AJR FOCUS ON:

Marco Essig[1]
Mark S. Shiroishi[2]
Thanh Binh Nguyen[3]
Marc Saake[1]
James M. Provenzale[4,5]
David Enterline[4]
Nicoletta Anzalone[6]
Arnd Dörfler[1]
Àlex Rovira[7]
Max Wintermark[8]
Meng Law[2]

Perfusion MRI: The Five Most Frequently Asked Technical Questions

OBJECTIVE. This and its companion article address the 10 most frequently asked questions that radiologists face when planning, performing, processing, and interpreting different MR perfusion studies in CNS imaging.

CONCLUSION. Perfusion MRI is a promising tool in assessing stroke, brain tumors, and patients with neurodegenerative diseases. Most of the impediments that have limited the use of perfusion MRI can be overcome to allow integration of these methods into modern neuroimaging protocols.

Keywords: CNS imaging, contrast agents, gadobutrol, perfusion MRI

DOI:10.2214/AJR.12.9543

Received June 30, 2012; accepted after revision August 26, 2012.

M. Essig, M. S. Shiroishi, and T. B. Nguyen contributed equally to this work.

M. Essig serves on scientific advisory boards for Bayer HealthCare and Medical Imaging Heidelberg, has received speaker honoraria from Bayer HealthCare and Bracco, and has received research support from Bayer HealthCare. M. S. Shiroishi is supported in part by the GE Healthcare/Radiological Society of North America Research Scholar Grant, Zumberge Research Grant, and Southern California Clinical and Translational Science Institute (CTSI) Pilot Grant (NIH CTSA grant 5 UL1 RR031986-02) and serves as a consultant for Bayer HealthCare. T. B. Nguyen has received grant support from the Brain Tumour Foundation of Canada and serves as a paid consultant for Bayer HealthCare. J. M. Provenzale has received research funding from GE Healthcare; serves as a scientific advisory board member for Bayer HealthCare; is a consultant for Millennium Pharmaceuticals, Amgen, and Biomedical Systems; serves on the Data Safety Management Board for Theradex; and is a stockholder in Amirsys. N. Anzalone has received speaker honoraria and serves as a consultant for Bayer HealthCare. À. Rovira serves on scientific advisory boards for NeuroTEC, Bayer HealthCare, and BTG International; has received speaker honoraria from Bayer HealthCare, Stendhal America, Sanofi-Aventis, Bracco, Merck-Serono, Teva Pharmaceutical Industries, and Biogen Idec; has received research support from Bayer HealthCare; and serves as a consultant for Novartis. M. Wintermark has received grants from Philips Healthcare and GE Healthcare. M. Law serves on scientific advisory boards for Bayer HealthCare and Toshiba Medical; has received speaker honoraria from Siemens Healthcare, iCAD, Bayer HealthCare, Bracco, and Prism Clinical Imaging; and has received research support from the National Institutes of Health and Bayer HealthCare.

AJR 2013; 200:24–34

0361–803X/13/2001–24

Since its introduction, MRI has been used in the assessment of a variety of CNS abnormalities, including tumors, metastases, infections, and vascular and degenerative diseases. Initially, most attention was focused on the improvement of visualization and resolution of morphologic characteristics. In recent years, however, there have been substantial improvements in MR protocols with a special focus on the assessment of functional tissue characteristics, such as perfusion or metabolism. The use of these functional imaging techniques has improved the differential diagnosis of CNS disease and the therapeutic management of patients and has enabled better assessment of treatment-related changes on follow-up. Multiple studies have shown that the optimized use of high-quality contrast media in perfusion MRI can substantially improve detection, characterization, and monitoring of CNS diseases [1–4].

In this context, perfusion is one of the most important physiologic and pathophysiologic parameters and can be assessed noninvasively with MRI. Today, we have several techniques to derive perfusion-related parameters using endogenous contrast methods or, more robustly and more widely used, exogenous gadolinium-based contrast agent dynamic methods [5].

In this article, we will address five questions that radiologists and radiographers frequently ask when planning, performing, processing, and interpreting different perfusion MRI studies in diseases of the CNS. In this article, we will also briefly address the technical requirements, including the use of contrast-enhanced techniques as well as the clinical applications in brain tumor imaging and acute stroke management.

Question 1: What Are the Impediments to the Routine Clinical Use of Perfusion MRI and How Can We Overcome Them?

In academic centers, the application of perfusion MRI in the assessment of acute stroke or intracranial tumors has been well established and thousands of publications have discussed the ability to perform noninvasive perfusion

[1]Department of Neuroradiology, University of Erlangen-Nuremberg, Maximiliansplatz 1, 91054 Erlangen, Germany. Address correspondence to M. Essig (marco.essig@uk-erlangen.de).
[2]Division of Neuroradiology, Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, CA.
[3]Department of Medical Imaging, The Ottawa Hospital, Ottawa, ON, Canada.
[4]Department of Radiology, Duke University Medical Center, Durham, NC.
[5]Departments of Radiology and Imaging Sciences, Oncology, and Biomedical Engineering, Emory University School of Medicine, Atlanta, GA.
[6]Scientific Institute H. S. Raffaele, Milan, Italy.
[7]MR Unit, Department of Radiology, Universitat Autònoma de Barcelona, Vall d'Hebron Hospital, Barcelona, Spain.
[8]Department of Neuroradiology, University of Virginia, Charlottesville, VA.

measurements using dynamic MRI techniques. Although these techniques have been available for more than 20 years, wide use in routine clinical practice has never been achieved despite the relative ease with which these techniques can be implemented on modern MRI scanner platforms [6, 7]. What are the impediments to the routine clinical use of perfusion MRI and how can we overcome them?

Lack of Awareness of Perfusion MRI by Referring Physicians

A general underappreciation or lack of awareness of the potential of modern MRI protocols, including perfusion imaging, by referring clinicians likely contributes to underutilization of these techniques. Because these methods might have a great impact on the management of patients, it is of great importance to discuss the perfusion results with referring physicians to gain a better insight of their needs and to make them aware of the technical possibilities. The perfusion information should be integrated into the reporting of studies and the differential diagnostic process. Processed perfusion maps should be transferred to the PACS, where they can be readily viewed by referring physicians. Improved understanding of perfusion MRI and its current capabilities through dissemination of the relevant literature may also help to bridge this gap and increase requests for the addition of perfusion MRI to conventional MRI.

Appreciation and Experience of Perfusion MRI by the Performing Radiologist: Apparent Complexity of Perfusion MRI for Nonexpert Radiologists

Outside of academic centers, there are likely to be few neuroradiologists in community practice who will be familiar with perfusion MRI. Coupled with this are the perceptions, some rightly so, of the apparent complexities of image acquisition, postprocessing, and interpretation of perfusion MRI. These perceptions can contribute to a lack of enthusiasm for routine implementation into clinical practice, and, consequently, few radiologists will maintain a sufficient volume of experience to be comfortable with performing and interpreting perfusion MRI.

Lack of Standardized and Optimized Perfusion MRI Protocols

In general, most modern MRI scanners allow us to run some perfusion sequences. The existence of a wide range of technical factors, including scanner types, pulse sequences, and hardware requirements, that need to be considered may also result in decreased enthusiasm among community radiologists. Another challenge rests in the optimization of the use of gadolinium-based contrast agents in neuroimaging protocols.

Lack of Simple and Standardized Perfusion Postprocessing Software and Lack of Straightforward Guidelines on How to Interpret Results

Traditionally, most postprocessing software solutions have been custom-designed institutionally based packages, and only a few commercial software packages have been available. Recently, most of the major MR scanner vendors have started to provide easy-to-use software solutions. Standardization of acquisition parameters and postprocessing software remains a major challenge and will require significant collaboration between the scanner and software manufacturers and the scientific and medical community.

Lack of Reimbursement for Perfusion MRI and Lack of High-Quality Data Showing Impact on Clinical Care

These are perhaps the major factors that have discouraged the widespread clinical acceptance of perfusion MRI. There is a lack of high-quality evidence to show that perfusion MRI makes a substantial impact on clinical decision making. This then influences payers' decisions as to whether perfusion MRI should be reimbursed, so that currently it is not. A substantial body of well-designed studies that show a significant clinical benefit from perfusion MRI is needed to overcome this critical barrier. Besides that, none of the gadolinium-based contrast agents has a specifically approved indication for perfusion MRI. However, as for MR angiography, the methodology and gadolinium-based contrast agents are frequently used off-label.

Question 2: Which Methods Are Currently Available to Assess Perfusion With MRI?—Overview of Technical Considerations

Perfusion is physiologically defined as the steady-state delivery of blood to an element of tissue. The term "perfusion" is also used to emphasize contact with the tissue, or in other words, capillary blood flow. Perfusion is variably used for different physiologic parameters that also affect the MR signal, e.g., blood volume, blood velocity, and blood oxygenation.

