Pulse sequences for contrast-enhanced magnetic resonance imaging

Martin J. Graves*

Departments of Radiology and Medical Physics, Cambridge University Hospitals NHS Foundation Trust, Cambridge, CB2 2QQ, UK

Received 31 July 2006; accepted 4 October 2006
Available online 28 November 2006

Abstract  The theory and application of magnetic resonance imaging (MRI) pulse sequences following the administration of an exogenous contrast agent are discussed. Pulse sequences are categorised according to the contrast agent mechanism: changes in proton density, relaxivity, magnetic susceptibility and resonant frequency shift. Applications in morphological imaging, magnetic resonance angiography, dynamic imaging and cell labelling are described. The importance of optimising the pulse sequence for each application is emphasised.

ª 2006 The College of Radiographers. Published by Elsevier Ltd. All rights reserved.

Introduction

Contrast agents have been used in NMR since the earliest days when Bloch added paramagnetic ferric ions in solution to shorten the longitudinal relaxation time ($T_1$) of protons in water. Development of the first commercially available contrast agent for MRI was started around 1981 with the first reported use in humans in 1984. Since then the range and applicability of contrast agents have grown tremendously, in many cases driving the development of MRI pulse sequences to exploit the behaviour of the contrast agent. This article will review some of the main pulse sequences for contrast-enhanced MRI. It is beyond the scope of this article to describe the principles of MRI sequences in detail,
2. **Relaxation times.** The $T_1$ and $T_2$ relaxation times of tissues can be reduced by the administration of an extracellular paramagnetic agent such as a chelate of the metal ion gadolinium ($\text{Gd}^{3+}$), or by the use of an intracellular agent such as superparamagnetic iron oxide (SPIO) particles.

3. **Magnetic susceptibility.** Contrast agents with a large magnetic moment such as $\text{Gd}^{3+}$ can reduce the local magnetic field homogeneity.

4. **Resonant frequency shift.** The resonant MRI frequency can be shifted by the use of agents that have negligible nuclear relaxation properties but large electron-spin relaxation characteristics such as dysprosium $\text{Dy}^{3+}$ or SPIO particles.

**Proton density**

In certain body areas, e.g. the gastrointestinal (GI) tract, it is possible to artificially change the proton density thereby improving the luminal contrast. For example, CO$_2$ may be used as a negative contrast agent for the stomach, small bowel or colon by reducing the proton density.\(^5\) Conversely it is possible to obtain a positive contrast, by increasing the proton density, using oral water alone\(^6\) or with polyethylene glycol (PEG),\(^7\) or to perform MR enteroclysis using water with methyl cellulose.\(^8\) These examples are slightly exceptional in our discussion of exogenous contrast material because we are using them primarily as a contrast media rather than as an agent.

The signal intensity observed from any standard MRI pulse sequence has a dependency on the proton density ($\rho$). Eq. 1 is a simplified expression that describes the signal intensity (SI) for a spin echo imaging sequence in which the repetition time (TR) is much longer than the echo time (TE).

$$\text{SI} \propto \rho \left[1 - e^{-\frac{\text{TE}}{T_2}}\right] e^{-\frac{\text{TE}}{T_1}}$$

Fig. 1 shows an example of negative colonography where the patients’ colon has been rectally insufflated with CO$_2$, resulting in a dark luminal signal. In this case a proton density weighted SSFSE sequence has been used with a short effective TE. Fig. 2 shows an example of an SSFSE sequence used to obtain an image of the stomach and small bowel following oral water. Water not only increases the proton density but it also has a long $T_2$ relaxation time. This means that using a long effective TE can further enhance the contrast between the stomach and the surrounding tissues.

Although the vast majority of MRI involves imaging of protons ($^1\text{H}$) it is possible to image other NMR active nuclei that do not occur naturally in the body such as hyperpolarized noble gases, e.g. helium ($^3\text{He}$) used for lung imaging.\(^12\) Other NMR active nuclei such as hyperpolarized carbon ($^{13}\text{C}$),\(^13\) and fluorine ($^{19}\text{F}$),\(^14\) are currently being investigated in animal models. A major advantage of using these techniques is that the images are free of any background, i.e. proton density signals.

