

DIFFUSION AND PERFUSION MRI IN ACUTE STROKE IMAGING

Andy Trowinger, RT (R) (MR) (CT) (CV), CMRT

INTRODUCTION

Brain attack is a term for stroke that has evolved as an outgrowth of the *heart attack*. A heart attack is an episode of chest pain resulting from an interruption of the blood supply to the heart muscle. Because a stroke is a set of symptoms that typically result from an interruption of the blood supply to the tissues of the brain, brain attack is quickly becoming a commonly used term in the health industry. Lending further support to this association, a transient ischemic attack (TIA) is analogous to angina pectoris, because both conditions are transient episodes that result from a temporary restriction of the blood supply to the heart or brain, respectively. Note that a heart/brain attack generally denotes a more serious condition wherein tissue death occurs, whereas angina/TIA denotes that tissue function is temporarily altered or impaired by a restriction in blood supply.

Improvements in magnetic resonance imaging (MRI) technology has led to the use of *diffusion* and *perfusion* MRI in the setting of acute cerebral ischemia. *Merriam Webster's Collegiate Dictionary* defines diffusion as the process whereby particles (liquid, gas, or solid) combine as the result of their spontaneous movement caused by thermal agitation. In the case of dissolved substances, diffusion is the movement from a region of higher to one of lower concentration. *Merriam Webster's Dictionary* defines perfusion as the "process of flowing or spreading through." In the context of MRI, perfusion generally refers to techniques that allow for the observation of blood flow (typically "tagged" with a contrast agent) through an organ; and diffusion refers to an imaging method that is used to assess the motion of water molecules on a minute level.

In this article the reader will become familiar with the use of diffusion and perfusion MRI in the setting

of acute cerebral ischemia or brain attack. Before we discuss diffusion and perfusion, a review of the available and evolving MRI technology, as well as advancements in imaging techniques is necessary.^{1,2} *Echo planar imaging* (EPI), *fast-spin echo imaging*, *turbo-spin echo imaging*, and *fast-gradient echo imaging* are some of these sequencing techniques.

ECHO PLANAR IMAGING (EPI)

The current techniques used for brain attack imaging are based on EPI. Conventional MRI collects the data for an image from a series of discrete signal samples. In contrast, the EPI method forms a complete image from a single data sample. EPI has the advantage of speed. For example, a typical T2-weighted imaging series requires that the time between excitation pulses, known as TR, be two to three times longer than the intrinsic tissue magnetization parameter, T1. The T1 of biologic samples takes approximately a second (although cerebrospinal fluid can have much longer T1's). TR must therefore be 3 seconds or more. Because a typical MRI is formed from 128 repeated samples, the imaging time for our T2-weighted scan is approximately 384 seconds, or more than 6.5 minutes. By comparison, the EPI approach collects data for an image of the same resolution in 40 to 150 milliseconds (depending on specific hardware and contrast considerations). Although there are many variations, EPI is essentially a trick of spatial encoding.

The EPI sequence is ideal for functional brain imaging because it is extremely sensitive to transient fluctuations in the local magnetic field (susceptibility) and can acquire data rapidly enough to permit very high temporal resolution (about one phase per second). A single acquired phase can consist of 8 to 12 slice locations, thus allowing for a reasonable sampling of cerebral territory.

DIFFUSION-PERFUSION MRI

The goal of brain attack imaging is usually to determine the age, character, and extent of an acute ischemic episode so that the appropriate treatment and/or intervention may be undertaken.^{3,4}

Diffusion-weighted imaging (DWI) is an EPI-based technique dependent on the random or *Brownian motion* of water molecules. Perfusion brain MRI is based on the principle of *dynamic susceptibility contrast* (DSC) imaging. In DSC imaging, a T2*-weighted EPI sequence

is acquired through portions of the brain in a multiphase scheme captured before, during, and after the rapid bolus injection of a paramagnetic gadolinium contrast agent. In the setting of acute cerebral ischemia, the two techniques are often grouped together and referred to as diffusion-perfusion MRI.

COMPARISON OF DIFFUSION AND PERFUSION TECHNIQUES

It is important to compare and contrast diffusion and perfusion techniques in order to understand the important role each application has in stroke imaging. Although both are based on EPI sequences, the structure and implementation of each is quite different.