During the past decades, several methods have been described that noninvasively measure perfusion with MRI. Most effort in this context has been directed toward MR perfusion imaging of the brain [7].

There are two major approaches to measure cerebral perfusion with MRI. The first is application of an exogenous, intravascular, nondiffusible contrast agent, usually a gadolinium-based contrast agent, that emphasizes either the susceptibility effects of gadolinium-based contrast agents on the signal echo, namely first-pass dynamic susceptibility contrast-enhanced (DSC) MR perfusion or the relaxivity effects of gadolinium-based contrast agents on the signal echo, namely dynamic contrast-enhanced (DCE) MR perfusion. The second is application of an endogenous contrast agent using magnetically labeled arterial blood water as a diffusible flow tracer in arterial spin labeling (ASL) MR perfusion.

Dynamic Susceptibility Contrast-Enhanced MR Perfusion

DSC MR perfusion, also known as bolus-tracking MRI or perfusion-weighted imaging, is a technique in which the first pass of a bolus of gadolinium-based contrast agent through brain tissue is monitored by a series of T2- or T2*-weighted MR images. The susceptibility effect of the paramagnetic contrast agent leads to a signal loss in the signal intensity–time curve. Using the principles of the indicator dilution theory, the signal information can then be converted into a contrast medium concentration–time curve on a pixel-by-pixel basis (Fig. 1). From these data, parametric maps of cerebral blood volume (CBV) and flow (CBF) can be derived. Regional CBF and CBV values can be obtained by region-of-interest analysis. The study by Østergaard [8] provides an in-depth review of the physical basics of DSC MR perfusion. In neurooncology, CBV is the most robust and widely used parameter [9]. For in-depth review articles about the basic principles of perfusion imaging in neurooncology, we refer to Cha et al. [9, 10] and Provenzale et al. [11].

Dynamic Contrast-Enhanced MR Perfusion

DCE MR perfusion, also widely referred to as "permeability" MRI, is based on the acquisition of serial T1-weighted images before, during, and after administration of extracellular low-molecular-weight MR contrast media, such as a gadolinium-based contrast agent. The resulting signal intensity–time curve reflects a composite of tissue perfusion, vessel permeability, and extravascular-extracellular space [12, 13].

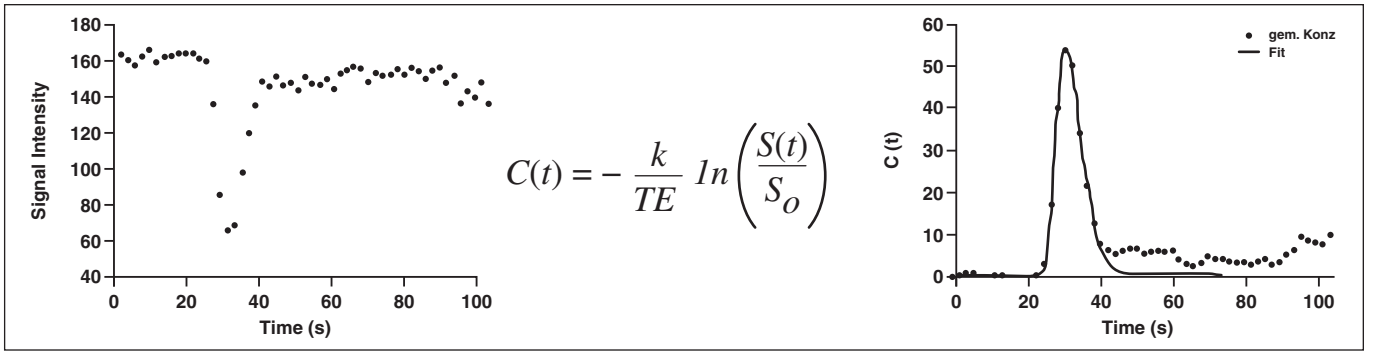

Fig. 1—Graphs show transformation of measured signal intensity–time curve into concentration-time curve that can be used to quantify regional cerebral blood volume and cerebral blood flow using equations of indicator dilution theory. $C_{(t)}$ = concentration over time, k = correction factor, TE = echo time, $S_{(t)}$ = signal intensity change after contrast agent administration, S_0 = baseline signal intensity, gem.Konz = measured concentration.

In contrast with conventional (static contrast-enhanced, T1-weighted) contrast-enhanced MRI, which simply displays contrast enhancement at a single point in time, DCE MR perfusion imaging depicts the wash-in, plateau, and washout contrast kinetics of the tissue, thereby providing insight into the nature of the bulk tissue properties at the microvascular level.

Most often, DCE MR perfusion imaging is based on a two-compartmental (plasma space and extravascular-extracellular space) pharmacokinetic model. The general steps are (in order): perform baseline T1 mapping, acquire DCE MR perfusion images, convert signal intensity data to gadolinium concentration, determine the vascular input function, and perform pharmacokinetic modeling. With pharmacokinetic modeling of DCE MR perfusion data, several metrics are commonly derived: the transfer constant (k^{trans}), the fractional volume of the extravascular-extracellular space (v_e), the rate constant (k_{ep}, where $k_{ep} = k^{trans} / v_e$), and the fractional volume of the plasma space (v_p) [14, 15].

The most frequently used metric in DCE MR perfusion is k^{trans}. It can have different interpretations depending on blood flow and permeability. When there is very high permeability, the flux of gadolinium-based contrast agent is limited only by flow, and thus k^{trans} mainly reflects blood flow. In situations in which there is very low permeability, the gadolinium-based contrast agent cannot leak easily into the extravascular-extracellular space, and thus k^{trans} mainly reflects permeability [16]. Despite this complexity, k^{trans} appears to reproducibly measure permeability in glioma patients [17]. Review articles by Paldino and Barboriak [14] and Tofts et al. [15] provide further details regarding the general principles of DCE MRI.

Arterial Spin Labeling MR Perfusion

ASL is a perfusion method that uses magnetically labeled blood as an endogenous tracer. Despite the existence of multiple acronyms in the literature, there are two main types of ASL technique: continuous ASL and pulsed ASL [18–20]. In continuous ASL, there is a prolonged radiofrequency pulse that continuously labels arterial blood water below the imaging slab until a steady state of tissue magnetization is reached [21]. One consequence of this prolonged radiofrequency pulse is that it leads to magnetization transfer effects [22]. If the magnetization transfer effects are present only during the labeling scheme, perfusion may be overestimated because the saturation effect of the macromolecular pool will result in reduced signal of the free water pool from the tissue of interest [23].

Although continuous ASL provides greater perfusion contrast, pulsed ASL is less technically demanding [24, 25]. In pulsed ASL, a short radiofrequency pulse is used to label a thick slab of arterial blood at a single point in time and imaging is performed after a period of time to allow distribution in the tissue of interest [26]. There are two categories of pulsed ASL technique depending on whether the labeling is applied in a symmetric or asymmetric fashion relative to the imaging volume [24]. A relatively new technique, called "pseudocontinuous ASL," represents a compromise between pulsed ASL and continuous ASL. This technique may provide improved balance between labeling efficiency and signal-to-noise ratio (SNR) compared with conventional ASL methods [27].

CBV derived from DSC MR perfusion has been the primary metric used in brain tumor perfusion imaging, although CBF, particularly from ASL, has been an emerging focus. With technical modifications, CBV and mean transit time (MTT) can theoretically be obtained using ASL; however, these methods are not yet widely used [28–32].

Because corrections for age- and patient-dependent mean perfusion must be made to derive absolute CBF, relative CBF appears to be sufficient in brain tumor evaluation [33]. However, the use of absolute values can allow comparisons for a given individual patient throughout the course of treatment.

Advantages and Disadvantages of the Available Perfusion Methods

DSC techniques are the most widely used method to measure brain perfusion with MRI. The software to postprocess these data is widely available and relatively straightforward to use. DSC-derived relative CBV is the most widely used and robust method to evaluate brain tumors. Some disadvantages of this technique include the difficulty in determining absolute quantification, susceptibility artifacts (i.e., blood product, calcification, metal, air, and bone), and user dependence.

DCE techniques offer the user the ability to examine the brain microvasculature from a different perspective from DSC MRI by allowing quantitative assessment of the blood-brain barrier and microvascular permeability. This can give a more complete assessment of brain tumor angiogenesis. Some drawbacks of DCE MRI include complexity in image acquisition and pharmacokinetic model postprocessing, user-dependence, and lack of widely available and easy-to-use postprocessing software.