All these other nuclei require special methods of generating the agents and MRI system hardware capable of operating at the different Larmor frequencies. Whilst it is possible to acquire images of these nuclei using conventional MRI techniques retuned to the Larmor frequency of interest optimal imaging may require further pulse sequence modifications that are beyond the scope of this article.

### Relaxation times

As discussed above the primary application of contrast agents is based upon their effect of reducing the $T_1$, $T_2$ and also the $T_2^*$ relaxation times of tissue water in the vicinity of operating at the different Larmor frequencies. Whilst it is possible to acquire images of these nuclei using conventional MRI techniques retuned to the Larmor frequency of interest optimal imaging may require further pulse sequence modifications that are beyond the scope of this article.

![Figure 1](image.png)

**Figure 1** Proton density weighted single shot fast spin echo (SSFSE, GE Healthcare Technologies, Milwaukee) image of the colon following rectal administration of CO$_2$. Note the negative luminal signal. A carcinoma of the sigmoid colon is shown (arrows).
of the agent. How close the tissue water needs to approach the agent depends upon the relaxation mechanism. In the case of $T_1$ and $T_2$ relaxation water molecules need to approach the outer shell electrons of the paramagnetic or ferromagnetic species in order to experience the large electron magnetic moment that causes relaxation. This effect is therefore very short range. However, these species also cause a perturbation of the local magnetic field over a much larger spatial extent which means that $T_2^*$ relaxation occurs over a much larger distance. Note that $T_2^*$ the effective transverse relaxation time is given by

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2^{0}}$$

(2)

where $T_2$ is the natural decay and $T_2^{0}$ is the effect of magnetic field inhomogeneities. The agent will reduce both the $T_2$ and the $T_2^{0}$ of the tissue with the primary effect being determined by the pulse sequence being used. Spin echo-based sequences will refocus the microscopic $T_2^{0}$ influences and the contrast will be primarily affected by the $T_2$ component, whereas gradient echo-based sequences will be influenced by both $T_2$ and $T_2^{0}$ effects, i.e. $T_2^*$. Contrast agents do not exclusively affect only the $T_1$ or $T_2$ of the tissue but will affect both according to the relativity of the agent and its concentration. Following the administration of a paramagnetic compound the observed tissue relaxivity ($1/T_{1,2}^{(observed)}$) becomes a linear combination of the intrinsic relaxivity ($1/T_{1,2}^{(intrinsic)}$) of the tissue and the relaxivity of the agent ($1/T_{1,2}^{(agent)}$).

$$\frac{1}{T_{1,2}^{(observed)}} = \frac{1}{T_{1,2}^{(intrinsic)}} + C \frac{1}{T_{1,2}^{(agent)}}$$

(3)

where $C$ is the concentration of the agent. It should be noted that since $T_2$ is generally an order of magnitude (10 times) longer than $T_2$ in most biological tissues there is a relatively larger reduction in $T_1$ for a given $C$ in comparison to $T_2$. For example using a gadolinium agent with a relaxivity of $3.4 \text{ mM}^{-1} \text{s}^{-1}$ and a concentration of $0.5 \text{ mM}$ will cause a pre-contrast $T_1$ of 1000 ms to reduce to 370 ms, whereas the pre-contrast $T_2$ of 100 ms will only be reduced to 84 ms.

Using Eqs. (1) and (2), Fig. 3 shows the change in signal intensity for a hypothetical tissue with an intrinsic $T_1$ of 1000 ms and a $T_2$ of 100 ms as a function of contrast agent concentration for a $T_1$-weighted spin echo sequence with a TR of 500 ms and a TE of 10 ms and a $T_2$-weighted sequence with a TR of 5 s and a TE of 100 ms.

