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THEME

Perfusion magnetic resonance imaging with continuous arterial spin labeling: methods and clinical applications in the central nervous system

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Abstract

Several methods are now available for measuring cerebral perfusion and related hemodynamic parameters using magnetic resonance imaging (MRI). One class of techniques utilizes electromagnetically labeled arterial blood water as a noninvasive diffusible tracer for blood flow measurements. The electromagnetically labeled tracer has a decay rate of T1, which is sufficiently long to allow perfusion of the tissue and microvasculature to be detected. Alternatively, electromagnetic arterial spin labeling (ASL) may be used to obtain qualitative perfusion contrast for detecting changes in blood flow, similar to the use of susceptibility contrast in blood oxygenation level dependent functional MRI (BOLD fMRI) to detect functional activation in the brain. The ability to obtain blood flow maps using a non-invasive and widely available modality such as MRI should greatly enhance the utility of blood flow measurement as a means of gaining further insight into the broad range of hemodynamically related physiology and pathophysiology. This article describes the biophysical considerations pertaining to the generation of quantitative blood flow maps using a particular form of ASL in which arterial blood water is continuously labeled, termed continuous arterial spin labeling (CASL). Technical advances permit multislice perfusion imaging using CASL with reduced sensitivity to motion and transit time effects. Interpretable cerebral perfusion images can now be reliably obtained in a variety of clinical settings including acute stroke, chronic cerebrovascular disease, degenerative diseases and epilepsy. Over the past several years, the technical and theoretical foundations of CASL perfusion MRI techniques have evolved from feasibility studies into practical usage. Currently existing methodologies are sufficient to make reliable and clinically relevant observations which complement structural assessment using MRI. Future technical improvements should further reduce the acquisition times for CASL perfusion MRI, while increasing the slice coverage, resolution and stability of the images. These techniques have a broad range of potential applications in clinical and basic research of brain physiology, as well as in other organs.

Keywords: Continuous arterial spin labeling; Neuroimaging; Perfusion MRI; Quantitative blood flow maps

1. Introduction

Several methods are now available for measuring cerebral perfusion and related hemodynamic parameters using MRI. One class of techniques utilizes electromagnetically labeled arterial blood water as a non-invasive diffusible tracer for blood flow measurements, in a manner analogous to that used for ^{15}O positron emission tomography (PET) scanning [1]. This method is schematically illustrated in Fig. 1. The electromagnetically labeled tracer has a decay rate of T1, which is sufficiently long to allow perfusion of the tissue and microvasculature to be detected. Because water is a diffusible tracer, blood flow can be quantified in well characterized physiological units of ml/100 g/min using this approach. Alternatively, electromagnetic

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arterial spin labeling (ASL) may be used to obtain qualitative perfusion contrast for detecting changes in blood flow, similar to the use of susceptibility contrast in blood oxygenation level dependent functional MRI (BOLD fMRI) to detect functional activation in the brain [2–5].

A variety of studies in both animal models and human subjects have demonstrated that blood flow can be accurately quantified using ASL [1,6–11]. Such quantitative measurements of regional perfusion were previously obtainable only with exogenous tracer methods and ionizing radiation using positron emission tomography (PET), single photon emission computed tomography (SPECT) or xenon enhanced X-ray computed tomography (XeCT). The ability to obtain blood flow maps using a non-invasive and widely available modality such as MRI should greatly enhance the utility of blood flow measurement as a means of gaining further insight into the broad range of hemodynamically related physiology and pathophysiology.

Using electromagnetically labeled arterial water as a tracer for measuring perfusion can be thought of as a standard diffusible tracer method as originally described by Kety [12]. Tissue water is in constant exchange with blood water flowing through capillaries and venules. ASL applied proximal to the tissue of interest is used to modulate the magnetization of the protons in the arterial water. Due to the constant exchange of water between blood and tissue compartments, proximal ASL alters the total magnetization in the distal tissue. The extent of this alteration is determined by comparison with images acquired with control labeling that does not modulate the magnetization of arterial water. With an additional knowledge of the regional T1 of tissue, quantitative blood flow maps can be generated [6].