Methods that use exogenous contrast agents have some advantages over ASL. In general, DSC and, even more, DCE MR perfusion achieve a substantially higher SNR that allows imaging at a higher temporal and spatial resolution, e.g., DSC MR perfusion allows the

visualization and quantification of the whole brain in less than a minute of acquisition time. Even though ASL could be improved with the use of high-quality and high field strength scanners, the overall SNR is still limited, which results in much longer scanning times, e.g., 8–10 minutes at 1.5 T or 4–5 minutes at 3 T. The main problem of the longer acquisition time is sensitivity to potential motion artifacts, which can be a significant problem in uncooperative patients, such as with acute stroke or neurodegenerative diseases. This intrinsically low SNR and complex acquisition procedure may, in part, explain the lower utilization of ASL compared with DSC MRI [21, 34]. In addition, a well-known disadvantage of ASL involves cases of severe ischemia in which prolonged arterial transit times can result in relaxation of the spin label and produce underestimation of CBF [35]. Furthermore, ASL can currently provide values only of CBF; however, some recent technical developments may be able to derive a blood volume value from ASL techniques in the future [36].

Although there are many brain tumor perfusion MRI studies that use exogenous contrast agents, ASL methods do offer some advantages. The main advantage is that there is no need for a gadolinium-based contrast agent. Thus, ASL can be considered completely noninvasive. This enables easier repeated measurements, which is particularly a concern given the recognition of nephrogenic systemic fibrosis with some older linear gadolinium-based contrast agents [37]. ASL can also be helpful in pediatric cases where IV access can be difficult. ASL may also allow the determination of absolute quantitative values of CBF—in contrast, DSC MR perfusion does not allow a robust absolute quantification, mainly because of the lack of a direct linear relationship between contrast concentration and signal changes, most pronounced in the presence of partial volume effects.

Permeability, a major confounder in DSC MR perfusion relative CBV measurement accuracy, is less of a concern in ASL because it relies on a diffusible tracer (labeled "arterial water") and thus appears to be relatively insensitive to permeability [38]. Interestingly, a recent study using a continuous ASL method with a twice-refocused spin-echo diffusion sequence appeared to be able to quantify permeability; this type of analysis may become more popular in the future [39]. In addition, there is also the potential for ASL to be completely operator independent [21].

Question 3: What Is Needed to Perform Perfusion MRI? Sequence, Injector, Gadolinium-Based Contrast Agent, Software—Protocol Recommendations

To perform a perfusion study there are technical requirements on the acquisition and on the postprocessing side. To acquire imaging data that can be used for a perfusion analysis, the requirements that are necessary for the scanner are generally not very specific. Some technical considerations must be fulfilled to allow raw data acquisition for the different methods (Table 1), and there are some substantial advantages of high-field systems. In general, the amount of contrast media used is 0.1 mmol/kg of body weight—contrast-enhanced imaging after perfusion should be performed at least 3 minutes after contrast media injection [2].

Dynamic Susceptibility Contrast-Enhanced MR Perfusion

Because the method is based on a fast echo-planar imaging acquisition, the scanner needs to be equipped with echo-planar imaging capabilities. Susceptibility changes on the basis of the injection of an exogenous tracer (gadolinium-based contrast agent) are not strongly field dependent. Therefore, perfusion measurements can be performed both at 1.5 T and 3 T, but even a 1-T system, if equipped with echo-planar imaging, can be used. For the sequence, the maximal temporal resolution should be 1.5 seconds; both 2D and 3D gradient-recalled echo or spin-echo echo-planar imaging sequences can be used.

Bolus injection of the gadolinium-based contrast agent should commence after about a 20-second delay (range, 5–30 seconds) from the start of the DSC MR perfusion sequence. A minimum 3 mL/s (range, 3–5 mL/s) bolus injection rate of gadolinium-based contrast agent is recommended to allow robust and compact bolus arrival in the cerebral tissue. This should be followed by a 25-mL (range, 10–30 mL) saline flush at the same rate to push the bolus toward the heart. Although at the beginning of MR perfusion use, a dose of up to 0.3 mmol/kg of body weight was recommended, today we perform the majority of our MR perfusion examinations at a dose of 0.1 mmol/kg. Higher doses are recommended only if older MR technology is used or if the perfusion study is combined with other contrast-enhanced techniques, such as contrast-enhanced MR angiography or DCE MR perfusion.

Dynamic Contrast-Enhanced MR Perfusion

For DCE MR perfusion, a fast T1-weighted spoiled gradient-recalled echo acquisition technique should be available, e.g., 2D or 3D FLASH (Siemens Healthcare) or turbo FLASH. Spoiled gradient-recalled echo (SPGR) sequences are preferred over standard gradient-recalled echo sequences because the latter have high T2 sensitivity, which is suboptimal because the T2-mediated signal decreases from tissue with a gadolinium-based contrast agent will counteract the desired T1-mediated signal increase [40]. Although 2D sequences do not require specific scanner hardware and are therefore more widely used, 3D sequences, such as SPGR (GE Healthcare), T1-weight-

TABLE 1: Typical Sequences Used and Minor Practical Requirements

	T1-Weighted (DCE)	T2*-Weighted (DSC)	ASL
Sequence	SPGR/MP RAGE/FLASH/FFE (Typically 3D)	GRE Echo-Planar Imaging (2D Multislice)	GRE Echo-Planar Imaging (2D Multislice)
Temporal resolution	~3–6 s	~1–2 s	3–5 s
Total acquisition time	3–5 min	2 min	3–5 min
Spatial resolution	1-mm in-plane × 5-mm slices	2-mm in-plane × 5-mm slices	3-mm in-plane × 5-mm slices
Geometric artifact	Low impact	Prone to problems at the skull base	Prone to problems at the skull base
Model parameters	k^{trans}, v_p, v_e, IAUC	CBV, CBF, MTT	CBF

Note—DCE = dynamic contrast-enhanced, DSC = dynamic susceptibility contrast-enhanced, ASL = arterial spin labeling, SPGR = spoiled gradient-recalled echo, MP RAGE = magnetization prepared rapid gradient echo, FFE = fast-field echo, GRE = gradient-recalled echo, k^{trans} = transfer constant, vp = fractional volume of the plasma space, v_e = fractional volume of the extravascular-extracellular space, IAUC = initial area under the contrast agent concentration-time curve, CBV = cerebral blood volume, CBF = cerebral blood flow, MTT = mean transit time.

ed fast-field echo (T1FFE, Philips Healthcare), volumetric interpolated breath-hold (VIBE, Siemens Healthcare), 3D fast spoiled gradient-echo (GE Healthcare), turbo field echo (Philips Healthcare), and magnetization prepared rapid gradient echo (MP RAGE, Siemens Healthcare), are technically more challenging but show less inflow effect on the arterial input function and less flow artifact in the tissue and provide improved SNR. However, for 3D sequences, the temporal resolution may be lower for the same amount of spatial coverage and these sequences also require a better gradient system on the scanner.

The acquisition time depends on the parameters that should be extracted and sums to 3 minutes' acquisition for only k^{trans} assessments to approximately 6- to 7-minute acquisitions for plasma volume and extravascular-extracellular space assessments. The temporal resolution of the single T1-weighted acquisition should be between 3.5 and 6 seconds depending on the scanner specifics and the field strength used. The injection should start 20 seconds after the start of the DCE MR perfusion sequence, with an injection speed of approximately 2–4 mL/s when using the Tofts model and an infusion over 30 seconds when using the Brix model for postprocessing the data. The contrast medium injection should be followed by a saline injection of a minimum of 10 mL at the same injection speed.

Slice thickness is dependent on spatial coverage, varying between 2 and 10 mm. A good trade-off between temporal and spatial resolution can be obtained with a matrix size of 128 × 128. The relationship between signal intensity and gadolinium-based contrast agent concentration is not always linear and will be affected by the native T1 values of the tissues. As a result, baseline T1 mapping before administration of the gadolinium-

