

# Intravoxel Incoherent Motion Perfusion MR Imaging: A Wake-Up Call<sup>1</sup>

Denis Le Bihan, MD, PhD

In an article published in this issue of *Radiology*, Luciani et al (1) report that perfusion, an important surrogate marker to evaluate the importance of liver fibrosis, was decreased in patients with chronic cirrhosis. Notably, the magnetic resonance (MR) imaging perfusion measurements were not obtained with contrast agents, but with diffusion MR imaging, or more exactly, intravoxel incoherent motion (IVIM) MR imaging. Another interesting finding was that water diffusion apparently remains normal in those patients, in contrast to results of earlier studies, which suggest that the apparent diffusion coefficient (ADC) decreases in patients with cirrhosis. Those results are, indeed, not as contradictory as they appear and point to an important aspect of diffusion and IVIM MR imaging.

This excellent article by Luciani et al (1) transported me back to the debut of diffusion MR imaging in the mid-1980s, and I thought this would be a good opportunity to share some “historical” moments. Diffusion MR imaging has been extraordinarily successful during the past 20 years (with more than 85 000 entries in Google Scholar for “diffusion MRI”), but its main clinical domain of application has been neurologic disorders, especially for the treatment of patients with acute stroke. It is also rapidly becoming a standard for white matter disorders, as diffusion-tensor imaging can help reveal abnormalities in white matter fiber structure and allow outstanding maps of brain connectivity (2) to be obtained (3), which may be of great potential in the evaluation of some psychiatric disorders.

However, it is perhaps not so well known that, in my hands at least, diffusion MR imaging started in the liver. Back in 1984 (when I was a radiology resident), Denis Lallemand, a pediatric radiologist from Necker Hospital in Paris, came to me with a challenge:

How would it be possible to differentiate liver tumors from angiomas? There were no available contrast media at that time. I had a fuzzy intuition that perhaps molecular diffusion measurement would result in low values in solid tumors because of molecular movement restriction, while diffusion would be somewhat enhanced in flowing blood. In a matter of weeks “diffusion MR imaging” was conceived, born, and implemented. Unfortunately, the method never worked in the liver, at least not until the 1999 landmark article by Yamada et al (4), which demonstrated that I was not completely wrong. First, the MR imager we used operated at 0.5 T (the almost homemade Magniscan imager by CGR [Buc, France]), and the signal was very low. Second, the gradient hardware barely allowed strengths beyond 8 or 10 mT/m to be reached (and these still had large eddy currents), and  $b$  values larger than 100 mm/sec<sup>2</sup> were not even in sight. Third, there was no echo-planar imaging, and we just used spin-echo sequences that were available. Acquisition times necessary for diffusion encoding were very long (close to 10 minutes per  $b$  value), and, as respiratory gating was not available, motion artifacts were atrocious in the body. So, I gave up and switched to the brain, as it was my background after all. That move resulted in a great achievement: Diffusion MR imaging was established (5,6), and the rest is history.

I continued to investigate the idea that diffusion MR imaging could provide information on perfusion. I came up with the view that perhaps the movement of blood in the microvasculature could be modeled as a pseudodiffusion process on a macroscopic scale. In the true (molecular) diffusion process, molecules move because of their own thermal energy and can be considered to be colliding with each other. (Actual diffusion of water is, indeed, much more

#### Published online

10.1148/radiol.2493081301

**Radiology** 2008; 249:748–752

<sup>1</sup> From NeuroSpin, I<sup>2</sup>BM, Bâtiment 145, CEA Saclay-Center, 91191 Gif-sur-Yvette, France. Received July 28, 2008; revision requested July 28; revision received July 29; accepted July 30; final version accepted July 31.

**Address correspondence** to the author (e-mail: [denis.lebihan@cea.fr](mailto:denis.lebihan@cea.fr)).

Author stated no financial relationship to disclose.

See also the article by Luciani et al in this issue.