Perfusion MRI is useful for acute stroke because this technique evaluates the blood flow in the brain's microvasculature (capillaries). Statistical information, such as *relative cerebral blood volume* (rCBV), *relative cerebral blood flow* (rCBF), and *relative mean transit time* (rMTT), can be calculated and/or extrapolated from the data provided by a perfusion MRI sequence.

Of the two techniques, DWI is more commonly used alone. DWI is based on principles similar to those employed in gradient flow compensation and phase-contrast magnetic resonance angiography (MRA). In a DWI sequence, the random movement (diffusion) of water molecules in different tissues is evaluated. This method is effective because structural and pathologic differences in brain tissue affect the local diffusion characteristics of water.

In normal cerebral gray matter, water molecule diffusion is random or *isotropic* (equal in all directions). White matter, however, consists of more structured fibers that permit free diffusion *along* the axes of the fibers, but exhibit restricted diffusion *across* the axes of the fibers. The *anisotropic* nature of white matter tracts poses an interesting but manageable challenge in DWI. To image the diffusion of the water molecules strong, symmetric, bipolar *diffusion-encoding* gradients are applied before and after a period of time known as the *B-value*. The B-value is the diffusion value expressed in seconds per square millimeter. The higher the B-value, the more sensitive the sequence becomes to local changes in diffusion. A typical range of clinically useful B-values is between 800 and 1500 s/mm².

To overcome the inherent diffusion anisotropy in white matter, diffusion images are acquired with gradients sensitized to diffusion in the three major orthogonal planes (right/left, anterior/posterior, superior/inferior). Some scanners allow for the images from the three individual diffusion axes to be reconstructed and viewed individually. Other scanners generate a reconstruction that mathematically combines the three diffusion axes into a single set of images that displays isotropic diffusion characteristics. These images are often referred to as isotropic or *trace DWI* images. These images overcome the anisotropy of white matter

by displaying only areas that exhibit restricted diffusion in all three axes (ie, pathology).

The interpretation of diffusion abnormalities on a DWI image is generally straight forward. On a simple, high-field B-value ($B = 800\text{-}1500\text{ s/mm}^2$) image, areas of restricted diffusion exhibit bright signal. In the setting of acute stroke, the area of infarcted tissue will have undergone changes at the cellular level. These changes cause a decrease in permeability of the cell membrane, thus restricting diffusion of water molecules within the insulted area. A typical DWI sequence on a high-field (1.0 T or greater) with high-performance gradients can be completed in under 1 minute. Although the spatial resolution of typical DWI scans is much less than that of routine MRI images (128 x 128 vs 256 x 192 matrices), the temporal and contrast resolutions are what is of true value. Much of the spatial resolution is sacrificed to allow for increased speed and to overcome limitations inherent to the core EPI sequence.

Now that the role of DWI in delineating infarcted tissue has been established, the importance of adding perfusion imaging to the work-up will be easier to understand. Early on, it was thought that the DWI sequence alone provided sufficient information for management of acute stroke patients. As perfusion imaging became more publicized and better understood, it became clear that the additional information provided by DSC imaging could affect the outcome and management of acute stroke. The key of DSC imaging is the inherent sensitivity of the T2*-weighted EPI sequence to magnetic susceptibility effects. The fact that these susceptibility effects could be induced locally and on a transient basis by the passage of a contrast bolus, coupled with the high temporal resolution of an EPI sequence, made perfusion imaging ideal for the evaluation of the brain in the setting of acute stroke.

The core competency of a perfusion scan is its ability to delineate already infarcted tissue areas as well as "at-risk" or ischemic areas surrounding the core of the infarct via time-relative flow and concentration information. The dynamic acquisition scheme inherent in this modality makes this possible. These surrounding at-risk areas are commonly referred to as the ischemic penumbra. These areas experience: (1) altered flow as a result of the spreading infarction, or (2) ischemia as a result of mechanical compression secondary to edema in the area of the infarction. It's also postulated that a biochemical process, equated to that of a wave effect, results in the infarct spreading into the penumbra region.