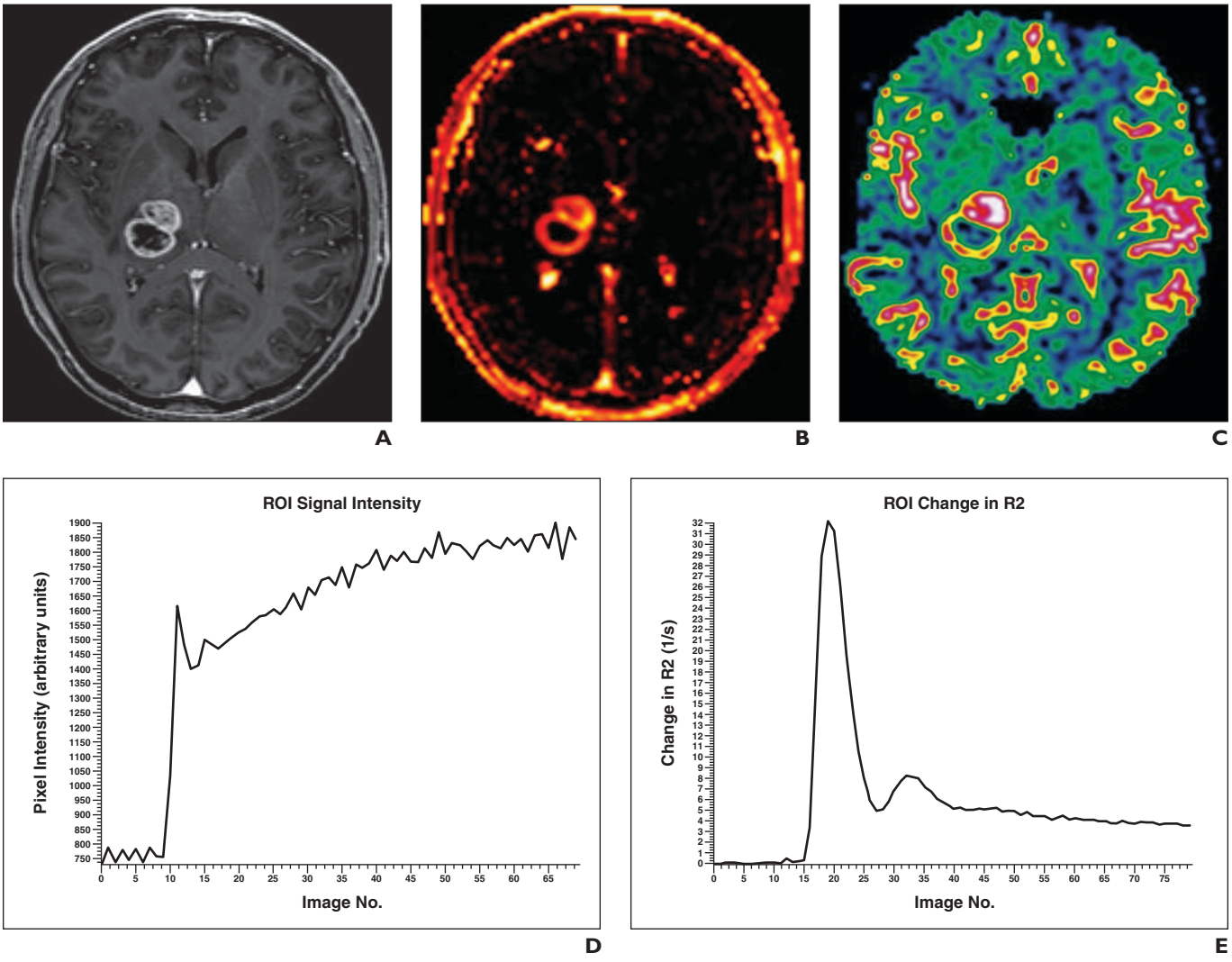

Fig. 2—49-year-old patient with high-grade glioma who underwent combined 3-T MR perfusion protocol.
A, Contrast-enhanced gradient-recalled echo T1-weighted image shows cystic rim-enhancing lesion with solid frontal parts.
B and **C,** In accordance with the Standardization of Acquisition and Post-Processing study, combined protocol of dynamic contrast-enhanced (DCE) MR perfusion (transfer constant map, **B**) was obtained first with 0.05 mmol/kg gadobutrol at 2 mL/s and 20 mL saline flush followed by dynamic susceptibility contrast-enhanced (DSC) MR perfusion imaging (relative cerebral blood volume map, **C**) with 0.05 mmol/kg gadobutrol at 5 mL/s and 20 mL saline flush.
D, Although small amount of contrast medium was used, signal intensity–time curve for DCE MR perfusion shows excellent contrast enhancement, resulting in high-quality perfusion maps.
E, Concentration-time curve for DSC MR perfusion shows short and sufficient bolus geometry and was not influenced by preload of contrast medium.

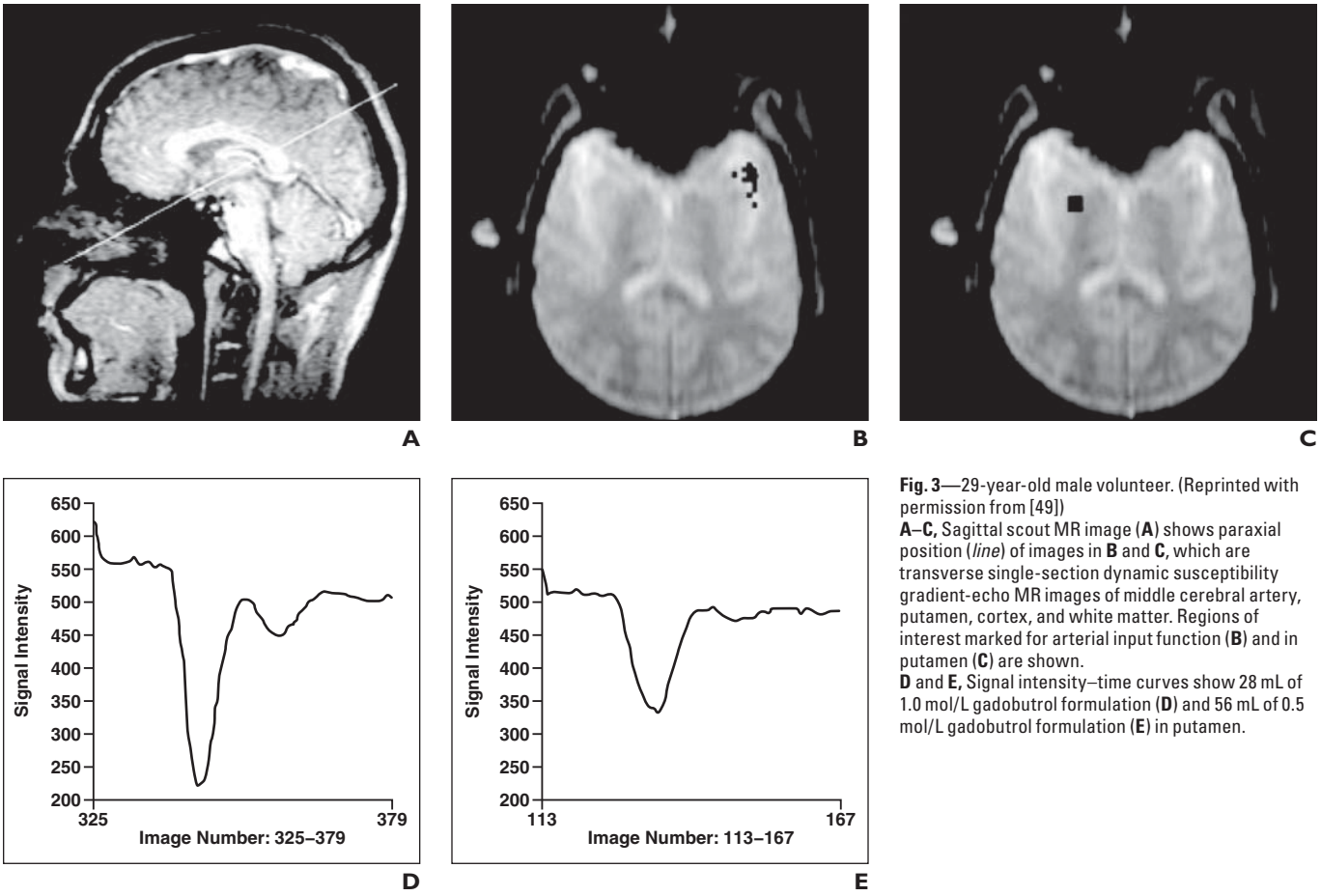

Fig. 3—29-year-old male volunteer. (Reprinted with permission from [49])
A–C, Sagittal scout MR image (**A**) shows paraxial position (*line*) of images in **B** and **C**, which are transverse single-section dynamic susceptibility gradient-echo MR images of middle cerebral artery, putamen, cortex, and white matter. Regions of interest marked for arterial input function (**B**) and in putamen (**C**) are shown.
D and **E,** Signal intensity–time curves show 28 mL of 1.0 mol/L gadobutrol formulation (**D**) and 56 mL of 0.5 mol/L gadobutrol formulation (**E**) in putamen.

based contrast agent has been recommended in DCE MR perfusion, most often using the variable flip angle approach [14, 41]. For the more sophisticated user who would like to quantify the data, T1 mapping with a variable flip angle has been proposed. Furthermore, obtaining T1 measurements both before and after dynamic imaging has also been proposed as a means of increasing the accuracy of the conversion of signal intensity versus time to gadolinium-based contrast agent concentration versus time [42–44].

Combined Dynamic Contrast-Enhanced and Dynamic Susceptibility Contrast-Enhanced MR Perfusion Protocols

When using advanced or multimodal MRI protocols, how can we integrate DCE and DSC MR perfusion into our protocols? What should we measure first, and how should we combine these with other functional methods?