The graph shows that the addition of the agent decreases the $T_1$ relaxation time resulting in an increase in signal on $T_1$-weighting (positive contrast) and a decrease in signal on $T_2$-weighting (negative contrast). It should also be noted that as the concentration increases above approximately 2 mM, $T_2$ effects start to dominate and the signal intensity starts to decrease on $T_1$-weighting. This effect explains the phenomenon of pseudolayering of Gd-DTPA often noted in the urinary bladder.

For gradient echo imaging the situation becomes a little more complex because we now have to take into consideration the excitation flip angle $\alpha$. A simplified expression for an incoherent gradient echo sequence, e.g. SPGR (GE Healthcare Technologies), FLASH (Siemens Medical Solutions) or $T_1$-FFE (Philips Medical Systems), is given by

$$SI \propto \rho \frac{\sin \left(1 - e^{-\frac{\alpha}{T_1}}\right)e^{-\frac{\alpha}{T_2}}}{1 - \cos \alpha e^{-\frac{\alpha}{T_2}}}$$

(4)

Note that in the case of a gradient echo sequence we use $T_2^*$ instead of $T_2$ since we are not using any refocusing pulses to eliminate the effects of the magnetic field inhomogeneities. If the TE is kept as short as possible to minimise $T_2^*$ effects then this sequence is quite effective at producing $T_1$-weighted images.

Figure 3  Graph showing the signal intensity changes with gadolinium concentration for a $T_1$-weighted (thin line) and $T_2$-weighted (thick line) standard spin echo pulse sequence. Note that the signal intensity decreases on the $T_2$-weighted image whereas the signal intensity initially increases on the $T_1$-weighted image until $T_2$ effects start to dominate and the signal intensity starts to decrease.
The expression for a coherent gradient echo sequence, e.g., FIESTA (GE Healthcare Technologies), True-FISP (Siemens Medical Solutions), balanced—FFE (Philips Medical Systems), is more complex but can be simplified for the case where the $TR < T_1, T_2$.

$$SI \propto \sin \alpha \left( \frac{T_2}{T_1} \right)$$

The evolution of the magnetisation in this sequence means that even though it is classed as a gradient echo sequence its contrast behaviour is dictated by the ratio of $T_2/T_1$ and $T_2^*$ does not feature. This can be explained by the fact that the dephasing induced by the magnetic field inhomoogenieties will be completely refocused at $TE = TR/2$ leading to the formation of a spin echo rather than a gradient echo. In addition the TE and TR do not feature, only the flip angle, which means that this sequence can, and in fact should, be run with the shortest possible $TE$ and TR and ideally balanced so that $TR = 2TE$.

Contrast-enhanced morphological imaging

The majority of morphological contrast-enhanced imaging utilises conventional spin echo imaging sequences for $T_1$-weighted imaging and usually fast spin echo sequences for $T_2$-weighted imaging. The insensitivity to $T_2^*$ effects makes the spin echo sequence ideally suited to post-contrast morphological imaging. One disadvantage of post-contrast $T_1$-weighted spin echo imaging is increased ghosting artefacts due to strong signal enhancement in moving structures or flowing blood, e.g., peristaltic ghosting artefacts in the bowel following administration of a positive oral contract agent. The ability to acquire fast spin echo images in a single breath-hold allows abdominal images to be acquired without respiratory artefacts which makes them the most suitable sequences for imaging negative contrast agents.

Contrast-enhanced magnetic resonance angiography

The most common application for contrast-enhanced gradient echo imaging is in the technique of contrast-enhanced magnetic resonance angiography (CE-MRA). In this application, volumetric (3D) data are acquired, using an incoherent ($T_1$-weighted) gradient echo sequence, during the first pass of a gadolinium-based paramagnetic contrast agent through the vascular anatomy of interest. The shortest possible TR is used to maximise the volumetric coverage in the shortest possible scan time, whilst the shortest possible TE, subject to SNR constraints, is used to minimise flow-related dephasing and also to minimise the effect of $T_2^*$ signal loss due to the transiently high concentration of gadolinium. Sequences often employ fractional, or partial, echo acquisition in order to further reduce TE and consequently TR. Once the volumetric slices have been acquired the data are usually displayed as a maximum intensity projection (MIP) where the brightest pixels along a line of sight through the volume are displayed in the final image.