© RSNA, 2008

complex; see reference 7 for a review.) Each collision results in a change in the motion direction of each molecule, and the overall process is well described by a random walk, as first realized by Einstein (8). Similarly, one may consider, at a macroscopic level, that in blood, in addition to diffusion, water molecules follow the stream and change direction between each capillary segment. If those segments are distributed in space in a pseudorandom manner, the overall movement mimics a random walk and the mathematical model used for diffusion should work as well. Although the difference in spatial scale between the processes of diffusion (nanometers) and pseudodiffusion (tens of micrometers) extends across five orders of magnitude, it is amazing to observe that the associated diffusion and pseudodiffusion coefficients differ only by roughly one order of magnitude ( $D$ , the molecular diffusion coefficient of water in tissues, is about  $1 \times 10^{-3}$  mm<sup>2</sup>/sec, while  $D^*$ , the pseudodiffusion coefficient associated with blood flow, is about  $10 \times 10^{-3}$  mm<sup>2</sup>/sec in the brain [9] and  $70 \times 10^{-3}$  mm<sup>2</sup>/sec in the liver [1]). This is because those coefficients combine effects of elementary particle velocity and distance (10,11). Molecular diffusion is a very fast process, as far as molecular distances are concerned, while blood flow pseudodiffusion is comparatively much slower but is over distances of tens of micrometers.

This might look like a great coincidence. However, one may also consider that perfusion and diffusion are the major ways for most molecular moieties to reach targets in tissues. If flow is too fast, molecules may not be able to reach vessel walls and diffuse into tissues. One may speculate that perhaps some balance between molecular diffusion and perfusion has always been kept during evolution, shaping up the vascular network. In any case, their proximity in values allows  $D$  and  $D^*$  to be evaluated together with the same diffusion MR imaging sequence, which is good news, but it also means that diffusion MR images are prone to contamination by blood microcirculation effects. It took a great deal of brainstorming with my mentor,

Maurice Guéron (at the Ecole Polytechnique where I was completing my PhD in physics), to come up with the concept of IVIM to cover the overall molecular displacements to which “diffusion” MR imaging could be sensitive (6). Hence, it was very clear that the results of diffusion measurement with MR imaging could include perfusion effects, among other things, and not only true diffusion, as beautifully demonstrated by Yamada et al (4) and now by Luciani et al (1), and the term *ADC* was introduced (6). The theoretical framework for IVIM and the demonstration of the validity of the concepts in phantoms and in vivo was introduced in a seminal *Radiology* article (10), accompanied by a terrific editorial by W. Thomas Dixon (12). Interestingly, Dixon recently told me that this editorial was one of his most cited articles, and, indeed, it is fair to say that IVIM has been a great subject of controversy.

Probably because of this article (10), diffusion MR imaging has been associated with perfusion imaging for many years, hence the many diffusion and perfusion sessions at meetings and workshops, books (13), and *Radiology* journal keywords; however, diffusion and perfusion refer to completely different phenomena, both physically and biologically. This unexpected association has been a little puzzling for some of my colleagues, and at some point, they teased me with such aphorisms as “diffusion, perfusion, . . . confusion.” Anyway, there were real technical issues. Separation of perfusion from diffusion requires good signal-to-noise ratios, which were difficult to reach with low-field-strength MR imaging systems and limited gradient hardware (14,15). It was not until the availability of echo-planar imaging on clinical MR imagers that diffusion and IVIM MR imaging could really take off (16), and, as results became much more reliable, be free of motion artifacts. Luckily, Luciani et al (1) benefited from tremendous advances in MR imaging technology, with the combination of echo-planar imaging with parallel imaging by using 18 channels, reduced echo times, acquisitions less vulnerable to motion because of re-

spiratory triggering, and state-of-the-art gradient hardware that reached 40 mT/m.

Several other groups have shown encouraging results in the brain (9,15,17,18), in the kidneys (19,20), and even in the heart (21). However, other researchers (11,22) have expressed concerns about the concepts beyond perfusion measurement with the IVIM method and its ability to measure “classical” perfusion, compared with tracer methods. “Perfusion” had to be redefined according to the viewpoint of the physiologist (blood flow) and the viewpoint of the radiologist (vascular density). Indeed, the exact nature of what is measured with IVIM MR imaging deserves further investigation, which is a point raised by the work of Luciani et al (1). The authors found that  $D^*$  was significantly reduced in patients with cirrhosis, which, according to the IVIM model, points to reduced blood velocity (and flow). (Another theoretical, rather unlikely interpretation would be that capillary segments become longer or straighter in those patients with liver fibrosis.) Interestingly, the perfusion fraction,  $f$ , which is linked to blood volume in the IVIM model, remained normal, confirming earlier results of Yamada et al (4). However, blood volume is expected to be reduced in liver cirrhosis. One has to keep in mind that IVIM imaging has a differential sensitivity to vessel types, according to the range of motion sensitization ( $b$  values) that is used (23,24). Signal from large vessels with rapid flow disappears quickly with very low  $b$  values, while smaller vessels with slower flow might still contribute to the IVIM signal acquired with  $b$  values larger than 200 sec/mm<sup>2</sup>. The very limited number of  $b$  values applied by Luciani et al, for practical reasons, precluded a fine analysis of the different vascular compartments, some of which could be preserved by the fibrosis process or by compensatory mechanisms as suggested by the authors. Furthermore, the limited accuracy of the estimation of  $f$ , as derived from only four  $b$  values, could mask real, but relatively modest, changes in blood volume. Clearly, there is room to