The information added by a perfusion scan, combined with the data provided by routine MRI sequences, can aid the clinician in determining the approximate age and extent of the event and if a hemorrhagic component exists. It is important to ascertain the presence of hemorrhage within an acute infarct because intervention with thrombolytic agents can exacerbate it.

A DSC sequence is intrinsically less complex than a DWI sequence. The DSC sequence does not employ

FIGURE 1. Understanding the Dynamic Susceptibility Curve

During a DSC perfusion scan, the passage of a bolus of gadolinium contrast agent is observed through the vasculature of the brain. During a typical bolus-tracking study, a single location is sampled (scanned) over a period of usually 30 to 60 seconds at a temporal resolution of at least one image every 1 to 2 seconds. From the scan data of this set, a graph can be generated that reflects the signal change in a region of interest (ROI) placed over an area of the image. This technique is often used to determine circulation time for body imaging using an ROI placed over the aorta. The graph that results is similar to the curve depicted in **Figure 1A**, wherein the horizontal axis represents time in seconds, the vertical axis represents relative enhancement, and each data point represents an image in the series.

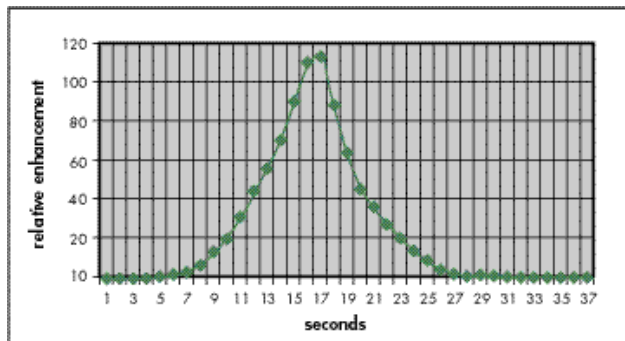


FIGURE 1A. Example of a Typical Aortic Enhancement Curve

The curve generated from a DSC perfusion acquisition differs from that in Figure 1A in that it reflects a negative relative enhancement due to the susceptibility-induced signal loss from the contrast bolus. A typical DSC curve might appear similar to that seen in **Figure 1B**. In this graph, the horizontal axis represents time in seconds and the vertical axis represents negative enhancement (or susceptibility enhancement); each data point represents a single image in the series.

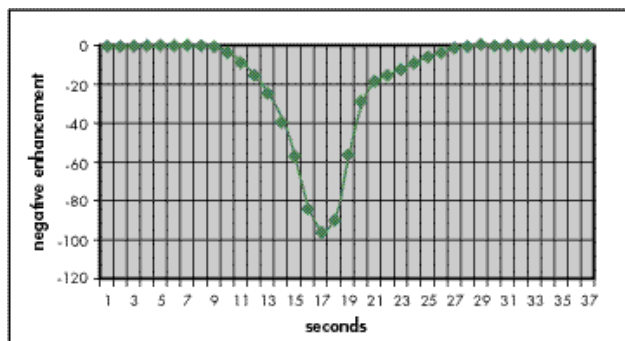


FIGURE 1B. Example of a Typical Normal DSC Perfusion Curve

During the dynamic susceptibility curve acquisition, the passage of the contrast bolus through the region of imaging causes a net drop in magnetic resonance signal. This is the susceptibility effect. The decrease in signal is proportional to the blood flow in the region sampled by the ROI. If an infarct has occurred in the right middle cerebral artery territory, then an ROI in the infarcted area should show no net decrease in signal. In the normal right middle cerebral artery territory, the drop would be observed. If an area of ischemia—the penumbra—is present, then a curve represented by an ROI in the area of ischemia might demonstrate a delay like that seen in **Figure 1C**.

