. Invest Radiol 1993; 28: 726.
52. Hollett MD, Aisen AM, Yeung HN, Francis IR, Bree RL. Magnetization Transfer Contrast Imaging of Hepatic Neoplasms. Magn Reson Imaging 1994; 12(1): 1-8.
53. Komu M, Alanen A. Magnetization Transfer in Fatty and Low-Fat Livers. Physiol Meas 1994; 15(3): 243-250.
54. Aisen AM, Doi K, Swanson SD. Detection of Liver Fibrosis with Magnetic Cross-relaxation. Magn Reson Med 1994; 31(5): 551-556.

Spine:
55. Finelli DA, Hurst GC, Karaman BA, Simon JE, Duerk JL, Bellon EM. Use of Magnetization Transfer for Improved Contrast on Gradient-Echo MR Images of the Cervical Spine. Radiology 1994; 193: 165-171.
56. Yoshioka H, Nishimura H, Masuda T, Nakajima K, Onaya H, Itai Y. Magnetization Transfer Imaging of the Cervical Spine at 0.3 T. J Comput Assist Tomogr 1994; 18(6): 947-953.

Mammography:
57. Pierce WB, Harms SE, Flamig DP, Griffey RH, Evans WP, Hagans JE. Three Dimensional Gadolinium-Enhanced MR Imaging of the Breast: Pulse Sequence with Fat Suppression and Magnetization Transfer Contrast. Radiology 1991; 181: 757-763.
58. Flamig DP, Pierce WB, Harms SE, Griffey RH. Magnetization Transfer Contrast in Fat-Suppressed Steady-State Three-Dimensional MR Images. Magn Reson Med 1992; 26: 122-131.
59. Dean KI, Komu M, Dean PB, Kormano M. Magnetization Transfer Contrast in Gadopentetate-Dimeglumine-Enhanced Breast Magnetic Resonance Imaging at 0.1 T. Invest Radiol 1994; 29 Suppl 2: S302-303.

Tissue characterization:
60. Niemi PT, Komu MES, Koskinen SK . Tissue Specificity of Low-Field Strength Magnetization Transfer Contrast imaging. Magn Reson Imaging 1992; 2: 197-201.
61. Saner M, McKinnon G, Boesiger P. Glycogen Detection by in vivo 13C NMR: a Comparison of Proton Decoupling and Polarization Transfer. Magn Reson Med 1992; 28: 65-73.
62. Kim DK, Ceckler TL, Hascall VC, Calabro A, Balaban RS. Analysis of Water-Macromolecule Proton Magnetization Transfer in Articular Cartilage. Magn Reson Med 1993; 29(2): 211-216.
63. Gomori JM, Grossman RI, Asakura T. In Vitro Study of Magnetization Transfer and Relaxation Rates of Hematoma. AJNR 1993; 14: 871.
64. Mittl RL jr, Gomori JM, Schnall MD. Magnetization Transfer Effects in MR Imaging of In Vivo Intracranial Hemorrhage. AJNR 1993; 14: 881.
65. Lexa FJ, Grossman RJ, Rosenquist AC. MR of Wallerian Degeneration in the Feline Visual System: Characterization by Magnetization Transfer Rate with Histopathologic Correlation. AJNR 1994; 15: 201.
66. Kucharczyk W, MacDonald PM, Stanisz GJ, Henkelman RM. Relaxivity and Magnetization Transfer of White Matter Lipids at MR Imaging: Importance of Cerebrosides and pH. Radiology 1994; 192: 521.
67. Yoshioka H, Onaya H, Anno I, Takahashi H, Niitsu M, Itai Y. Fat Tissue: Relationship between Chemical Shift and Magnetization Transfer. Radiology 1995; 195: 573-575.
68. De Boer RW. Magnetization Transfer Contrast. Part 1: MR Physics. Medicamundi 1995; 40,2: 64-73.
69. Santyr GE, Mulkern RV. Magnetization Transfer in MR Imaging. Magn Res Imaging 1995; 121-124.