When injecting gadolinium as a bolus there is a transient increase in the blood concentration [Gd] that results in a decrease in the observed $T_1$ of the blood from its intrinsic value of approximately 1200 ms. Fig. 4 shows the decrease in $T_1$, with increasing [Gd] together with the increasing signal intensity in a spoiled gradient echo sequence (SPGR) with a TE of 2 ms, a TR of 4 ms and a flip angle of 45°. A typical CE MRA study with an injection rate of 2 cc/s will reduce the $T_1$ of blood to around 25 ms. Fig. 5 shows MIPs of a 3D coronal acquisition through the thorax before and after bolus administration of Gd-DTPA. In the pre-image the blood flow is saturated due to the relatively long $T_1$ of blood, whereas in the post-image the vasculature is bright due to the considerably shortened $T_1$ of blood.

Whilst the underlying principle of contrast-enhanced MRA is the use of a $T_1$-weighted gradient echo imaging sequence there has been enormous technical developments in recent years directed at optimising the data acquisition with respect to the administration of the contrast agent. When injecting the agent as a bolus there is a short time window between the agent appearing in the arterial circulation but not reaching the venous circulation. This window is substantially shorter than a complete MRA acquisition so it is necessary to tailor the acquisition such that the centre of the MRA raw data matrix, or $k$-space, is acquired during this arterial window. In this way the bulk of the contrast in the angiogram represents the signal in the arterial vasculature uncontaminated by venous enhancement. The periphery of $k$-space, that provides the “detail” in the image, may then be acquired. Signal in the venous circulation during this time will have very little deleterious effect on the images. Therefore synchronising the acquisition with the peak first pass of the contrast agent requires knowledge of the delay, or circulation, time between the injection and the contrast reaching the area of interest and a means of acquiring the centre of $k$-space first.

![Figure 4](image.png)

**Figure 4** Graph showing the decrease in the $T_1$ of blood with increasing gadolinium concentration (thin line) together with the increase in signal intensity on 3D spoiled gradient echo (SPGR) sequence (thick line). A bolus injection rate of 2–3 cc/s is sufficient to produce a transient increase in the blood gadolinium concentration of approximately 10 mM.
The circulation time can be estimated for each patient individually or even standardized, however, the best and most consistent results are obtained by optimising the timing, either retrospectively or prospectively. The retrospective method involves the injection of a small test bolus, typically 2 ml, of contrast whilst rapidly and repeatedly imaging a slice through the vessel at the level of interest. Performing a region of interest analysis of the images shows a peak in the signal intensity at the time when the contrast reaches the area of interest. If imaging is started at the same time as the injection then this time is the circulation time.

There are currently two prospective triggering methods. The first uses a rapid one-dimensional (1D) monitoring sequence that detects the increase in signal intensity as the contrast agent arrives in the area of interest (or lower in the arterial path) and starts the 3D MRA sequence automatically. The second method uses rapid “fluoroscopic” imaging at the level of interest so that the operator can see the contrast arrive and then manually start the MRA sequence. For both triggering methods the MR system also needs to provide a rapid switch over between the monitoring sequence and the actual 3D CE MRA sequence.

The true centre of 3D k-space is most effectively sampled using elliptic centric ordering or one of its variants. In a conventional encoded 3D sequence the entire slice-encoding (kSS) loop is acquired before the kPE phase encoding step is changed. So even if the phase encoding were centrically ordered (i.e. starting at zero and increasing to the maximum, alternating between positive and negative) we would be acquiring central kSS lines right through the acquisition. The elliptic centric ordering acquires the kSS and kPE lines in a spiral fashion starting from the centre and moving outwards depending upon the actual spacing in k-space for each kPE and kSS step. In this way all the central k-space lines are acquired together. This ordering means that the centre of k-space is acquired almost a factor of 10 times faster than a conventional centric acquisition. Therefore scans with a much higher spatial resolution can be obtained even though the overall scan time will be many times longer than the arterial-venous transit time.