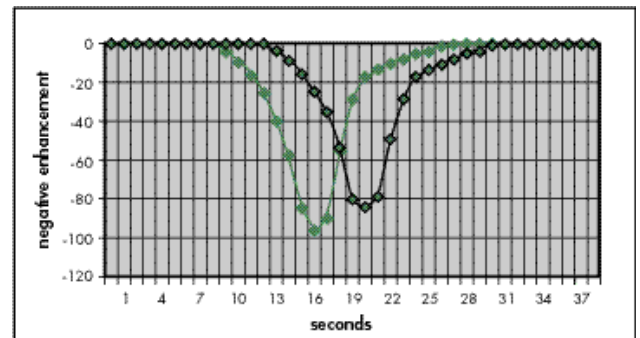


FIGURE 1C. Example of a Curve Displaying Delayed Enhancement

Note that the temporal dysplasia between the two curves has been exaggerated for the purposes of illustrating this point. Typically, the delay between the normal and ischemic tissue might be only several milliseconds. The delay in enhancement may be due to collateral blood flow supplying the area surrounding the infarcted tissue. A smaller degree of enhancement may also be demonstrated relative to the normal region as a result of the overall decrease in blood flow to the ischemic area. These phenomena all form the basis for the maps (rCBF [relative cerebral blood flow], rCBV [relative cerebral blood volume], and rMTT [relative mean transit time]) that help to delineate the penumbra area.

any diffusion gradients or have any B-values. The basic sequence used is a single-shot EPI sequence. Most of the literature suggests using an SE-based EPI sequence acquired over a range of 60 to 90 seconds. Most sequences use 10 to 12 slice locations of 5- to 6-mm thickness and 35 to 50 phases (acquisitions of each slice group). Again, spatial resolution is traded for reduced scan time and fewer EPI artifacts (spatial distortion). In most cases, the recommended dose of paramagnetic contrast agent is 0.2 mmol/kg (roughly double the typical dose). The agent is universally administered at a high flow rate (3-5 cc/sec) 10 to 12 seconds after scan initiation. Generally, an MRI-compatible injector such as the Spectris injector (Medrad, Inc., Pittsburgh) is to deliver a consistent flow rate that aids in maintaining the statistical integrity of post processed data. Simply stated, once the slice locations for the DSC scan are determined, the sequence is initiated and the contrast agent is injected at a predetermined delay time.

After the acquisition is completed, data is collected through post processing, starting with routine map generation. The first and simplest to generate is the relative cerebral blood volume map. This is essentially a mathematical integration of the *area under the curve* (AUC) of the susceptibility curve (Figure 1). This map corresponds to the relative volume of the cerebral capillaries and venules. From the rCBV, a second map, the rCBF, can be extrapolated. This rCBF map is somewhat more complicated in the MRI setting because the paramagnetic agent is not completely dispersible; so to correct for second- and third-pass effects, the calculation may require adding an arterial input function that adjusts for the level of contrast agent in the circulating arterial blood pool. The rCBF map is representative of the instantaneous capillary flow in the brain tissue. Through the combination of these maps (rCBV/rCBF), a third map can be calculated. The relative mean transit time (rMTT) map is a measure of the time that a given particle (contrast agent or blood) spends in the cerebral capillary circulation. Regional differences in the rMTT values can be indicative of delayed perfusion and/or perfusion resulting from collateral flow.

The physiologic data obtained from the DWI and DSC sequences, coupled with the anatomic and pathologic data collected from the routine MRI brain images, provides a considerable amount of information to the clinician for the management of the acute stroke patient. For infarcts less than 3 hours old, without a hemorrhagic component, treatment with thrombolytic agents resulted in an increase in 3-month functional outcome without an associated increase in mortality.⁵ It is worth mentioning that one author⁶ (Tievsky, A., MD) suggests that using a gradient echo-based EPI (GRE-EPI) sequence may have contrast-saving implications. This advantage is likely a function of the increased susceptibility/sensitivity of the GRE-EPI sequence. It is reasonable to expect that as a result of this increase in contrast-induced susceptibility,

a concomitant decrease in contrast dose (0.1 mmol/kg versus 0.2 mmol/kg) would be possible. This technique, however, was not described in detail by other authors.