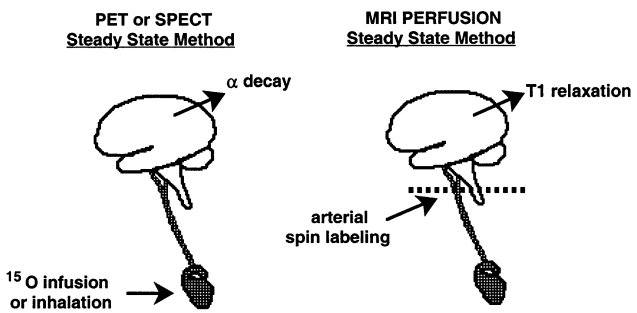

Fig. 1. Schematic diagram illustrating CASL in comparison to steady-state nuclear medicine approaches. In the nuclear medicine approach, a radioactive tracer is administered at a constant rate, resulting in a constant arterial concentration. Regional tissue blood flow can then be calculated based on the regional tracer concentration in the tissue determined by imaging, the arterial concentration of the tracer and a knowledge of the decay rate of the tracer. In CASL perfusion MRI, the arterial supply is continuously inverted, producing a known degree of arterial labeling. The regional accumulation of the label is measured in the tissues by comparison with a control image acquired without labeling. The decay rate for the tracer is the measurable quantity, T1.

This article will describe the biophysical considerations pertaining to the generation of quantitative blood flow maps using a particular form of ASL in which arterial blood water is continuously labeled, termed continuous arterial spin labeling (CASL). This approach has been chosen because it maximizes the sensitivity of the method to blood flow [13] and is most readily quantified. In addition, a variety of applications of CASL perfusion MRI to central nervous system disorders will be described. Studies of cerebral blood flow (CBF) are likely to have clinical utility in diagnosing and managing many central nervous system disorders. Because flow can be quantified directly, this approach is also ideal for comparison of resting cerebral blood flow across patient groups or before and after pharmacological interventions. However, the general principles of ASL and CASL are not limited to studies of the brain, and are likely to have a broad range of applications in other tissues as well.

2. Methodological considerations for CASL perfusion MRI

Over the past few years, theoretical and methodological developments have done much to improve the accuracy and reliability of perfusion quantification with ASL. Recently a quantitative validation of CASL perfusion MRI with arterial spin labeling by comparison with ^{15}O PET measurements of CBF was reported by Ye et al. [14]. This study was carried out in 12 volunteers and demonstrated an excellent correlation both in perfusion contrast and in quantitative CBF values across modalities.

2.1. Continuous arterial inversion

CASL was the first method used for ASL imaging of perfusion [6]. CASL can be implemented either with pseudo-continuous saturation or by flow driven adiabatic inversion [15,16]. Since inversion produces twice the signal of saturation, it is generally preferred. Adiabatic inversion is achieved by applying a constant magnetic field gradient and a constant radiofrequency (RF) irradiation at a frequency determined by the desired inversion plane, as illustrated in Fig. 2. Simulations and experimental data indicate that flow driven inversion is quite efficient over a physiologically relevant range of velocities [17]. Adiabatic inversion is relatively simple to implement, but it has certain disadvantages. Many MR scanners use pulsed radiofrequency (RF) amplifiers which cannot be operated continuously, though continuous RF can be closely approximated by using multiple shorter pulses spaced closely together. The continuous

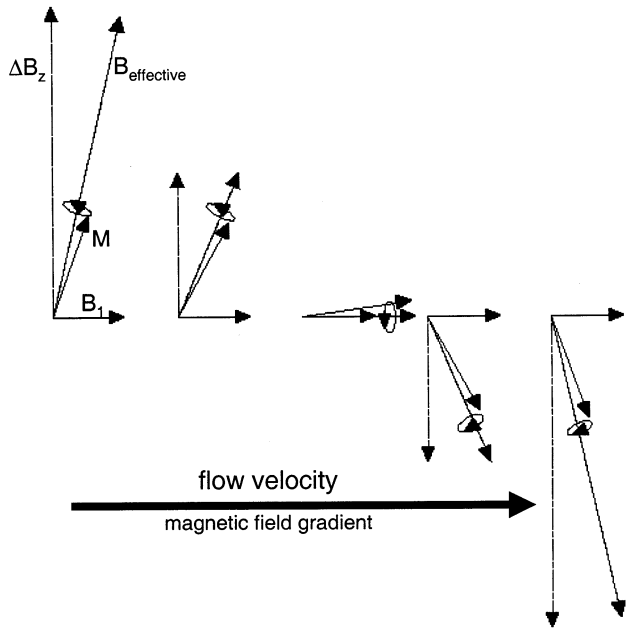

Fig. 2. Schematic diagram illustrating velocity driven adiabatic inversion used for CASL. Blood flowing along the direction of a magnetic field gradient in the presence of constant or pseudo-constant radiofrequency (B_1, gray arrow) experiences a frequency sweep. The diagram shows changes in magnetization in the rotating frame of the applied radiofrequency. As long as the conditions for adiabatic fast passage are met, the magnetization (M, black arrow) follows the $B_{\text{effective}}$ (dotted arrow) until it is inverted.

irradiation can also deposit significant RF power into the subject which may be limiting as CASL is implemented at higher magnetic fields, though human perfusion scans at 1.5 T can be performed within standard safety guidelines for RF deposition. The greatest complication of adiabatic inversion labeling is the off-resonance saturation of the imaged tissue by labeling RF [18]. Since the effects of CASL on distal image intensity can only be measured in comparison to a control labeling condition, off-resonance effects of the control labeling condition must be identical.