Recently parallel imaging techniques such as SENSE, SMASH and GRAPPA have been developed that exploit multi-channel coil arrays to allow reductions in MR imaging times without sacrificing spatial resolution, albeit at a reduction in SNR. When applied in combination with elliptic centric acquisitions SENSE has been demonstrated to reduce venous contamination by 20% and to produce higher SNR with reduced truncation artefacts at higher injection rates.

In comparison to conventional angiography, CE-MRA is generally a static imaging technique and gives very little information on flow dynamics. There are a number of methods by which multiphase 2D single-slice projection or 3D volume CE-MRA acquisitions can be performed. A 3D volume could be repeated multiple times but the temporal resolution would be quite poor unless the time for an individual volume is reduced. The most common methods for reducing scan time in 3D CE MRA are to use the shortest possible TR, to use partial Fourier acquisitions and to decrease the resolution, particularly in the phase-encoding and slice-selection directions. The reduction in acquisition resolution can be partly offset through the use of zero-filling interpolation methods. If repeated fast enough then a pure arterial phase volume should occur in at least one of the acquisitions. Alternatively only the central k-space data can be repeatedly acquired, a technique known as keyhole imaging. This has been demonstrated to acquire 3D volumes of the carotid at a rate of 3.6 per second. As discussed above, parallel imaging techniques such as SENSE can also be employed to reduce the acquisition time for an individual volume. Alternatively methods that leverage the relationship between the bulk of the image contrast and the acquisition of the centre of k-space can be used to acquire volumes at a greater temporal resolution. Time-resolved imaging of contrast kinetics (TRICKS) is one such method that segments k-space into a central volume and multiple concentric peripheral volumes. During the TRICKS acquisition the volumes nearer...
the centre of \( k \)-space are repeatedly acquired more rapidly than the outer volumes. Multiple volumes are then reconstructed with a higher temporal resolution than could be obtained by acquiring a complete 3D acquisition for each phase, although there will be some compromise in spatial resolution.\(^4\) These dynamic techniques also obviate the need for operator triggering, potentially making them more robust.\(^4\) Fig. 6 shows eight frames from a time-resolved TRICKS acquisition in the calf. Time-resolved techniques also permit the application of sophisticated post-processing techniques to improve the separation of arteries and veins.\(^4\)

The use of standard extracellular gadolinium agents, e.g. Gd-DTPA has driven the technical development of pulse sequences for MRA. However, the recent commercialisation of a gadolinium-based blood-pool agent (Vasovist, Schering, Berlin) opens up the possibility of imaging in the equilibrium phase. Following injection this agent binds strongly to human serum albumin and remains intravascular for several hours, allowing the possibility of high-resolution \( T_1 \)-weighted imaging to be performed in multiple planes. Whilst the agent can still be imaged during the first pass, potentially giving an improved CE MRA study since it has a considerably higher \( T_1 \) relaxivity than Gd-DTPA, in the equilibrium phase both arteries and veins enhance equally posing problems in separation.

**Dynamic contrast-enhanced (DCE) MRI**

Conventional contrast-enhanced imaging demonstrates the spatial uptake of a contrast agent, however, variations in microvascular structure and pathophysiology give rise to temporospatial variations in the enhancement of tissues that can provide valuable information for diagnosis and therapeutic follow-up. Dynamic contrast-enhanced (DCE) MRI acquires repeated images, at an appropriate rate, i.e. dynamically, during the passage of a contrast agent through the anatomy/pathology of interest. These images may then be subjected to simple visual analysis or more sophisticated mathematical analysis of the signal changes. Such analyses may range from basic semi-quantitative summary parameters such as the maximum slope of the signal changes through to quantitative pharmacokinetic modelling. Typical applications for DCE-MRI include myocardial ‘perfusion’ and tumour imaging.