improve the IVIM model and understand better its relationship with the functional vascular architecture and its biologic relevance.

Another very important practical and conceptual point raised by Luciani et al (1) is that water diffusion was also unchanged in patients with cirrhosis. While other groups (25–27) have reported decreased ADC values, Luciani and colleagues (1) rightly point out that the ADC contains both perfusion and diffusion terms. Furthermore, in a given voxel, diffusion may arise from different compartments with different diffusion coefficients. As a result, the dependence of the diffusion-weighted signal (in log plots) on the  $b$  value is no longer straight, as would be expected for free diffusion, but it is curved, reflecting the multiplicity of the underlying processes. Given the relative values for  $D^*$  and  $D$ , perfusion is expected to contribute to this curvature in a biexponential mode (10) for  $b$  values in the very low range (0–200 sec/mm<sup>2</sup> or even higher for very slow flow). Any ADC estimation with only two  $b$  values (eg, 0 and 1000 sec/mm<sup>2</sup>), as classically performed for clinical studies, would miss the curvature, include perfusion effects, and obviously result in an ADC that is an overestimation of the true diffusion coefficient,  $D$  (28). This perfusion contamination gets larger when using even lower  $b$ -value ranges, as often is the case for body diffusion MR imaging, where tissues with short T2 preclude long echo times, which in turn limits the gradient pulse duration used for diffusion encoding. The decreased ADC values in cirrhosis observed in the literature could thus result from a sole decrease in  $D^*$  (perfusion), while  $D$  remains intact, as reported by Luciani et al (1). In summary, ADC values are meaningful only when reported with  $b$  values used for their measurement. In the brain, ADCs tend to better reflect true diffusion, as larger  $b$  values can generally be used and blood volume is very small (2%–4%) (29).

It remains that the conclusion by the authors that  $D$  was unchanged in liver fibrosis can be challenged. Diffusion in tissues is not free, but largely impeded and restricted by obstacles, mainly cell

membranes. Beyond the low  $b$ -value range (above 600 sec/mm<sup>2</sup>), diffusion plots still present a net curvature, although perfusion effects are no longer contributing. By using  $b$ -value ranges extending more than 3000 sec/mm<sup>2</sup>, one may reveal different diffusion behaviors or compartments. The ADC concept applies here again, but now to reflect the presence of different diffusion contributions instead of a single diffusion coefficient. The origin of this curvature is still debated (30–32), but, as it can be well described by a biexponential law, many groups (33,34) have suggested that it arises from the presence of two main diffusing water pools in slow or intermediate exchange. One is associated with a somewhat fast diffusion coefficient (about  $1.3 \times 10^{-3}$  mm<sup>2</sup>/sec in the brain), and the other is associated with a slow diffusion coefficient (about  $1.3 \times 10^{-3}$  mm<sup>2</sup>/sec); the ADC depends on the relative contribution of those two compartments in each voxel. The fractions associated with those compartments, 70% and 30% for the fast and the slow components, respectively, invalidate an initial assumption that those pools could correspond to the extra- and intracellular compartments, respectively. A recent, still speculative model (7) suggests that the slow pool could correspond to a thin layer of water molecules bound to the cell membranes through the particular distribution of their electrostatic charges. This model accommodates previous reports (35,36) linking changes in cell volume (and associated membrane surface) with the ADC, such as the decrease in ADC observed during cytotoxic edema in acute stroke. It also provides a framework to explain diffusion anisotropy in some tissues with elongated structures, such as brain myelin fibers, by the difference in the number of membrane (and myelin) interfaces encountered by water molecules according to the measurement direction. It also predicts that the ADC should decrease in tissue undergoing cell proliferation, as observed in cancer (37,38), as membrane density would rise. Diffusion MR imaging with very high  $b$  values may thus reflect changes in tissue structure with greater

sensitivity. The largest  $b$  value used by Luciani et al (800 sec/mm<sup>2</sup>) was clearly too small to allow those slow diffusion pools to have a noticeable effect on diffusion MR imaging signal, and it might be that water diffusion is altered in liver fibrosis. With further improvements in gradient hardware performance that are expected, it is hoped that very high  $b$  values can be reached in a clinical setting to more definitely answer these questions.

