Dynamic susceptibility contrast MRI

Matthias J.P. van Osch (m.j.p.van_osch@lumc.nl)

C.J. Gorter Center for high field MRI, Department of Radiology
Leiden University Medical Center, Leiden, The Netherlands

Introduction

Quantitative dynamic susceptibility contrast perfusion MRI (DSC-MRI) is based on the monitoring of the first passage of a bolus of contrast agent through the brain tissue and a brain-feeding artery. The contrast agent is injected rapidly by means of an MR-injector in the antecubital vein in the patients arm and a saline flush is used to push the contrast agent into the direction of the heart. Continuously dynamic $T_2^{(*)}$ weighted scanning with a temporal resolution of approximately 1- 2 seconds is used to monitor the passage of the contrast agent through the brain tissue and an artery. The change in MR signal is subsequently converted into the concentration of contrast agent based on the physical properties of the contrast agent. The passage of the contrast agent through the brain-feeding artery is called the arterial input function (AIF). Deconvolving the passage through the brain tissue with the arterial input function, results in the tissue response function. Based on the theory of tracer kinetics, perfusion parameters are calculated from this tissue response function, i.e. cerebral blood flow (CBF) is the maximum value of the response function, cerebral blood volume (CBV) the area under the curve, and the mean transit time (MTT) follows from the central volume theorem: MTT=CBV/CBF. In this presentation, the acquisition, post-processing and pitfalls of DSC-MRI will be discussed and it will be highlighted on which topics more research is needed.

Use of contrast agent

One of the main limitations of DSC-MRI arises from the fact that a contrast agent injection is required, which limits the possibility to apply this technique in normal volunteers. Moreover, in 2006 it was proven that Gadolinium based contrast agents can lead to an increased risk for nephrogenic systemic fibrosis, mainly in patients with renal failure (1-3). Finally, the clearance rate of the contrast agent from the body is on the order of a few hours, therefore limiting the possibility of repeated measurements. The contrast agent is injected at a fast rate to achieve a sharp bolus profile. To ensure fast delivery of the bolus to the heart, the contrast agent injection is followed by a chaser of saline (at least 25 ml) to push the contrast agent into the direction of the heart. Injection speeds higher than 5 ml/s do not lead to sharper bolus profile, because dispersion in the heart and lungs becomes dominant.

Acquisition and temporal resolution

DSC-MRI exploits the $T_2^{(*)}$-effect of the contrast agent and therefore fast T_2, T_2^* or combined T_2/T_2^* sequences are employed. Simulations by Boxerman and more recent analytical models have shown that spin echo sequences have the advantage of a more exclusive small vessel sensitivity compared to gradient echo (4-6). Gradient echo is, however, still the acquisition of choice on 1.5Tesla scanners due to the higher SNR. Readout is frequently performed by either single shot EPI or spiral trajectories. Since DSC-MRI is based on the dynamic monitoring of the bolus of contrast agent through the brain tissue and the fact that the mean transit time of brain tissue is approximately 4 sec, the temporal resolution of the acquisition needs to be faster than 1.5 s to ensure accurate sampling (7). Whereas this resulted in early experiments in a limited coverage, the introduction of parallel imaging has led to whole brain coverage at the necessary high temporal resolution. The combined use of gradient and spin echo imaging has emerged as an attractive alternative in the last few years, due to the microvascular sensitivity of spin echo, better AIF options for short gradient echoes and the possibilities for vessel size imaging by combing spin and gradient echo information (8,9). Obtaining more complex information on the layout of the microvascular bed based on combined spin and gradient echo is an active field of research (10).

Measurements of the concentration of contrast agent in brain tissue

Early work of DSC-MRI showed a linear dependence of the $\Delta R_2^{(*)}$ on the concentration of paramagnetic contrast agents (11). By using the MR-signal before arrival of the contrast agent as a reference, the concentration of the contrast agent can be determined from $C_{[Gd-DTPA]}(t) = \frac{1}{r_2^{(*)} \cdot TE} \cdot \ln\left(\frac{S(0)}{S(t)}\right)$, with C the concentration, $r_2^{(*)}$ the relaxivity of the contrast agent, TE the echo time, S the MR signal, and S(0) the mean MR signal before arrival of the contrast agent. The underlying assumption of this relationship is that T_1-changes, that are also induced by the presence of contrast agent, do not influence the MR-signal. T_1-effects can be avoided by choosing an appropriate, small flip angle with respect to the repetition time (12). To obtain quantitative values for the concentration, the exact value of the relaxivity needs to be known. Whereas earlier studies used the relaxivity as measured in aqueous solution, more recent theoretical studies have shown that for the in vivo situation a much larger value should be used (4,5). Moreover these theoretical studies show deviations from linear behaviour for spin echo sequences.

Arterial input function measurements

To measure the AIF, several approaches have been proposed. These approaches differ based on the location of the AIF measurement (inside vs outside the vessel), the used component of the MR-signal (amplitude, phase, or both), and the targeted vessel (large arteries for a global AIF or smaller arteries for a local AIF) (13-18). When measuring the AIF inside a large artery, a short TE should be used to avoid signal depletion due to the high concentration of contrast agent within an artery as compared to a

tissue voxel (brain tissue contains only a small volume fraction of blood) (19). Furthermore, the linear relation between $\Delta R_2(*)$ and concentration contrast agent does not hold true in human blood, since the presence of red blood cells introduces a quadratic term (20,21). Finally, a sufficient high spatial resolution should be used to avoid partial volume effects (16,22). Magnetic field changes outside the vessel caused by the contrast agent within the artery, result in a smaller transversal relaxation time due to dephasing and diffusion through magnetic field inhomogeneities. The extent of field inhomogeneities and thus the influence on the transversal relaxation rate depends on the angle of the vessel, the distance to the vessel wall, voxel size, etc (16). Therefore, measuring the AIF outside an artery does enable the measurement of the shape of the AIF, but the concentration cannot be quantified. The magnetic field changes within arteries results in a change of the precession frequencies enabling the use of the phase of MR-signal to determine the concentration of contrast agent. When the angle of the vessel is known the concentration can be quantified.