2.2. Off-resonance effects and multislice CASL

Due to magnetization transfer, off-resonance RF in biological tissues causes a decrease in both signal and T1 [19]. In the original implementations of CASL perfusion MRI, control images were acquired with labeling applied an equal distance distal to the perfusion imaging slice by reversing the frequency offset of the RF [9]. Because off-resonance saturation is highly symmetric with frequency, this largely controls for differences in off-resonance saturation. Cycling of the gradient amplitude was additionally proposed as a method to remove residual errors due to small asymmetries in the off-resonance response [20]. Unfortunately, the distal control method works for only one slice parallel to the labeling plane and at an intermediate location between ASL and control labeling. An additional complication of off-resonance saturation is that both the T1 and resting magnetization of the brain tissue (M_b^0) are reduced, which decreases the observed signal, affecting quantification and reducing the signal-to-noise ratio. For correct quantification, T1 should be measured while the RF irradiation is on, but M_b^0 should be measured in its absence [13]. Usually the reverse is done, but since the ratio of M_b^0 to 1 in tissue is usually independent of off-resonance saturation [13,21], quantification is unaffected.

To allow multislice imaging, several approaches to circumventing the off-resonance limitations have been proposed. A hardware approach using a separate coil placed proximal to the image slice to label arterial spins while a second volume coil is used for imaging was proposed by Silva et al. [8], and implemented for imaging of the rat. With active decoupling between the two coils, the labeling coil produces negligible RF power in the imaged tissue so off-resonance saturation is virtually eliminated. While this approach is highly successful in the rat, the extra hardware requirements can be cumbersome for human applications and it can restrict the physical location of ASL. The second coil must be large enough to produce sufficient RF at the vessels for inversion while remaining small enough and distant enough to produce negligible RF in the imaged area. A two coil implementation for human perfusion imaging has been reported [22] but the labeling efficiency has not yet been optimized.

A single coil approach to controlling for off-resonance effects utilizes an alternative control irradiation which mimics the frequency dependent off-resonance effects of the labeling pulse. The control is an amplitude modulated version of the labeling [23]. When a constant RF irradiation at a fixed frequency, f_0, is multiplied by a sine wave at frequency f_1, the signal produced is mathematically identical to continuous irradiation at two different frequencies, f_0+f_1 and f_0-f_1. The combined effect is that spins will be inverted twice, resulting in no net effect. This is illustrated in Fig. 3. Because the average power and center frequency of the amplitude modulated control are identical to the labeling RF irradiation, the off-resonance effects of the control are nearly identical to those of the labeling. This frequency independent matching of the off-resonance of labeling and control pulse makes multislice CASL readily possible. In addition, as with the two coil approach, the orientation of perfusion images is no longer restricted to a plane parallel to the ASL plane. For clinical applications, a multislice technique is highly desirable both to increase coverage through the brain and because it is not always possible to know which slices are of interest prior to scanning. The extension of ASL MRI to a multislice modality has

been a major technical advance which has greatly increased the feasibility of clinical use.

2.3. Motion effects

ASL perfusion imaging involves the subtraction of two images with signal intensities differing by only a few percent or less. Motion between scans can therefore potentially lead to large errors in the measured perfusion. Single excitation imaging techniques such as echoplanar imaging [24] have helped to dramatically reduce motion related errors. Using echoplanar imaging, motion is rarely a problem except with the most uncooperative subjects. Single excitation imaging reduces motion errors in two ways. First, individual images are free from the nonlocal phase artifacts that motion can produce in multi-excitation images. Second, label and control images can be interleaved on the time scale of seconds. This rapid interleaving acts to attenuate the low frequency components of motion and other spurious signals which tend to be much larger than the higher frequencies [25]. Echoplanar imaging itself does suffer from geometric distortion and chemical shift artifacts. Recently single shot rapid aquisition with relaxation enhancement (RARE) sequences have been evaluated for ASL perfusion imaging [26] and show promise.