In terms of pulse sequences there are two major approaches to the acquisition of DCE-MRI data. Relaxivity-based methods use \( T_1 \)-weighted acquisitions, whilst dynamic susceptibility contrast (DSC) techniques use \( T_2 \) or more commonly \( T_2^* \)-weighted acquisitions. DSC acquisitions are covered in more detail below. Acquisition of DCE images using relaxivity effects most commonly involves the use of a \( T_1 \)-weighted gradient echo sequence in order to achieve an acceptable temporal resolution. Standard gradient echo sequences can provide a moderate degree of \( T_1 \)-weighting, but pre-pulses such as saturation (90\(^\circ\)) or inversion (180\(^\circ\)) allow a significantly higher \( T_1 \)-weighting to be achieved.\(^4\) Fig. 7 shows six phases during the first pass of Gd-DTPA through the myocardium in the short axis plane. The increase in signal intensity can be seen as the contrast-enhanced blood passes through the right ventricle, then the left ventricle and finally into the myocardium. Note the lack of enhancement in the subendocardial region indicative of a perfusion defect.

Even using a gradient echo sequence it is still generally necessary to optimise the imaging parameters in order to achieve an appropriate trade-off between spatial and temporal resolution as well as coverage.\(^4\) Various techniques have also been employed to try and reduce the

---

**Figure 6** Eight frames from a time-resolved imaging of contrast kinetics (TRICKS) acquisition showing maximum intensity projections from each 3D volume in the calf. Note the differential flow patterns between the normal right leg and the arteriovenous malformation in the left leg.
acquisition time, and thereby allow greater slice coverage for a given temporal resolution. Short echo-planar imaging (EPI) readouts have been employed, where a small number of echoes, typically four, are acquired after a single excitation pulse. Such short echo trains are used as a trade-off between reducing the acquisition time whilst minimising the artefacts that arise from extended echo trains. Other approaches include the use of the “keyhole” imaging technique, whereby only the central segment (keyhole) of a pre-contrast full k-space acquisition is updated for each temporal phase, i.e. the pre-contrast peripheral k-space segment is reused for each phase. Spatial parallel imaging techniques mentioned above can be used to reduce the acquisition time for each phase. In addition temporal acceleration techniques can also be used such as TSENSE, UNFOLD and k-t BLAST/k-t SENSE.

Magnetic susceptibility

Magnetic susceptibility is the degree of magnetisation of a material in response to a magnetic field. Paramagnetic materials strengthen the magnetic field whereas diamagnetic materials weaken it. Gadolinium has seven unpaired electrons in its outer shell making it a paramagnetic metal ion. Therefore it has a large magnetic moment that causes a local spatial variation or inhomogeneity in the magnetic field. This spatial inhomogeneity causes the transverse relaxation of spins to be accelerated, resulting in the $T_2^*$ signal decay described above. In many cases $T_2^*$ relaxation is undesirable; indeed spin echo sequences were developed in part to ameliorate this effect. However, in those situations where this effect is desirable the sensitivity of gradient echo-based imaging sequences to $T_2^*$ relaxation means that they are well suited to visualising this particular property of a contrast agent. The most important imaging parameter for susceptibility imaging is the amount of phase dispersion caused by the combination of the pulse sequence parameters and the contrast agent. As the phase spread increases then signal cancellation starts to occur. The phase spread $\Delta \phi$ within a single voxel is given by the equation:

$$\Delta \phi \propto \Delta \chi \Delta r \cdot TE$$  \hspace{1cm} (6)

where $\gamma$ is the gyromagnetic ratio, $\Delta r$ the voxel size, $TE$ the echo time and $\Delta \chi$ is the difference in the local magnetic susceptibilities between the agent compartment and the surrounding tissue and is given by

$$\Delta \chi \propto 4 \pi \chi_m C$$  \hspace{1cm} (7)

where $\chi_m$ is the agent molar susceptibility and $C$ is the agent concentration.