Both sequences can be performed in a single MRI protocol, with the DCE sequence performed before the DSC sequence (Fig. 2). The first injection serves two functions: first as a preload of gadolinium-based contrast agent to help compensate for leakage correction for DSC imaging and, second, to provide dynamic data for calculation of permeability metrics. Because there is an approximate 5- to 8-minute interval recommended between the two injections, an intervening sequence, such as diffusion-weighted imaging, can be performed between DCE and DSC MR perfusion sequences. If combined permeability and perfusion MRI is being performed, it is recommended that the dose be split into two equivalent injections followed by a minimum 10-mL saline flush for each.

A single dose (0.1 mmol/kg of body weight) can only be split if a new-generation gadolinium-based contrast agent (e.g., gadobutrol, a high-relaxivity and high-concentration gadolinium-based contrast agent) and a modern or high-field scanner are used. With standard equipment or a standard gadolinium-based contrast agent, a higher total dose should be considered when two injections are used.

The recommended injection scheme for the single or combined use of DSC and DCE MRI is as follows: For DCE MRI, the recommended injection protocol is 2 mL/s for 0.05 mmol/kg of gadobutrol. Hand injection or lower rate of injection is acceptable, but automated injection is preferred for reliability and consistency. For DSC MRI, the recommended injection protocol is 5 mL/s for 0.05 mmol/kg of gadobutrol at a minimum rate of injection of 3 mL/s. Automated injection is required. The IV catheter that is used must be able to sustain these injection rates. This information can be found on the catheter label.

Injection Device

Because both contrast-enhanced methods (DSC and DCE MR perfusion) are based on dynamic acquisition of imaging data while a contrast bolus is passing through the tissue of interest, the use of a power injector for bolus injection is mandatory. The automated injection is used to allow a fast injection as needed for DSC MR perfusion and to deliver a standardized and reproducible administration of gadolinium contrast agent as recommended for DCE MR perfusion [12, 13]. IV injection into the right arm can decrease the risk of significant contrast agent reflux into the jugular vein [45].

The use of a power injector should allow the injection of a second bolus of saline at the same speed immediately after the contrast media injection. Ideally, this saline flush should be 25 mL (range, 10–30 mL) injected at the same rate to push the gadolinium-based contrast agent bolus toward the heart.

Contrast Media

For DSC MR perfusion and DCE MR perfusion, we need to inject gadolinium-based contrast agent. The first MR contrast agent, gadopentetate dimeglumine (Magnevist, Bayer HealthCare), entered clinical trials for MRI of the brain in 1985 [46] and was marketed initially in parts of Europe and Asia in 1988 and later in the United States. Since then, other gadolinium-based contrast agents have been developed and are now available in many countries.

All gadolinium-based contrast agents are paramagnetic, i.e., they gain magnetic properties in a strong magnet field and reduce the T1 and T2 relaxation times of nearby water protons. The gadolinium-based contrast agents currently approved for the diagnosis of CNS diseases are gadopentetate dimeglumine (Magnevist), gadoteridol (ProHance, Bracco), gadodiamide (Omniscan, GE Healthcare), gadoversetamide (OptiMark, Mallinckrodt), gadobenate dimeglumine (MultiHance, Bracco), and gadoterate meglumine (Dotarem, Guerbet), which is only available in Europe, Latin America, and Asia. The next-generation gadolinium-based contrast agent is gadobutrol (Gadovist, Bayer HealthCare), the first agent with a double-gadolinium concentration (1 molar). The size of this compound is comparable with that of conventional gadolinium chelates and, in addition to its double concentration, its in vitro relaxivity has been shown to be higher (approximately 20–25% in plasma at 1.5 T) compared with other non–protein-binding gadolinium chelates [47]. The higher relaxivity has been shown to be beneficial in many applications [2, 48], leading to better contrast enhancement and therefore better diagnostic performance. The double concentration of this agent reduces the bolus volume, which has been shown to be preferential for MR angiography and specific neuroimaging applications such as DSC MR perfusion and DCE MR perfusion [1, 49].

When using fast acquisitions with a short or ultrashort temporal resolution, we can expect an advantage for agents with higher concentrations, such as gadobutrol. The short bolus geometry enables better determination of the peak for arterial input function, which is of importance for quantification of perfusion measurements, e.g., in stroke and other indications that require accurate measurements of the perfusion results.

The advantage of a higher gadolinium concentration was first presented in a direct comparison of gadobutrol at two concentrations (with the same total dose) in volunteers [49]. In this study, the authors showed the benefits of the 1-M over a 0.5-M concentration of gadobutrol for CNS perfusion imaging, which is attributable to the sharper bolus peak and the increased first-pass gadolinium concentration related to the lower injection volume [49] (Figs. 3 and 4).

In a recent study by Giesel et al. [5], 1-M concentrated gadobutrol was compared with a half-molar agent for DSC MR perfusion at 3 T using an intraindividual comparative study design. A significant difference in the maximal signal change after contrast media administration was found, with a stronger signal drop for the 1-M concentrated agent both in gray and white matter, also leading to better delineation of the tumor boundaries in five of six tumor cases (Fig. 5).

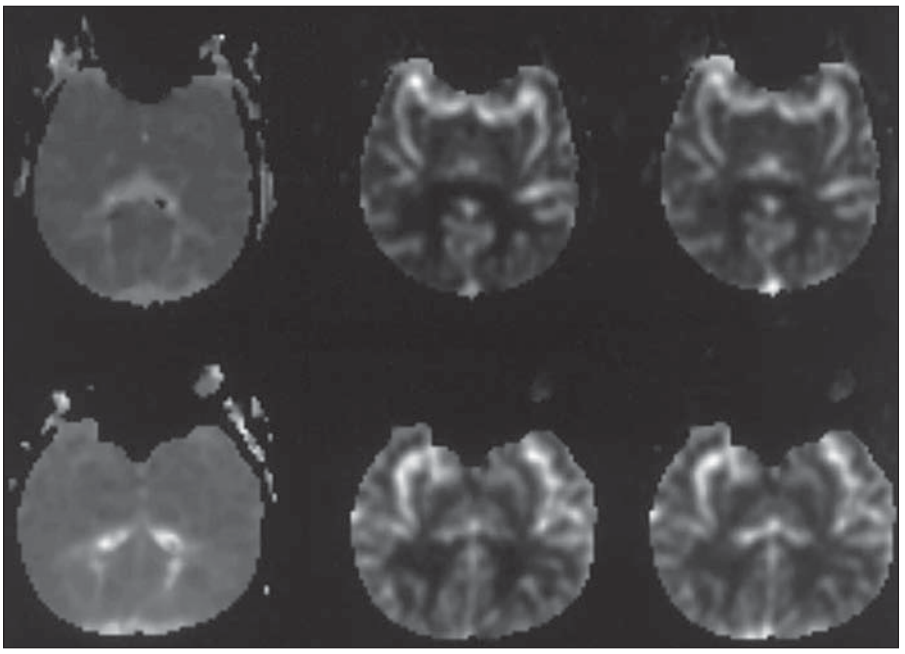

Fig. 4—Mean transit time (*left*), relative cerebral blood flow (*middle*), and relative cerebral blood volume (*right*) maps obtained in 36-year-old man after administration of 0.5 mol/L (*top*) and 1.0 mol/L (*bottom*) gadobutrol formulations. Dynamic susceptibility contrast-enhanced MRI T2* (delay of 6 minutes based on Hu et al. [72]). Acquisition time was 45–60 seconds. If measuring T2 relaxation time (R2), then measure up to 2.5 min. (Reprinted from [49])

Question 4: Is Perfusion MRI Safe?

In general, both DSC and DCE perfusion MRI are very safe imaging methods. Besides the general MRI risks and contraindications, both methods require IV infusion of a gadolinium-based contrast agent at a fairly rapid injection rate, especially for the DSC MR perfusion acquisition.

Scanner-Related Safety Aspects in Perfusion MRI

There are no additional safety concerns regarding MRI scanners with respect to the different perfusion MRI techniques. Neither the echo-planar imaging techniques used for DSC MR perfusion and ASL MR perfusion nor the gradient-echo technique used for DCE MR perfusion have a specific safety concern. They are available on most modern MRI scanners and do not impact the specific absorption rates for radiofrequency deposition [50, 51].