2.4. Vascular transit time errors

The ASL label decays with T1, approximately 1 s at 1.5 T, permitting far greater time resolution than with any other perfusion imaging technique. While this property is advantageous for brain activation studies, it can be limiting in efforts to measure extremely low

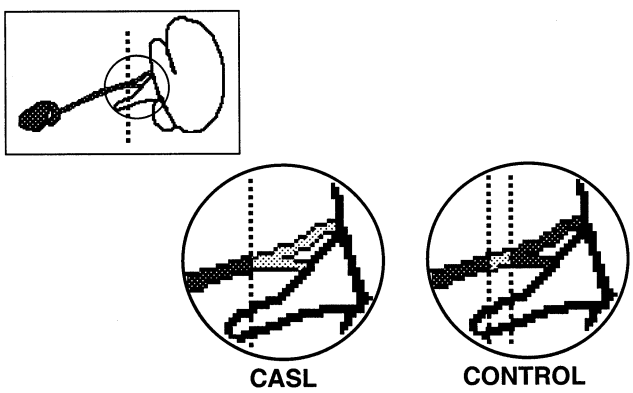

Fig. 3. Illustration of the amplitude modulated control for CASL. The figure shows changes in magnetization from a region magnified as indicated in the inset. CASL (left) results in inversion of arterial spins. The amplitude modulated control pulse (right) is effectively two inversion pulses which invert and then immediately 'uninvert' the arterial spins. While the efficiency of uninversion is not 100%, the spatial distribution of the radiofrequency power is identical to that of the CASL condition, allowing multislice imaging in any orientation.

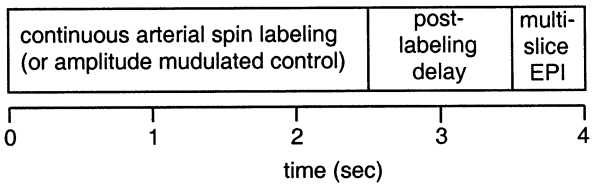

Fig. 4. Schematic diagram illustrating the introduction of a post-labeling delay in the pulse sequence. The duration of this delay is chosen to minimize transit effects while preserving sufficient spin labeling to visualize perfusion. Delays of 900–1500 ms are typically used.

flow, particularly as it is typically associated with long arterial transit times. Considerable evidence also suggests that microvascular transit times are highly variable both anatomically and under varying physiological conditions. The arterial transit time can have important effects on the measured signal and consequently on flow quantification. Our recent studies demonstrate large changes in arterial transit time with functional activation in the brain [27] and that arterial transit times vary anatomically.

Because of the close similarity between the T1 of blood and the T1 of brain tissue, especially gray matter, transit time errors can be largely eliminated using a slight modification of the basic CASL experiment. If T1 is similar in blood and tissue, then as long as the label ultimately ends up in the image the precise time that labeled spins spend in blood or tissue can be neglected. The transit time error can then be viewed as an uncertainty in how much of the labeled blood remains in the feeding arteries outside of the tissue rather than in the tissue. If one waits long enough after the labeling for all of the labeled blood to enter the tissue, no transit time related errors will occur. In practice, this involves introducing a delay between labeling and image acquisition [13], as illustrated in Fig. 4. An added benefit of the post-labeling delay is that off-resonance effects are markedly reduced.

The selection of the duration of the post-labeling delay is governed by the competing interests of allowing most of the labeled spins to reach the tissue from the labeling plane while at the same time avoiding the wholesale loss of label due to T1 decay. Our studies in normal subjects suggest that a post-labeling delay of around 1 s is adequate [13], while for patients with cerebrovascular disease and consequently prolonged arterial transit times, a post-labeling delay of at least 1.5 s is required [28].

2.5. Vascular volume errors

A source of error that is closely related to transit time errors is that induced by residual signal from labeled spins located within arterial vessels. Signal in larger vessels can degrade the spatial resolution and

image quality by introducing bright linear or point-like artifacts in the perfusion images. The methods discussed above for eliminating transit time sensitivity also eliminate vascular volume signal because they allow the labeled blood reach the tissue. However, it is difficult to verify that there is no residual label in smaller vessels which are too small to produce gross artifacts or degrade resolution. Indeed, it may be too stringent to require that the all of the signal be in the tissue since this would mandate an extremely long post-labeling delay that severely reduces the sensitivity of the measurement. Theoretical analyses using two transit times, one from the labeling plane to vessels within the image which are too small to degrade image resolution and a longer one to the tissue itself, suggest that labeled signal in small vessels need not degrade quantification [13]. It is nonetheless important to minimize any aspects of the imaging sequence which might differentially affect arterial blood and tissue spins. These aspects include T2 weighting, since arterial blood T2 is approximately twice that of brain, and flow attenuation as might be introduced by strong bipolar gradients. Strong bipolar gradients have previously been used to eliminate the large vessel vascular volume artifacts in perfusion sensitive images without post-labeling delays [9,29].