MANAGEMENT IN THE ACUTE CARE SETTING

In a patient exhibiting acute stroke-like symptoms, expedience is critical. Although computed tomographic (CT) scanning with xenon cerebral blood flow (Xe-CT CBF) analysis has been deemed highly accurate, and CT screening is a quick study, MRI may potentially provide more information in about the same amount of time. Using standard MRI sequences, a patient with suspected acute stroke can be screened for tumor or hemorrhage in less than 10 minutes on most EPI-capable MRI scanners. If neither tumor or hemorrhage is present, DWI and DSC imaging can be performed; DWI takes less than a minute, and DSC takes about 1 to 2 minutes. In addition, post-contrast images may also be obtained in another 1 to 2 minutes, thus increasing the sensitivity of the MRI scan. It is important to note that while DWI and DSC are powerful tools for imaging of acute stroke, they alone cannot provide a full clinical picture. This is because both sequences are (1) highly specialized, and (2) have extreme spatial resolution limitations.

COMMON BRAIN ATTACK PROTOCOLS

Most brain attack protocols include a T2-weighted fast-spin echo series, a fluid-attenuated inversion recovery T2 series (FLAIR), and a T1-weighted spin echo scan in at least one plane. Some radiologists also find it valuable to include a standard resolution T2*-weighted gradient echo (MPGR or FLASH) sequence to take advantage of the series' susceptibility sensitivity in imaging blood and blood products such as methemoglobin and hemosiderin.

In centers where a brain attack protocol is in use, patients who fit candidate criteria for thrombolytic therapy must be triaged and imaged as quickly as possible. This approach ensures that if thrombolytic therapy is indicated, it can be commenced as soon as possible from the onset of symptoms. In patients with strokes more than 3 hours old, a statistical increase in hemorrhage resulting in mortality was noted when thrombolytic therapy was undertaken.⁵ This increased mortality is thought to be a result of the degradation of vessel wall integrity in infarcted tissue.

DIFFUSION-PERFUSION MRI IN THE OUTPATIENT SETTING

Regrettably, acute stroke imaging is of little benefit to the patient unless it is performed in a setting where prompt treatment is possible (eg, a hospital emergency room as opposed to an isolated outpatient imaging center). However, this does not preclude the use of DWI and DSC imaging in an outpatient setting. The clinical role of DSC perfusion imaging in patients with brain tumors and demyelinating and inflammatory disease is being explored. Because treatment for these pathologic pro-

cesses is not as time-dependent as it is for acute stroke, an outpatient setting may be suitable. Diffusion imaging may be useful for multiple sclerosis. Early findings suggest that active demyelinating plaques exhibit similar diffusion restriction to infarcted tissue, and, as such, may be imaged effectively. Though this technique is still being explored, its findings thus far appear promising.

CONCLUSION

The clinical ramifications of acute stroke intervention are indeed promising in terms of improved long-term patient function and reduction in stroke-associated morbidity. The role of MRI has expanded and become more integral to the early assessment, characterization, and qualification of acute stroke patients for thrombolytic therapy.^{7,8} As DWI and DSC become more widely available and accessible, the positive impact for patients who might otherwise suffer permanent neurologic impairment is hardly measurable by conventional means. To fully evaluate the advantages of the evolving technology of brain attack imaging, other salient issues, such as quality of life and the economics of long term care that is required by stroke patients, must be addressed. From the perspective of insurers, it would seem preferable to cover early diagnosis and treatment of stroke as opposed to the higher costs of chronic care. Although the techniques of perfusion and diffusion are still viewed with some skepticism, research and statistics seem to strongly support their utility in acute stroke imaging, and their relative ease and speed of performance make them a viable tool for the clinician.