Injection-Related Safety Aspects in Perfusion MRI

A second important safety aspect of perfusion MRI is the IV injection of the gadolinium-based contrast agents, including the injection rate. Because there is no general recommendation for the injection rate in standard MRI examinations, higher injection speeds are especially recommended as is the use of an automated injection device for perfusion sequences (see Question 3: What Is Needed

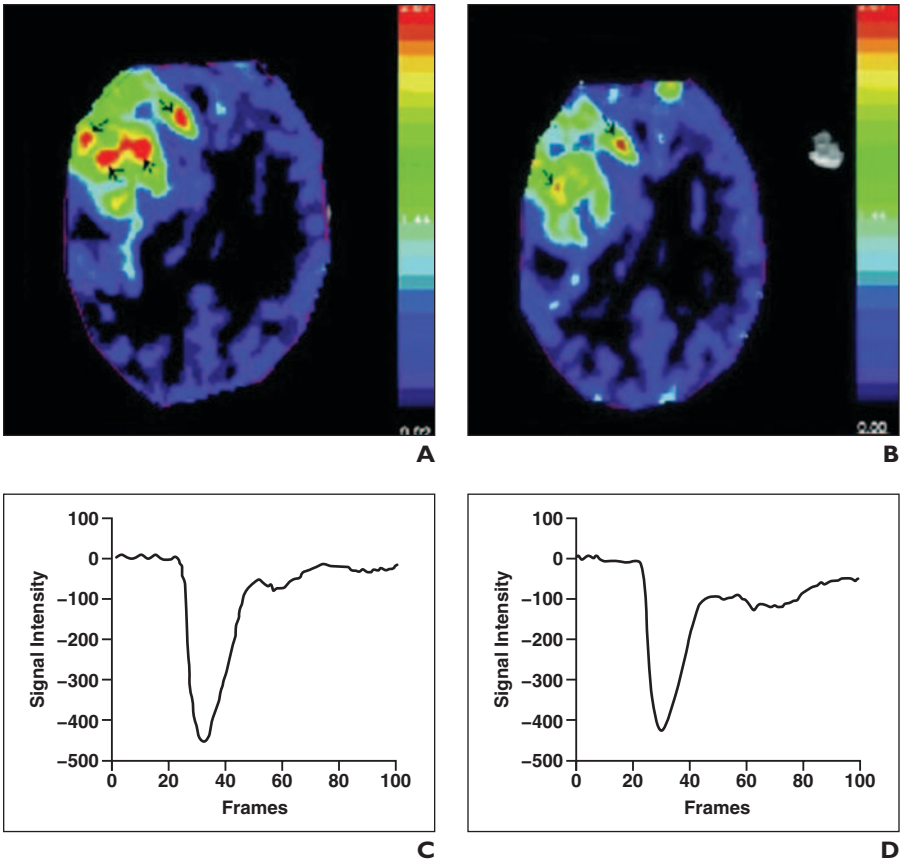

Fig. 5—Intraindividual comparison between gadobutrol and gadopentetate dimeglumine for MR perfusion in intracranial tumor at 3 T. (Reprinted with permission from [5])
A and **B**, Maximum concentration color maps show perfusion-weighted images with gadobutrol (**A**) and gadopentetate dimeglumine (**B**).
C and **D**, Graphs show signal intensity–time curves for whole tumor with gadobutrol (maximum signal drop, 446.98; full width at half-maximum [FWHM], 15.14) (**C**) and gadopentetate dimeglumine (maximum signal drop, 421.59; FWHM, 13.82) (**D**).

to Perform Perfusion MRI?). Explicit evaluations of the injection rate are often combined with questions regarding the image quality for special indications such as MR perfusion. Consequently, safety information on the injection rate may be drawn from the clinical studies. Even in early reports on the safety of gadolinium-based contrast agents, no effects from the injection speed were recorded [52]. However, investigators reported some minor injection-site reactions and pain.

Gadolinium-Based Contrast Agent–Related Safety Aspects in Perfusion MRI

Gadolinium-based contrast agents are considered generally safe, with a less than 1% rate of acute adverse reactions in retrospective analyses, and they lack the nephrotoxicity associated with iodinated contrast media [53–55].

Minor adverse effects occur infrequently and include nausea, taste alteration, and hives. Whereas the different agents have all proven to be safe with respect to the different mild adverse effects, recent studies have indicated differences in the rate of both mild and severe side effects.

Abujudeh et al. [56] compared 32,659 injections and reported that rates of acute adverse reactions to gadopentetate dimeglumine and gadobenate dimeglumine were 0.14% and 0.28%, respectively. They also reported cases of anaphylaxis, which were associated only with the use of gadobenate dimeglumine, providing additional evidence that such reactions can occur, albeit rarely.

In a recent report, Prince et al. [57] evaluated the severe side effects of gadolinium-based contrast agents and raised the possibility that nonionic linear gadolinium-based contrast agents and gadopentetate dimeglumine may have fewer severe immediate adverse events compared with gadobenate dimeglumine.

Other than acute reactions, gadolinium-based contrast agents also differ with regard to chelate stability, with clinical laboratory abnormalities shown for the less-stable agents. Gadolinium-based contrast agents can be categorized by their molecular structure into linear and macrocyclic groups. Relative to agents in the linear group, gadolinium-based contrast agents with a macrocyclic structure (gadobutrol, gadoterate dimeglumine, and gadoteridol) showed increased stability and a reduced propensity to release gadolinium ions in preclinical experiments that included conditions mimicking renal impairment [58].

The dissociation of gadolinium ions from MR contrast material chelating agents in certain contrast media has been associated with the rare condition of nephrogenic systemic fibrosis in patients with severe renal impairment. In separate initiatives, the U.S. Food and Drug Administration and the Committee for Medicinal Products for Human Use of the European Medicines Agency have issued guidance on the risk of nephrogenic systemic fibrosis associated with each gadolinium-based contrast medium, placing the macrocyclic agents into lowest-risk groups [59, 60].

Question 5: What Are the Future Perspectives for Perfusion MRI? New Technologic Developments, Standardization

Although there remain many limitations in the different contrast-enhanced perfusion methods and we are still far from a sufficient standardization of the clinically available perfusion techniques, the acquired parameters are of importance, e.g., for tumor grading and assessing patient prognosis as well as treatment guidance and assessing treatment response in both stroke and tumors.

With improvements of image acquisition techniques and the improvement and standardization of postprocessing software in the future, DSC, DCE, and ASL MR perfusion may receive greater acceptance in the everyday clinical routine.

Improvement of Acquisition Techniques

Technical improvements may come from the broader use of higher-field systems [61–63], compressed sensing [64], view sharing, and parallel imaging. Using a higher field provides a substantially higher SNR that one can invest in an improved speed or higher resolution.

Compressed sensing has become an important tool for the acceleration of imaging times in MRI and is achieved by enabling the recon-

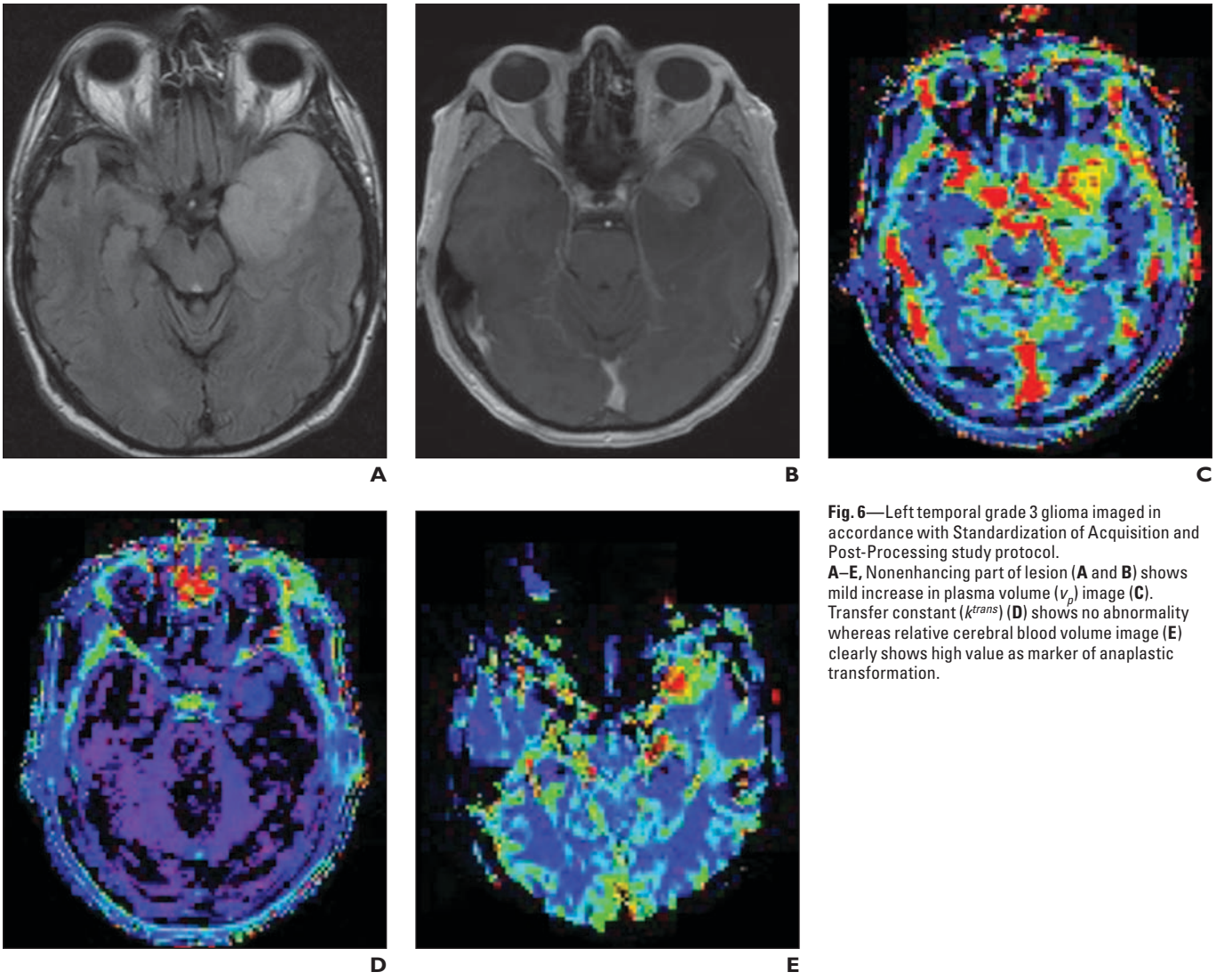

Fig. 6—Left temporal grade 3 glioma imaged in accordance with Standardization of Acquisition and Post-Processing study protocol.
A–E, Nonenhancing part of lesion (**A** and **B**) shows mild increase in plasma volume (v_p) image (**C**). Transfer constant (k^{trans}) (**D**) shows no abnormality whereas relative cerebral blood volume image (**E**) clearly shows high value as marker of anaplastic transformation.