Fig. 4 shows an example of multislice CASL perfusion MRI from a normal volunteer obtained using the amplitude modulated control. In this case, a fractional echo imaging scheme was used to increase the number of slices which could be acquired before decay of the ASL, though much of our clinical data has been acquired from a lesser number of slices using full echo imaging. Images shown in Fig. 4 were acquired with a repitition time (TR) of 4 s, an echo time (TE) of 12 ms, an acquisition time per image of 40 ms and a post-labeling delay of 1000 ms for the inferior-most slice. The matrix is 64×40 in a 24×15 cm field of view with a slice thickness of 5 mm. Image acquisition took 6 min (45 averages).

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3. Results of clinical applications of CASL in the central nervous system

3.1. Cerebral perfusion in acute stroke

Since hypoperfusion is the proximate cause of all stroke, it is an obvious application for perfusion imaging methods. The measurement of cerebral perfusion using MRI, in combination with diffusion MRI, is becoming an important part of the evaluation of acute stroke. These data are used to confirm the diagnosis of stroke, to establish a baseline against which stroke therapies can be assessed, and to contribute to prognosis. Most perfusion studies in acute stroke have utilized a bolus-tracking approach in which the first passage of an MRI contrast agent is imaged dynamically. Such data can be analyzed to yield maps of mean transit time and blood volume which are related to perfusion. Although the bolus tracking method provides relatively high signal-to-noise for perfusion abnormalities, its successful implementation requires administration of contrast through a large bore intravenous catheter, often with a power injector. The cost of the contrast agent can also represent a considerable expense, particularly if multiple repeated measurements are desired. CASL perfusion MRI provides a means of noninvasively quantifying cerebral perfusion in the acute setting and is ideal in instances where intravenous access is difficult to obtain or where serial perfusion measurements are required, Fig. 5.

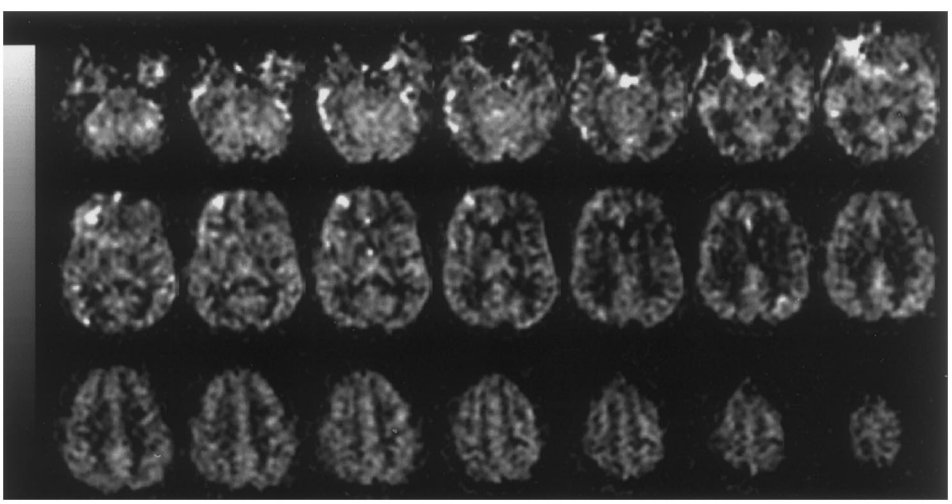

Fig. 5. Example of a multislice perfusion map acquired from a normal volunteer using a post-labeling delay of 1 s and a fractional echo echoplanar imaging scheme which allows up to 24 slices to be acquired within 1 s. The grayscale shows CBF ranging from 0–150 ml/100 g/min.