A major goal for IVIM imaging at the end of the 1980s was to produce maps of brain perfusion to investigate brain function. However, other competing methods appeared at about the same time, especially the blood oxygen level-dependent (BOLD) concept (39). BOLD functional MR imaging was clearly much easier to implement and much more sensitive, so there was no real room for the challenging IVIM method. Studies (40–42), however, have proved the validity of the IVIM concept, with an increase in the IVIM perfusion parameters in brain-activated regions and the potential of the approach to understand different vascular contributions to the functional MR imaging signal. Interestingly, IVIM MR imaging has also been used in the context of functional MR imaging in a negative way. A limitation for BOLD functional MR imaging is its spatial resolution, as flow increase in somewhat large arteries or veins feeds or drains large neuronal territories. By inserting “diffusion” gradient pulses in the MR imaging sequence (corresponding to low  $b$  values), one may crush the contribution of the largest vessels (with high  $D^*$  values associated with fast flow) in the BOLD signal and improve the spatial resolution of the activation maps (43–47). Several groups have relied on this trick, however, not always considering to refer to the IVIM concept. This IVIM concept has also been borrowed to improve other applications, such as arterial spin labeling (48,49), or to suppress signal from extracellular flowing fluid in perfused cell systems (50,51). It remains that there are genuine potential applications for IVIM MR imaging. Perfusion is a very important surrogate marker of many physiologic or patho-

logic processes. MR imaging perfusion parameters can be obtained by using gadolinium-based contrast agents, either injected as a bolus (to determine blood flow, transit times, etc) or in a steady-state mode (to address blood volume, vessel permeability, etc). With the rising concern of nephrogenic systemic fibrosis, some patients cannot be examined with such an approach. IVIM MR imaging may then appear as an interesting alternative to provide crucial clues on perfusion in tissues, such as the kidneys (52), the liver (1,4), or even the placenta during pregnancy (53,54). Clearly, thanks to the work by Luciani et al (1), IVIM MR imaging is waking up after some time of hibernation; let us further explore its potential.