Deconvolution technique

To obtain the residue function from which the CBF, CBV and MTT are calculated the tissue passage curve needs to be deconvolved with the AIF. Since these curves are both noisy, the deconvolution method needs to include some kind of regularization to suppress the noise. Furthermore, the deconvolution method needs to be delay-insensitive, that is the calculated perfusion parameters should be independent of the relative timing of the AIF compared to the tissue passage curve. This is important since collateral blood flow can lead to severe arrival time differences within a single patient. Many different deconvolution approaches have been proposed and for most of these delay-insensitive alternatives are available (23-26). Recently, growing interest in the shape of the residue function, have led to deconvolution approaches that better reflect the shape of the residue function (27,28). From the shape of the residue function the distribution of transit times can be obtained, which could provide a new indicator of hemodynamic impairment (29).

Rescaling of DSC-MRI data

Because quantification of the AIF is difficult, different scaling approaches have been proposed to recalibrate the relative values of CBF and CBV-values obtained from DSC-MRI into quantitative numbers. Rescaling can be performed based on data of a pre-bolus, the ratio of the post-bolus baseline of the AIF and the venous output function, or other MR sequences, such as pre and post-contrast T_1 (Bookend), phase contrast MRA and arterial spin labeling (30,31).

Cross-validation of DSC-MRI with other perfusion techniques

DSC-MRI has been validated in patients and in normal volunteers by comparing the quantitative values with other perfusion measurements, like SPECT, PET, CT-perfusion, arterial spin labeling MRI, etc (32-35). From all these studies one can conclude that DSC-MRI most frequently overestimates CBF, but also that a good qualitative correspondence is obtained with the other modalities.

Discussion and concluding remarks

Whereas many limitations and pitfalls can be identified in DSC-MRI, one should keep in mind that MRI provides a very sensitive measurement of the passage of contrast agent. This implies that even in poorly perfused tissue like the white matter, clear signal changes can be observed during the passage of contrast agent. Furthermore, DSC-MRI has a high spatial resolution, therefore minimizing partial volume effects (36,37). Therefore, DSC-MRI provides probably the most sensitive method for perfusion imaging at a high spatial resolution, although there are still several unsolved quantification issues that impede absolute quantification.

Reference List

1. Thomsen . Radiol.Clin.North Am. 47(5): 871-5, vii (2009)
2. Idee et al. Radiol.Clin.North Am. 47(5): 855-69, vii (2009)
3. Wang et al. Radiology(2011)
4. Kjolby et al. Magn Reson.Med 56(1): 187-197 (2006)
5. Kiselev . Magn Reson.Med. 46(6): 1113-1122 (2001)
6. Boxerman et al. Magn.Reson.Med. 34: 555-566 (1995)
7. van Osch et al. Magn Reson Med 50(3): 614-622 (2003)
8. Schmiedeskamp et al. Magn Reson.Med. 68(1): 30-40 (2012)
9. Tropres et al. Magn Reson.Med. 45(3): 397-408 (2001)
10. Emblem et al. Nat.Med. 19(9): 1178-1183 (2013)
11. Rosen et al. Magn.Reson.Med. 19: 285-292 (1991)
12. Calamante et al. Magn Reson Med 58(3): 544-553 (2007)
13. van Osch et al. J.Magn Reson Imaging 22(6): 704-709 (2005)
14. Conturo et al. J Magn Reson.Imaging(2005)
15. Bleeker et al. J.Cereb.Blood Flow Metab(2009)
16. Duhamel et al. 2199-2199 (2003)
17. Calamante et al. Magn Reson.Med. 52(4): 789-797 (2004)
18. Kellner et al. Magn Reson.Med. 69(3): 771-780 (2013)
19. Smith et al. Magn Reson.Med 49(1): 122-128 (2003)
20. van Osch et al. Magn Reson Med 49(6): 1067-1076 (2003)
21. Akbudak et al. Proceedings of the ISMRM 6th annual meeting, Sydney: 1197-1197 (1998)
22. van Osch et al. Magn Reson Med 45(3): 477-485 (2001)
23. Vonken et al. Magn.Reson.Med. 41: 343-350 (1999)
24. Wu et al. Magn Reson Med 50(1): 164-174 (2003)
25. Smith et al. Magn Reson.Med. 51(3): 631-634 (2004)
26. Calamante et al. Magn Reson Med 50(6): 1237-1247 (2003)
27. mouridsen et al. Neuroimage. 33(2): 570-579 (2006)
28. Mehndiratta et al. Neuroimage. 64: 560-570 (2013)
29. Jespersen et al. J.Cereb.Blood Flow Metab 32(2): 264-277 (2012)
30. Srour et al. J.Cereb.Blood Flow Metab 31(5): 1272-1282 (2011)
31. Bonekamp et al. Magn Reson.Med.(2011)
32. Ibaraki et al. Magn Reson Med Sci. 4(1): 27-34 (2005)
33. Ibaraki et al. J.Cereb.Blood Flow Metab 27(2): 404-413 (2007)
34. Ludemann et al. Eur.J.Radiol. 70(3): 465-474 (2009)
35. Knutsson et al. J.Magn Reson Imaging 26(4): 913-920 (2007)
36. Donahue et al. NMR Biomed. 19(8): 1043-1054 (2006)
37. Meltzer et al. J Comput.Assist.Tomogr. 14(4): 561-570 (1990)