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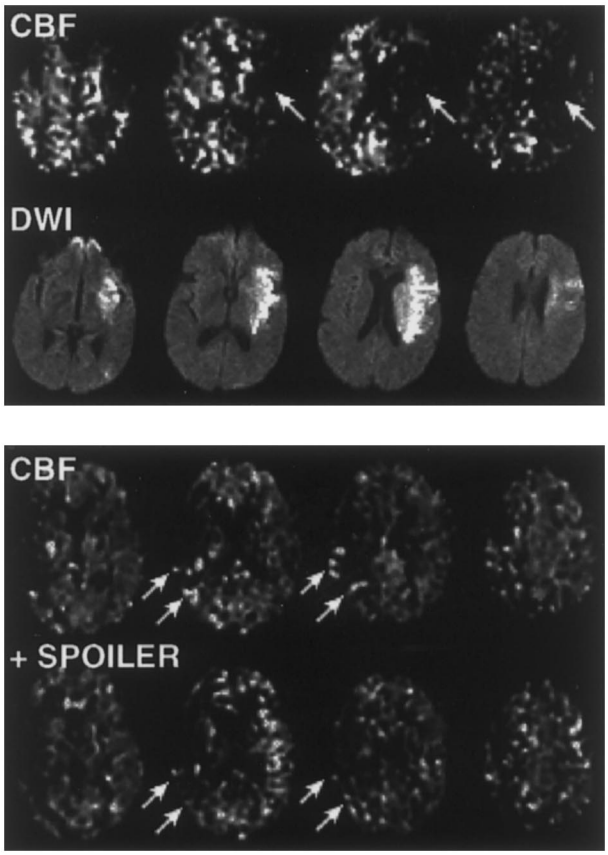

Fig. 6. CASL perfusion MRI data acquired from patients presenting with acute stroke. (Top) Data acquired from a patient presenting with acute right hemiparesis and aphasia. A large perfusion deficit is visible in the left middle cerebral artery distribution (arrows). Diffusion weighted imaging obtained concurrently shows a smaller volume of ischemic change in the same vascular distribution. (Bottom) Data illustrating transit effect acquired from a patient presenting with acute left hemiparesis found to have right middle cerebral artery occlusion. Within the perfusion deficit in the right middle cerebral artery distribution, bright linear features are present due to intraluminal spins with arterial transit times exceeding the 1.5-s post-labeling delay (arrows). These are markedly attenuated following the application of spoiler gradients to dephase coherently flowing spins, confirming an intraluminal origin. Images are in radiological orientation, with the left hemisphere shown on the right.

Interpretable data has been acquired from numerous patients with acute stroke studied using CASL perfusion MRI. Focal perfusion deficits corresponding to the vascular distribution of patients' symptoms were usually observable with the exception of patients who had received intravenous tissue plasminogen activator (rt-PA) for treatment of acute stroke several hours prior to the MRI scan. The absence of perfusion deficits in such patients presumably reflects successful restoration of cerebral perfusion by this therapy. Perfusion deficits observed in patients using CASL have ranged from small focal deficits of a similar size to diffusion lesions, to large deficits extending well beyond the diffusion lesion. An example of this is shown in Fig. 6 (top). In some instances, bright linear features were present in CASL perfusion MRI scans, suggesting effects of delayed arterial transit. This was confirmed by alterations of these features following the application of spoiler gradients, as shown in Fig. 6 (bottom).

While ASL methods are sensitive to arterial transit effects, it remains possible to identify areas of hemodynamic compromise and transit effects themselves may provide diagnostically relevant information. Because ASL techniques signal average CBF over brief (4–8 s) intervals, they may be less susceptible to motion effects than dynamic methods which fit data acquired over approximately 1 min.

3.2. Cerebral perfusion in chronic cerebrovascular disease

While embolism rather than primary hypoperfusion has recently been considered to be the cause of most cerebrovascular symptoms, patients presenting with stroke, transient ischemic attack (TIA) or severe carotid stenosis may have clinical features suggesting hypoperfusion as the primary etiology of their symptoms. Our initial studies using CASL perfusion MRI in such a cohort suggest that resting perfusion abnormalities are indeed prevalent [28]. In our experience, abnormalities in cerebral perfusion are commonly observed in patients with high grade stenotic lesions of the cerebral vasculature both intracranially and extracranially. These findings are consistent with other reports in which cerebral perfusion or perfusion reserve were correlated with the presence of extracranial stenoses of the carotid arteries [30–33]. Although most studies have failed to clearly implicate primary hypoperfusion as a cause of large vessel stroke, hypoperfusion has been found to be predictive of recurrent stroke [34–36]. This discrepancy has begun to be reconciled through the hypothesis that hypoperfusion may influence the outcome from cerebral embolization [37]. This hypothesis, if true, suggests an increasingly important role for perfusion imaging in predicting cerebrovascular ischemia, particularly in situations of increased embolization such as cardiovascular surgery.