## References

- Luciani A, Vignaud A, Cavet M, et al. Liver cirrhosis: intravoxel incoherent motion MR imaging—pilot study. *Radiology* 2008;249(3):891–899.
- Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. *Nat Rev Neurosci* 2003;4:469–480.
- Hagmann P, Kurlant M, Gigandet X, et al. Mapping human whole-brain structural networks with diffusion MRI. *PLoS ONE* 2007;2:e597.
- Yamada I, Aung W, Himeno Y, Nakagawa T, Shibuya H. Diffusion coefficients in abdominal organs and hepatic lesions: evaluation with intravoxel incoherent motion echo-planar MR imaging. *Radiology* 1999;210:617–623.
- Le Bihan D, Breton E. Imagerie de diffusion in vivo par résonance magnétique nucléaire. *C.R. Acad.Sc.Paris* 1985; T. 301, Série II: 1109–1112.
- Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology* 1986;161:401–407.
- Le Bihan D. The 'wet mind': water and functional neuroimaging. *Phys Med Biol* 2007;52:R57–R90.
- Einstein A. Über die von der molecularkinetischen Theorie der Wärme geforderte Bewegung von in ruhenden Flüssigkeiten suspendierten Teilchen. *Ann Phys (Leipzig)* 1905;17:549–569.
- Le Bihan D, Moonen CT, Van Zijl PC, Pekar J, Des Pres D. Measuring random microscopic motion of water in tissues with MR imaging: a cat brain study. *J Comput Assist Tomogr* 1991;15:19–25.
- Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion (IVIM) MR imaging. *Radiology* 1988;168:497–505.
- Le Bihan D, Turner R. The capillary network: a link between IVIM and classical perfusion. *Magn Reson Med* 1992;27:171–178.
- Dixon WT. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging: a modest proposal with tremendous potential. *Radiology* 1988;168:566–567.
- Le Bihan D. In: Le Bihan D, ed. *Diffusion and perfusion magnetic resonance imaging: applications to functional MRI*. New York, NY: Raven, 1995.
- Pekar J, Van Zijl PC, Moonen CT. Signal to noise requirements for quantitative measurements of diffusion and capillary perfusion in brain using IVIM-MRI. *Magn Reson Med* 1991;23:1222–1229.
- Wirestam R, Brockstedt S, Lindgren A, et al. The perfusion fraction in volunteers and in patients with ischaemic stroke. *Acta Radiol* 1997;38:961–964.
- Turner R, Le Bihan D, Maier J, Vavrek R, Hedges LK, Pekar J. Echo-planar imaging of intravoxel incoherent motions. *Radiology* 1990;177:407–414.
- Chenevert TL, Pipe JG, Williams DM, Brunberg JA. Quantitative measurement of tissue perfusion and diffusion in vivo. *Magn Reson Med* 1991;17:197–212.
- Neil JJ, Bosch CS, Ackerman JJ. An evaluation of the sensitivity of the intravoxel incoherent motion (IVIM) method of blood flow measurement to changes in cerebral blood flow. *Magn Reson Med* 1994;32:60–65.
- Powers TA, Lorenz CH, Holburn GE, Price RR. Renal artery stenosis: in vivo perfusion MR imaging. *Radiology* 1991;178:543–548.
- Pickens DR 3rd, Jolgren DL, Lorenz CH, Creasy JL, Price RR. Magnetic resonance perfusion/diffusion imaging of the excised dog kidney. *Invest Radiol* 1992;27:287–292.
- Callot V, Bennett E, Decking UK, Balaban RS, Wen H. In vivo study of microcirculation in canine myocardium using the IVIM method. *Magn Reson Med* 2003;50:531–540.
- Henkelman RM. Does IVIM measure classical perfusion? *Magn Reson Med* 1990;16:470–475.
- Lorenz CH, Pickens DR 3rd, Puffer DB, Price RR. Magnetic resonance diffusion/perfusion phantom experiments. *Magn Reson Med* 1991;19:254–260.
- Kennan RP, Gao JH, Zhong J, Gore JC. A general model of microcirculatory blood flow effects in gradient sensitized MRI. *Med Phys* 1994;21:539–545.
- Ichikawa T, Haradome H, Hachiya J, Nitatori T, Araki T. Diffusion-weighted MR imaging with a single-shot echoplanar sequence: detection and characterization of focal hepatic lesions. *AJR Am J Roentgenol* 1998;170:397–402.
- Taouli B, Tolia AJ, Losada M, et al. Diffusion-weighted MRI for quantification of liver fibrosis: preliminary experience. *AJR Am J Roentgenol* 2007;189:799–806.
- Lewin M, Poujol-Robert A, Boelle PY, et al. Diffusion-weighted magnetic resonance imaging for the assessment of fibrosis in chronic hepatitis C. *Hepatology* 2007;46:658–665.
- Sakuma H, Tamagawa Y, Kimura H, et al. Intravoxel incoherent motion (IVIM) imaging using an experimental MR unit with small bore [in Japanese]. *Nippon Igaku Hoshasen Gakkai Zasshi* 1989;49:941–943.
- Grubb RL Jr, Raichle ME, Eichling JO, Ter-Pogossian MM. The effects of changes in PaCO<sub>2</sub> on cerebral blood volume, blood flow, and vascular mean transit time. *Stroke* 1974;5:630–639.
- Yablonskiy DA, Bretthorst GL, Ackerman JJ. Statistical model for diffusion attenuated MR signal. *Magn Reson Med* 2003;50:664–669.
- Chin CL, Wehrli FW, Hwang SN, Jaggard DL, Hackney DB, Wehrli SW. Feasibility of probing boundary morphology of structured materials by 2D NMR q-space imaging. *J Magn Reson* 2003;160:20–25.
- Stanisz GJ, Szafer A, Wright GA, Henkelman RM. An analytical model of restricted diffusion in bovine optic nerve. *Magn Reson Med* 1997;37:103–111.
- Niendorf T, Dijkhuizen RM, Norris DG, Van Lookeren Campagne M, Nicolay K. Biexponential diffusion attenuation in various states of brain tissue: implications for diffusion-weighted imaging. *Magn Reson Med* 1996;36:847–857.
- Assaf Y, Cohen Y. Non-mono-exponential attenuation of water and N-acetyl aspartate signals due to diffusion in brain tissue. *J Magn Reson* 1998;131:69–85.
- Sotak CH. Nuclear magnetic resonance (NMR) measurement of the apparent diffusion coefficient (ADC) of tissue water and its