struction of subsampled data. Similarly the applied algorithms can be used to improve both the temporal and spatial resolution of DCE MR perfusion, and several works describing retrospective simulations have shown the feasibility of such improvements.

View sharing allows a faster acquisition for MR angiography but can also be applied for DCE MR perfusion assessments. Initial results exist for lung perfusion [65], and a recently described fat-suppressed approach [66] might improve the DCE MR perfusion results in head and neck indications.

Methodologic and first clinical studies describe a significant artifact reduction, the possibility of faster acquisition, and a more robust assessment of the structural and functional parameters with the use of parallel imaging [67].

For ASL, the use of higher-field strengths (i.e., 3 T or higher), use of a phased-array coil as the receiver, and introduction of fast 3D sequences as an alternative to traditional echo-planar imaging approaches are some technical modifications that may improve SNR and image quality of ASL [25, 51, 68–72].

Improvement of Postprocessing and Standardization

Standardization of an optimized protocol across centers is an important objective, with benefits for the uniform performance and interpretation of MRI studies. However, variability between centers in the equipment and the data-interpretation software that are available and a lack of trial evidence to confirm the clinical benefit of novel MR techniques represent barriers to standardized protocol implementation.

Efforts such as the Acute Stroke Imaging Standardization Group [73], Stroke Imaging Repository Consortium [74], Radiological Society of North America Quantitative Imaging Biomarkers Alliance [75], the National Cancer Institute Quantitative Imaging Network [76], and Standardization of Acquisition and Post-Processing Study [77] have been created to facilitate the standardization, development, and validation of quantitative imaging biomarkers (Fig. 6). To transform radiology from a qualitative effort into a quantitative science, work must progress on making "measuring" devices rather than "imaging" devices [75].

References

1. Essig M, Lodemann KP, Le-Huu M, Brüning R, Kirchin M, Reith W. Intraindividual comparison of gadobenate dimeglumine and gadobutrol for cerebral magnetic resonance perfusion imaging at 1.5 T. *Invest Radiol* 2006; 41:256–263
2. Essig M, Anzalone N, Combs SE, et al. MR imag-

ing of neoplastic central nervous system lesions: review and recommendations for current practice. *AJNR* 2012; 33:803–817

3. Lacerda S, Law M. Magnetic resonance perfusion and permeability imaging in brain tumors. *Neuroimaging Clin N Am* 2009; 19:527–557
4. Shiroishi MS, Habibi M, Rajderkar D, et al. Perfusion and permeability MR imaging of gliomas. *Technol Cancer Res Treat* 2011; 10:59–71
5. Giesel FL, Mehndiratta A, Risse F, et al. Intraindividual comparison between gadopentetate dimeglumine and gadobutrol for magnetic resonance perfusion in normal brain and intracranial tumors at 3 Tesla. *Acta Radiol* 2009; 50:521–530
6. Sorensen AG. Perfusion MR imaging: moving forward. *Radiology* 2008; 249:416–417
7. Villringer A, Rosen BR, Belliveau JW, et al. Dynamic imaging with lanthanide chelates in normal brain: contrast due to magnetic susceptibility effects. *Magn Reson Med* 1988; 6:164–174
8. Østergaard L. Principles of cerebral perfusion imaging by bolus tracking. *J Magn Reson Imaging* 2005; 22:710–717
9. Cha S, Knopp EA, Johnson G, Wetzel SG, Litt AW, Zagzag D. Intracranial mass lesions: dynamic contrast-enhanced susceptibility-weighted echo-planar perfusion MR imaging. *Radiology* 2002; 223:11–29
10. Cha S. Perfusion MR imaging of brain tumors. *Top Magn Reson Imaging* 2004; 15:279–289
11. Provenzale JM, Mukundan S, Barboriak DP. Diffusion-weighted and perfusion MR imaging for brain tumor characterization and assessment of treatment response. *Radiology* 2006; 239:632–649
12. Brix G, Semmler W, Port R, Schad LR, Layer G, Lorenz WJ. Pharmacokinetic parameters in CNS Gd-DTPA enhanced MR imaging. *J Comput Assist Tomogr* 1991; 15:621–628
13. Tofts PS, Kermode AG. Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts. *Magn Reson Med* 1991; 17:357–367
14. Paldino MJ, Barboriak DP. Fundamentals of quantitative dynamic contrast-enhanced MR imaging. *Magn Reson Imaging Clin N Am* 2009; 17:277–289
15. Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging* 1999; 10:223–232
16. Miller JC, Pien HH, Sahani D, Sorensen AG, Thrall JH. Imaging angiogenesis: applications and potential for drug development. *J Natl Cancer Inst* 2005; 97:172–187
17. Jackson A, Jayson GC, Li KL, et al. Reproducibility of quantitative dynamic contrast-enhanced MRI in newly presenting glioma. *Br J Radiol* 2003; 76:153–162
18. Edelman RR, Siewert B, Adamis M, Gaa J, Laub G, Wielopolski P. Signal targeting with alternating radiofrequency (STAR) sequences: application to MR angiography. *Magn Reson Med* 1994; 31:233–238
19. Kim HS, Kim SY. A prospective study on the added value of pulsed arterial spin-labeling and apparent diffusion coefficients in the grading of gliomas. *AJNR* 2007; 28:1693–1699
20. Kwong KK, Chesler DA, Weisskoff RM, et al. MR perfusion studies with T1-weighted echo planar imaging. *Magn Reson Med* 1995; 34:878–887
21. Petersen ET, Zimine I, Ho YC, Golay X. Non-invasive measurement of perfusion: a critical review of arterial spin labelling techniques. *Br J Radiol* 2006; 79:688–701
22. Wolff SD, Balaban RS. Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. *Magn Reson Med* 1989; 10:135–144
23. Henkelman RM, Huang X, Xiang QS, Stanisz GJ, Swanson SD, Bronskill MJ. Quantitative interpretation of magnetization transfer. *Magn Reson Med* 1993; 29:759–766
24. Golay X, Hendrikse J, Lim TC. Perfusion imaging using arterial spin labeling. *Top Magn Reson Imaging* 2004; 15:10–27
25. Wang J, Alsop DC, Li L, et al. Comparison of quantitative perfusion imaging using arterial spin labeling at 1.5 and 4.0 Tesla. *Magn Reson Med* 2002; 48:242–254
26. Thompson G, Mills SJ, Stivaros SM, Jackson A. Imaging of brain tumors: perfusion/permeability. *Neuroimaging Clin N Am* 2010; 20:337–353
27. Wu WC, Jiang SF, Yang SC, Lien SH. Pseudocontinuous arterial spin labeling perfusion magnetic resonance imaging: a normative study of reproducibility in the human brain. *Neuroimage* 2011; 56:1244–1250
28. Kim T, Kim SG. Quantification of cerebral arterial blood volume and cerebral blood flow using MRI with modulation of tissue and vessel (MOTIVE) signals. *Magn Reson Med* 2005; 54:333–342
29. Kim T, Kim SG. Quantitative MRI of cerebral arterial blood volume. *Open Neuroimag J* 2011; 5:136–145
30. Petersen ET, Lim T, Golay X. Model-free arterial spin labeling quantification approach for perfusion MRI. *Magn Reson Med* 2006; 55:219–232
31. Thomas DL, Lythgoe MF, Calamante F, Gadian DG, Ordidge RJ. Simultaneous noninvasive measurement of CBF and CBV using double-echo FAIR (DEFAIR). *Magn Reson Med* 2001; 45:853–863
32. Wang J, Alsop DC, Song HK, et al. Arterial transit time imaging with flow encoding arterial spin tagging (FEAST). *Magn Reson Med* 2003; 50:599–607
33. Warmuth C, Gunther M, Zimmer C. Quantification of blood flow in brain tumors: comparison of arterial spin labeling and dynamic susceptibility-weighted contrast-enhanced MR imaging. *Radiology* 2003; 228:523–532
34. Golay X, Guenther M. Arterial spin labelling: final steps to make it a clinical reality. *MAGMA* 2012; 25:79–82
35. Wolf RL, Detre JA. Clinical neuroimaging using arterial spin-labeled perfusion magnetic resonance imaging. *Neurotherapeutics* 2007; 4:346–359
36. van Westen D, Petersen ET, Wirestam R, et al. Correlation between arterial blood volume obtained by arterial spin labelling and cerebral blood volume in intracranial tumours. *MAGMA* 2011; 24:211–223
37. Grobner T. Gadolinium: a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006; 21:1104–1108
38. Wolf RL, Wang J, Wang S, et al. Grading of CNS neoplasms using continuous arterial spin labeled perfusion MR imaging at 3 Tesla. *J Magn Reson Imaging* 2005; 22:475–482
39. Wang J, Fernandez-Seara MA, Wang S, St. Lawrence KS. When perfusion meets diffusion: in vivo measurement of water permeability in human brain. *J Cereb Blood Flow Metab* 2007; 27:839–849
40. Haase A. Snapshot FLASH MRI: applications to T1, T2, and chemical-shift imaging. *Magn Reson Med* 1990; 13:77–89
41. Buckley D, Parker G. Measuring contrast agent concentration in T1-weighted dynamic contrast-enhanced MRI. In: Jackson A, Buckley D, Parker G, eds. *Dynamic contrast-enhanced magnetic resonance imaging in oncology.* Berlin, Germany: Springer-Verlag, 2005:69–79
42. Cron GO, Santyr G, Kelcz F. Accurate and rapid quantitative dynamic contrast-enhanced breast MR imaging using spoiled gradient-recalled echoes and bookend T(1) measurements. *Magn Reson Med* 1999; 42:746–753
43. Cron GO, Kelcz F, Santyr GE. Improvement in breast lesion characterization with dynamic contrast-enhanced MRI using pharmacokinetic modeling and bookend T(1) measurements. *Magn Reson Med* 2004; 51:1066–1070
44. Nguyen TB, Cron GO, Mercier JF, et al. Diagnostic accuracy of dynamic contrast-enhanced MR imaging using a phase-derived vascular input function in the preoperative grading of gliomas. *AJNR* 2012; 33:1539–1545
45. Jackson A. Analysis of dynamic contrast enhanced MRI. *Br J Radiol* 2004; 77(spec no 2):S154–S166
46. Claussen C, Laniado M, Schorner W, et al. Gadolinium-DTPA in MR imaging of glioblastomas and intracranial metastases. *AJNR* 1985; 6:669–674
47. Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weinmann HJ. Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. *Invest Radiol* 2005; 40:715–724