In several patients with reduced blood flow and hemispheric asymmetries, T2-weighted structural imaging has also revealed asymmetries in white matter signal intensities, suggesting internal borderzone ischemia. Anterior and posterior cortical watershed infarcts occurring at the interface between anterior and middle cerebral artery and/or middle and posterior cerebral artery territories represent the most widely recognized structural correlate of hemodynamic infarction (typically due to global hypoperfusion). However, a number of studies have suggested that white matter infarcts at the terminal distributions of vessels, so-called 'internal borderzone' infarcts, may be a more common conse-

quence of hypoperfusion [38,39]. While borderzone infarctions have clearly been associated with reduced systemic perfusion, the contribution of this mechanism to overall stroke incidence was thought to be low. However, the presence of borderzone ischemic changes in patients presenting with TIA carries an extremely poor prognosis [40].

Under non-pathological conditions, CBF is maintained over a broad range of perfusion pressures [41]. This property of the cerebrovascular system is termed 'autoregulation'. Because autoregulatory mechanisms in the cerebral vasculature can maintain CBF through vasodilatation, it has been suggested that CBF alone is an inadequate measure of hemodynamic compromise [42]. While resting reductions in perfusion are clearly abnormal, alterations in hemodynamic reserve are also significant because they suggest that the autoregulatory capacity of the cerebral vasculature may be exhausted. In the absence of intact autoregulation, cerebral perfusion becomes dependent on arterial blood pressure. Cerebrovascular reserve is tested by measuring the increase in CBF induced by carbon dioxide inhalation or acetazolamide administration ('cerebrovascular reactivity'). A number of studies have demonstrated that cerebrovascular reserve impairment is particularly significant in patients with borderzone ischemia [43,44] and that abnormalities in augmentation are predictive of stroke [35,36,45]. Perfusion MRI provides a convenient method for quantitatively and non-invasively measuring the effects of pharmacological augmentation throughout the brain. An example of CASL perfusion MRI obtained before and after intravenous acetazolamide is shown in Fig. 7 and demonstrates impaired cerebrovascular reserve in the vascular distribution of a right middle cerebral artery stenosis.

3.3. Cerebral perfusion in degenerative disease

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Functional imaging studies of Alzheimer's disease (AD) and frontotemporal dementia (FD) with PET and SPECT have demonstrated specific deficits in metabolism and flow in cortical association areas that are characteristic for the type of dementia. Structural MRI has also been used to quantify hippocampal and cortical atrophy. CASL perfusion MRI in conjunction with structural MRI offers the possibility of obtaining both functional and structural information during a single scanning session. Sandson et al. [46] have reported an initial evaluation of single-slice qualitative pulsed ASL imaging for functional studies of AD. They were able to detect temporoparietal flow deficits relative to controls.

We have evaluated multislice CASL perfusion MRI in a cohort of 14 patients with AD and 11 patients with FD as determined by clinical criteria. Statistical comparison of CBF and gray matter density across subjects was possible because of brain registration. We used a modification of the methods of statistical parametric mapping (SPM; Wellcome Institute of Cognitive Neurology) to perform statistical analysis of the three-dimensional dataset to assess both the significance and the magnitude of the group differences. Our between group analysis consisted of comparing CBF in the two dementias with nine normal elderly controls. An F statistic for group differences was calculated on a pixel by pixel basis and then converted to an approximate z

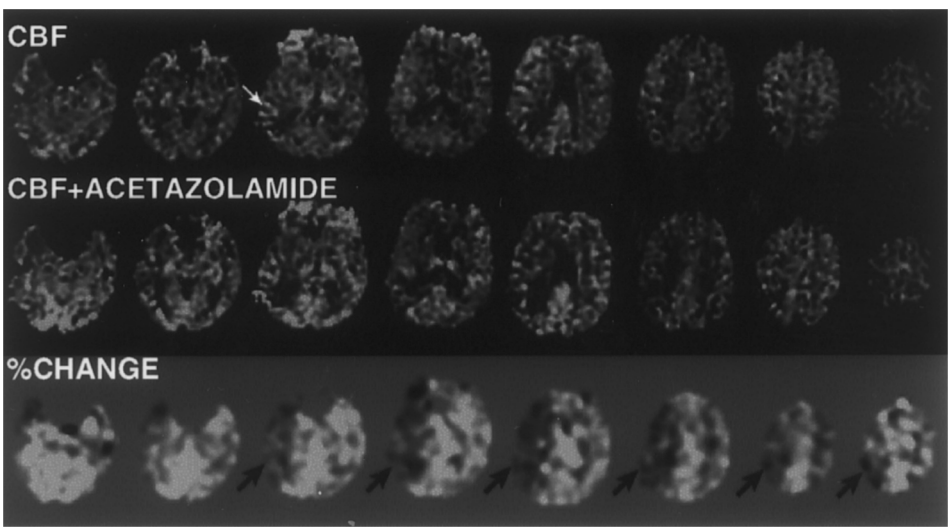

Fig. 7. Effect of acetazolamide challenge in a patient with right middle cerebral artery stenosis. Resting CBF (top row) appears symmetrical, though some transit effect is observed in the right middle cerebral artery distribution (arrow). Following 1 g intravenous acetazolamide, flow is increased everywhere except in the right middle cerebral artery distribution (middle row). This is best observed in the percent change map (bottom row) in which a reduction of flow in the right middle cerebral artery distribution is observed, indicating an impaired hemodynamic reserve. Images are in radiological orientation.