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DIFFUSION AND PERFUSION MRI IN ACUTE STROKE IMAGING POST TEST

Expires: May 15, 2013 Approved for 1 ARRT Category A CE Credit

1. **Angina is often a warning signal of a heart attack. Conversely, a warning signal of a brain attack is**
 - a. a transient ischemic attack.
 - b. difficulty breathing.
 - c. chest pain.
 - d. frequent urination.
2. **Echo planar imaging (EPI) differs from conventional magnetic resonance imaging (MRI) in that**
 - a. it is much easier to use.
 - b. it can be done much quicker.
 - c. it uses ionizing radiation.
 - d. it does not use spatial encoding.
3. **Diffusion-weighted imaging (DWI) is an EPI-based technique that is dependent on random motion of**
 - a. gadolinium molecules.
 - b. the patient's heart.
 - c. the magnetic pulse.
 - d. water molecules.
4. **Perfusion MRI is advantageous for acute stroke patients because**
 - a. it is most commonly used alone.
 - b. it can evaluate the blood flow in the brain's microvasculature.
 - c. it does not require the use of EPI.
 - d. the principles are similar to those used in phase-contrast magnetic resonance angiography (MRA).
5. **In normal cerebral gray matter, water molecule diffusion**
 - a. is isotropic.
 - b. consists of structured fibers which permit free diffusion along the axes of the fibers.
 - c. consists of structured fibers which exhibit restricted diffusion across the axes of the fibers.
 - d. is anisotropic.
6. **Because of its more structured nature, _____ matter exhibits _____ diffusion characteristics on single axis diffusion scans and poses a challenge in DWI.**
 - a. gray; anisotropic
 - b. white; isotropic
 - c. gray; metatropic
 - d. white; anisotropic
7. **The B-value is expressed in**
 - a. mL/sec.
 - b. mm/min.
 - c. sec/mm².
 - d. min/cm³.
8. **A mathematical combination of diffusion scans acquired in three orthogonal planes is referred to as**
 - a. ADC maps.
 - b. rCBF map.
 - c. rMTT map.
 - d. isotropic or trace DWIs.
9. **The spatial resolution of typical DWI scans is**
 - a. 512 x 512.
 - b. inferior to that of routine MRI images.
 - c. roughly equal to routine MRI images.
 - d. superior to routine MRI images.
10. **Dynamic susceptibility contrast (DSC) imaging is**
 - a. always performed without contrast enhancement.
 - b. performed using a T1-weighted sequence.
 - c. based on an EPI pulse sequence.
 - d. not helpful in the assessment of acute stroke.
11. **The "at risk" tissue surrounding an area of infarcted tissue is called the**
 - a. nidus.
 - b. paraganglion.
 - c. penumbra.
 - d. the periscapsular zone.
12. **The dynamic susceptibility contrast (DSC) sequence**
 - a. is less complex than a DWI sequence.
 - b. has a minimum of three B-values.
 - c. employs a series of diffusion gradients.
 - d. uses a 1-mm slice thickness.
13. **Most commonly, DSC perfusion MRI is performed using a contrast dose of**
 - a. 0.05 mmol/kg.
 - b. 0.1 mmol/kg.
 - c. 0.2 mmol/kg.
 - d. 0.5 mmol/kg.
14. **When injecting gadolinium contrast agent for a DSC perfusion MRI, the contrast should be injected**
 - a. manually.
 - b. as soon as the scan is initiated.
 - c. at a low flow rate (0.4-0.8 cc/sec).
 - d. at a high flow rate (3-5 cc/sec).
15. **The initial and simplest map generated from a DSC scan is the**
 - a. rCBV map.
 - b. area under the curve (AUC).
 - c. rCBF map.
 - d. rMTT map.
16. **Which of the following is NOT post processed from a DSC perfusion MRI scan?**
 - a. rMTT map
 - b. rCBF map
 - c. ADC map
 - d. rCBV map
17. **Thrombolytic therapy has a high success rate when treatment is started**
 - a. within 3 hours of symptom onset.
 - b. within 8 hours of symptom onset.
 - c. within 12 hours of symptom onset.
 - d. no sooner than 24 hours after symptom onset.

- 18. On most scanners, perfusion and diffusion MRI scans can both be completed in**
- under 2 minutes.
 - under 10 minutes.
 - 10 to 20 minutes.
 - 25 to 35 minutes.
- 19. Thrombolytic therapy started after strokes older than 3 hours was associated with**
- an increase in patient functionality at 3-months post stroke.
 - a reduction in healthcare expenses.
 - an increased risk of hemorrhage.
 - a reduced mortality rate.
- 20. In addition to stroke imaging, DSC MRI shows potential for the imaging of**
- lesions of the bony calvaria.
 - abscesses with air-fluid levels.
 - demyelinating disease.
 - acoustic neuromas.



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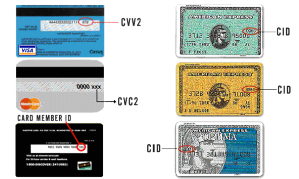
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