- relationship to cell volume changes in pathological states. *Neurochem Int* 2004;45:569–582.
36. van der Toorn A, Sykova E, Dijkhuizen RM, et al. Dynamic changes in water ADC, energy metabolism, extracellular space volume, and tortuosity in neonatal rat brain during global ischemia. *Magn Reson Med* 1996;36:52–60.
  37. Takahara T, Imai Y, Yamashita T, Yasuda S, Nasu S, van Cauteren M. Diffusion-weighted whole-body imaging with background body signal suppression (DWIBS): technical improvement using free breathing, STIR and high-resolution 3D display. *Radiat Med* 2004;22:275–282.
  38. Ross BD, Moffat BA, Lawrence TS, et al. Evaluation of cancer therapy using diffusion magnetic resonance imaging. *Mol Cancer Ther* 2003;2:581–587.
  39. Ogawa S, Tank DW, Menon RS, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci U S A* 1992;89:5951–5955.
  40. Song AW, Wong EC, Tan SG, Hyde JS. Diffusion weighted fMRI at 1.5 T. *Magn Reson Med* 1996;35:155–158.
  41. Gangstead SL, Song AW. On the timing characteristics of the apparent diffusion coefficient contrast in fMRI. *Magn Reson Med* 2002;48:385–388.
  42. Jin T, Zhao F, Kim SG. Sources of functional apparent diffusion coefficient changes investigated by diffusion-weighted spin-echo fMRI. *Magn Reson Med* 2006;56:1283–1292.
  43. Boxerman JL, Bandettini PA, Kwong KK, et al. The intravascular contribution of fMRI signal change: Monte Carlo modeling and diffusion-weighted studies in vivo. *Magn Reson Med* 1995;34:4–10.
  44. Song AW, Li T. Improved spatial localization based on flow-moment-nulled and intravoxel incoherent motion-weighted fMRI. *NMR Biomed* 2003;16:137–143.
  45. Michelich CR, Song AW, MacFall JR. Dependence of gradient-echo and spin-echo BOLD fMRI at 4 T on diffusion weighting. *NMR Biomed* 2006;19:566–572.
  46. Duong TQ, Yacoub E, Adriany G, Hu XP, Ugurbil K, Kim SG. Microvascular BOLD contribution at 4 and 7 T in the human brain: gradient-echo and spin-echo fMRI with suppression of blood effects. *Magn Reson Med* 2003;49:1019–1027.
  47. Lee SP, Silva AC, Kim SG. Comparison of diffusion-weighted high-resolution CBF and spin-echo BOLD fMRI at 9.4 T. *Magn Reson Med* 2002;47:736–741.
  48. Silva AC, Williams DS, Koretsky AP. Evidence for the exchange of arterial spin-labeled water with tissue water in rat brain from diffusion-sensitized measurements of perfusion. *Magn Reson Med* 1997;38:232–237.
  49. Kim T, Kim SG. Quantification of cerebral arterial blood volume using arterial spin labeling with intravoxel incoherent motion-sensitive gradients. *Magn Reson Med* 2006;55:1047–1057.
  50. Van Zijl PC, Moonen CT, Faustino P, Pekar J, Kaplan O, Cohen JS. Complete separation of intracellular and extracellular information in NMR spectra of perfused cells by diffusion-weighted spectroscopy. *Proc Natl Acad Sci U S A* 1991;88:3228–3232.
  51. Zhao L, Sukstanskii AL, Kroenke CD, et al. Intracellular water specific MR of microbead-adherent cells: HeLa cell intracellular water diffusion. *Magn Reson Med* 2008;59:79–84.
  52. Tsuda K, Murakami T, Sakurai K, et al. Preliminary evaluation of the apparent diffusion coefficient of the kidney with a spiral IVIM sequence [in Japanese]. *Nippon Igaku Hoshasen Gakkai Zasshi* 1997;57:19–22.
  53. Moore RJ, Issa B, Tokarczuk P, et al. In vivo intravoxel incoherent motion measurements in the human placenta using echo-planar imaging at 0.5 T. *Magn Reson Med* 2000;43:295–302.
  54. Moore RJ, Strachan BK, Tyler DJ, et al. In utero perfusing fraction maps in normal and growth restricted pregnancy measured using IVIM echo-planar MRI. *Placenta* 2000;21:726–732.