In terms of the pulse sequence it can therefore be seen that increasing either the pixel size, at the expense of spatial resolution, or increasing TE at the expense of overall image signal-to-noise ratio (SNR) can increase the amount of phase spread within a voxel.

Dynamic susceptibility contrast (DSC) MRI

One example of the advantageous effects of $T_2^*$ relaxation is in dynamic susceptibility contrast (DSC) imaging using MRI. The approach is similar to the DCE technique described above but in this case we are using the susceptibility effect of the contrast agent rather than the relaxivity effect. For DSC imaging a bolus injection of the paramagnetic contrast agent is administered and dynamic, $T_2^*$-weighted imaging is...
then used to monitor the first pass of the agent’s passage through the organ of interest. $T_2^*$-weighted imaging is often used in imaging blood flow within the brain because the contrast agent does not cross the intact blood–brain barrier and, since the capillary density is only 4%, there is a necessity to use an agent that causes a “long-range” effect in order to be detectable.\textsuperscript{51} Fortunately techniques such as single shot echo-planar imaging (ssEPI) fulfil the two requirements of being sensitive to $T_2^*$ effects, by virtue of a long effective TE, and fast enough to track the transient passage of the contrast agent throughout the entire brain with sufficient temporal resolution.\textsuperscript{52} Fig. 8 shows 12 images from a dynamic EPI acquisition before and during the first pass of a paramagnetic contrast agent through the brain. Note that during the first pass of the agent there is a marked decrease in the signal intensity within the brain parenchyma compared to the pre-image. This is due to the $T_2^*$ signal reduction caused by the magnetic field inhomogeneity that occurs as the agent passes through the capillaries. Note that despite the capillaries only occupying 4% of the brain tissue there is a marked signal reduction. These dynamic images can be analysed to produce parametric images that represent the spatial distribution of the cerebral blood volume and potentially cerebral blood flow.\textsuperscript{53}

(Ultra)-small paramagnetic iron oxide ((U)SPIO) imaging

Another application of $T_2^*$-weighted imaging is following the administration of SPIO or USPIO agents. In this situation accumulation of the particles causes a decrease in signal intensity due to susceptibility-induced relaxation. The majority of studies that have used USPIO particles have used long TE (10–20 ms) gradient echo sequences; however, it should also be noted that USPIO particles of less than 10 nm in size also cause a large reduction in $T_1$. Indeed some USPIO agents are developed as blood-pool agents for magnetic resonance angiography.\textsuperscript{54,55} Therefore depending upon the concentration and biodistribution of the agent it may have a confounding $T_1$ signal enhancing effect in addition to the signal decay due to $T_2^*$ resulting in the presence of the agent being obscured.\textsuperscript{56} Therefore the optimal visualisation of the agent should involve the use of a gradient echo sequence where the effects of $T_1$ can be minimised.

Figure 8  Twelve phases from a dynamic susceptibility contrast (DSC) study in the brain using an echo planar imaging sequence (EPI). The time between images is 1 s. Note that as the Gd-DTPA contrast agent bolus passes through the cerebral circulation there is a strong, but transient, signal intensity decreases due to the $T_2^*$ dephasing caused by the agent.
by, for example, the use of a long TR and low flip angle. The optimal choice of echo time is also difficult to determine a priori since too short a TE may not allow sufficient susceptibility-induced phase spread and hence signal loss whilst too long a TE may result in unnecessary sacrificing of image signal-to-noise ratio (SNR). Multi-echo gradient echo sequences are very useful in these applications since they allow multiple images acquisitions at different echo times. The individual echoes can be visually inspected to illustrate the change in signal intensity or, if the appropriate software is available, they can be used to calculate the $T_2^*$ relaxation time on a pixel-by-pixel basis.\(^5\)\\