48. Lövblad KO, Anzalone N, Dorfler A, et al. MR imaging in multiple sclerosis: review and recommendations for current practice. *AJNR* 2010; 31: 983–989
49. Tombach B, Benner T, Reimer P, et al. Do highly concentrated gadolinium chelates improve MR brain perfusion imaging? Intraindividually controlled randomized crossover concentration comparison study of 0.5 versus 1.0 mol/L gadobutrol. *Radiology* 2003; 226:880–888
50. Talagala SL, Ye FQ, Ledden PJ, Chesnick S. Whole-brain 3D perfusion MRI at 3.0 T using CASL with a separate labeling coil. *Magn Reson Med* 2004; 52:131–140
51. Wang Z, Wang J, Connick TJ, Wetmore GS, Detre JA. Continuous ASL (CASL) perfusion MRI with an array coil and parallel imaging at 3T. *Magn Reson Med* 2005; 54:732–737
52. Niendorf HP, Haustein J, Cornelius I, Alhassan A, Clauss W. Safety of gadolinium-DTPA: extended clinical experience. *Magn Reson Med* 1991; 22: 222–228
53. Murphy KJ, Brunberg JA, Cohan RH. Adverse reactions to gadolinium contrast media: a review of 36 cases. *AJR* 1996; 167:847–849
54. Li A, Wong CS, Wong MK, Lee CM, Au Yeung MC. Acute adverse reactions to magnetic resonance contrast media: gadolinium chelates. *Br J Radiol* 2006; 79:368–371
55. Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Frequency and severity of acute allergic-like reactions to gadolinium-containing IV contrast media in children and adults. *AJR* 2007; 189:1533–1538
56. Abujudeh HH, Kosaraju VK, Kaewlai R. Acute adverse reactions to gadopentetate dimeglumine and gadobenate dimeglumine: experience with 32,659 injections. *AJR* 2010; 194:430–434
57. Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. *AJR* 2011; 196:402; [web]W138–W143
58. Frenzel T, Lengsfeld P, Schirmer H, Hütter J, Weinmann HJ. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. *Invest Radiol* 2008; 43:817–828
59. European Medicines Agency Website. European Medicines Agency makes recommendations to minimise risk of nephrogenic systemic fibrosis with gadolinium containing contrast agents. www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000408.jsp&mid=WC0b01ac058004d5c1. Accessed June 2012
60. U.S. Food and Drug Administration Website. FDA news release. New warnings required on use of gadolinium-based contrast agents: enhanced screening recommended to detect kidney dysfunction. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm225286.htm. Accessed June 2012
61. Lee SK. Diffusion tensor and perfusion imaging of brain tumors in high-field MR imaging. *Neuroimaging Clin N Am* 2012; 22:123–134 [ix]
62. Lövblad KO, Haller S, Pereira VM. Stroke: high-field magnetic resonance imaging. *Neuroimaging Clin N Am* 2012; 22:191–205 [x]
63. Prabhakaran V, Nair VA, Austin BP, et al. Current status and future perspectives of magnetic resonance high-field imaging: a summary. *Neuroimaging Clin N Am* 2012; 22:373–397 [xii]
64. Han S, Paulsen JL, Zhu G, et al. Temporal/spatial resolution improvement of in vivo DCE-MRI with compressed sensing-optimized FLASH. *Magn Reson Imaging* 2012; 30:741–752
65. Attenberger UI, Ingrisch M, Dietrich O, et al. Time-resolved 3D pulmonary perfusion MRI: comparison of different k-space acquisition strategies at 1.5 and 3 T. *Invest Radiol* 2009; 44:525–531
66. Le Y, Kroeker R, Kipfer HD, Lin C. Development and evaluation of TWIST Dixon for dynamic contrast-enhanced (DCE) MRI with improved acquisition efficiency and fat suppression. *J Magn Reson Imaging* 2012; 36:483–491
67. Newbould RD, Skare ST, Jochimsen TH, et al. Perfusion mapping with multiecho multishot parallel imaging EPI. *Magn Reson Med* 2007; 58:70–81
68. Fernández-Seara MA, Wang Z, Wang J, et al. Continuous arterial spin labeling perfusion measurements using single shot 3D GRASE at 3 T. *Magn Reson Med* 2005; 54:1241–1247
69. Fernández-Seara MA, Wang J, Wang Z, et al. Imaging mesial temporal lobe activation during scene encoding: comparison of fMRI using BOLD and arterial spin labeling. *Hum Brain Mapp* 2007; 28:1391–1400
70. Ye FQ, Frank JA, Weinberger DR, McLaughlin AC. Noise reduction in 3D perfusion imaging by attenuating the static signal in arterial spin tagging (ASSIST). *Magn Reson Med* 2000; 44:92–100
71. Yongbi MN, Fera F, Yang Y, Frank JA, Duyn JH. Pulsed arterial spin labeling: comparison of multisection baseline and functional MR imaging perfusion signal at 1.5 and 3.0 T: initial results in six subjects. *Radiology* 2002; 222:569–575
72. Hu LS, Baxter LC, Pinnaduwage DS, et al. Optimized preload leakage-correction methods to improve the diagnostic accuracy of dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging in post-treatment gliomas. *AJNR* 2010; 31:40–48
73. Acute Stroke Imaging Standardization Group-Japan Website. asist.umin.jp/index-e.htm. Accessed September 20, 2012
74. Stroke Imaging Repository Consortium Website. stir.ninds.nih.gov. Accessed September 20, 2012
75. Radiological Society of North America Website. RSNA Quantitative Imaging Biomarkers Alliance. www.rsna.org/QIBA_.aspx. Accessed September 20, 2012
76. National Cancer Institute Website. Quantitative Imaging Network. imaging.cancer.gov/informatics/qin. Accessed September 20, 2012
77. University of Erlangen Website. Standardization of Acquisition and Post-Processing Study. www.neuroradiologie.uk-erlangen.de/e1846/e777/e780/index_ger.html). Accessed September 20, 2012