Resonant frequency shift

In addition to the bulk magnetic susceptibility effect caused by a paramagnetic agent it is also possible for the agent to shift the local resonant frequency. If we mathematically model the compartment as an infinitely long cylinder, i.e. like a blood vessel at an angle $\theta$ to the static magnetic field $B_0$ then it can be shown that the frequency shift, $\delta f$, is given by

$$\delta f = \frac{\gamma B_0}{4\pi} \Delta \chi \left( \cos^2 \theta \right)$$

Whilst metal ions like gadolinium are efficient relaxivity agents as well as susceptibility agents, ions such as dysprosium ($\text{Dy}^{3+}$) are mainly efficient susceptibility agents. Indeed a $\text{Dy}^{3+}$-based contrast agent has been used as an improved $T_2^*$ perfusion agent although toxicity issues have limited its application to a phase I clinical trial.\(^5\)

A major disadvantage of the use of SPIO agents is that the bulk magnetic susceptibility effect results in regions of hypointensity or negative contrast on $T_2$- or $T_2^*$-weighted imaging that can be difficult to separate from naturally occurring voids in the image. Recently there has been interest in the imaging of the frequency shift caused by the dipolar field that surrounds the particles as a positive contrast or "white marker" effect, particularly for the imaging of the frequency shift caused by the dipolar field that allows the contrast agent kinetics to be measured, potentially providing quantitative information on organ or tumour function. Finally the combination of novel MRI pulse sequences together with the recent developments in targeted contrast agents discussed in the paper by Yan and Hogg in this issue offers the potential for practical cellular and molecular imaging by MRI.

Summary

This review has outlined some of the pulse sequence approaches that have been used to image tissue following the administration of contrast agents. The primary application remains morphological imaging following the administration of either a positive or a negative relaxivity-based agent. Magnetic resonance angiography is probably the next biggest application requiring rapid image acquisition during the first pass of a positive relaxivity-based agent. Dynamic contrast-enhanced imaging is a rapidly developing field that allows the contrast agent kinetics to be measured, potentially providing quantitative information on organ or tumour function. Finally the combination of novel MRI pulse sequences together with the recent developments in targeted contrast agents discussed in the paper by Yan and Hogg in this issue offers the potential for practical cellular and molecular imaging by MRI.

References

7. Sood RR, Joubert I, Franklin H, Doyle T, Lomas DJ. Small bowel MRI: comparison of a polyethylene glycol preparation and...
water as oral contrast media. J Magn Reson Imaging 2002;15:
401–8.
ysis images with conventional enteroscopy and surgical find-
17. Scheffker K, Hennig J. Is TrueFISP a gradient-echo or a spin-
19. Grubnic S, Padhani AR, Revell PB, Husband JE. Comparative ef-
22. Levy RA, Prince MR. Arterial-phase three-dimensional contrast-
29. Fain SB, Riederer SJ, Bernstein MA, Huston III J. Theoretical limits of spatial resolution in elliptical-centric contrast-
36. Hennig J, Scheffker F, Laubenberger J, Strecker R. Time-re-
37. Levy RA, Maki JH. Three-dimensional contrast-enhanced MR angiography of the extracranial carotid arteries: two tech-
41. Fellner C, Lang W, Janka R, Wutke R, Bautz W, Fellner FA. Magnetic resonance angiography of the carotid arteries using three different techniques: accuracy compared with intraarte-
43. Korosec FR, Turski PA, Carroll TJ, Mistretta CA, Grist TM. Con-
45. Krishnan S, Chenevert TL. Spatio-temporal bandwidth-based acquisition for dynamic contrast-enhanced magnetic reso-
46. Ding S, Wolff SD, Epstein FH. Improved coverage in dynamic contrast-enhanced cardiac MRI using interleaved gradient-
47. Oesterle C, Strohschein R, Kohler M, Schnell M, Hennig J. Benefits and pitfalls of keyhole imaging, especially in first-