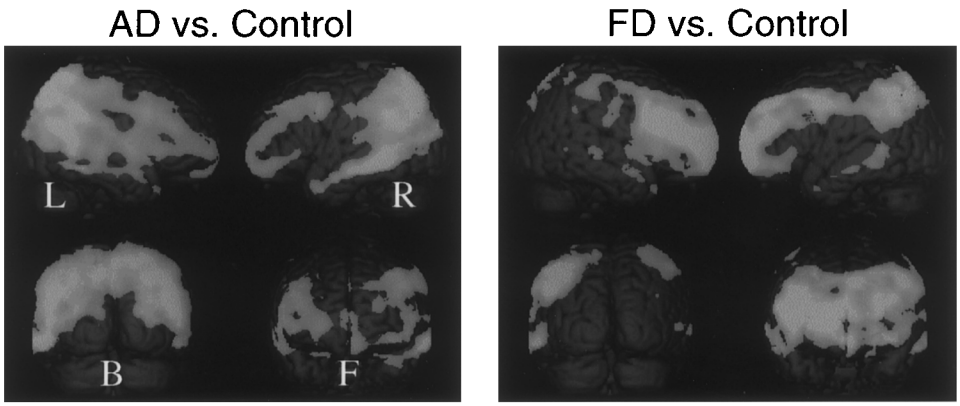

Fig. 8. Statistical maps showing regional reductions in CBF in patients with dementia as compared to age-matched controls. Regions with significant cortical flow reductions are superimposed upon a surface rendered brain in a standard space. (Left) Patients with Alzheimer's disease (AD) show prominent temporoparietal flow changes with lesser changes frontally. (Right) Patients with frontal dementia (FD) show more widespread flow reductions frontally, though parietal flow changes are also observed. Orientation of the maps is indicated as left (L), right (R), front (F) and back (B).

statistic. To permit intuitive display of the three-dimensional data, surface projections on a rendered three-dimensional brain was used. The z scores along the projection line were integrated over the 3 cm closest to the surface. The integrated values were corrected for the correlations induced by the 10 mm smoothing and remapped to z scores. Projection was performed for all voxels above a threshold of $P < 0.05$ after correction for multiple voxel comparisons.

CBF in Alzheimer's patients demonstrated very significant deficits bilaterally in parietal temporal, frontal and posterior cingulate cortex (Fig. 8, left). In contrast, CBF deficits in frontotemporal dementia occurred in the anticipated frontal and anterior temporal regions as well as superior parietal cortex (Fig. 8, right). Since little pathology has been reported in superior parietal cortex in FD, low flow in this region may represent a diaschisis phenomenon brought on by destruction of closely connected frontal association cortex. Initial analysis of a very mildly demented cohort indicate a similar pattern of flow deficits but with reduced amplitude.

By correlating changes in regional cerebral perfusion with cognitive task performance, it is possible to identify brain regions in which significant perfusion abnormalities are associated with specific cognitive deficits. Statistical analysis was also performed to compare the flow decreases in the AD patients with the nature and severity of their cognitive dysfunction. Correlations with several measures were very significant. The mini-mental state exam score (MMSE) correlated most strongly with left temporoparietal junction and posterior cingulate CBF, as illustrated in Fig. 9. Dorsolateral prefrontal cortex was also significant. The strong laterality of this measure, given the bilateral average flow decrease in the patients is notable. This approach represents a method of functional imaging that yields task-specific patterns of functional abnormality. However, since only resting perfusion is measured, the interpretation of the imaging data is not confounded by task performance.

3.4. Cerebral perfusion in temporal lobe epilepsy

Epilepsy is among the most common neurological disorders, affecting approximately 1% of the population. The most common seizure type in adults with medically intractable epilepsy is complex partial seizures, typically arising from the temporal lobe. Temporal lobectomy has been validated as a highly effective treatment for temporal lobe epilepsy (TLE). The success of resection of mesial temporal structures corre-

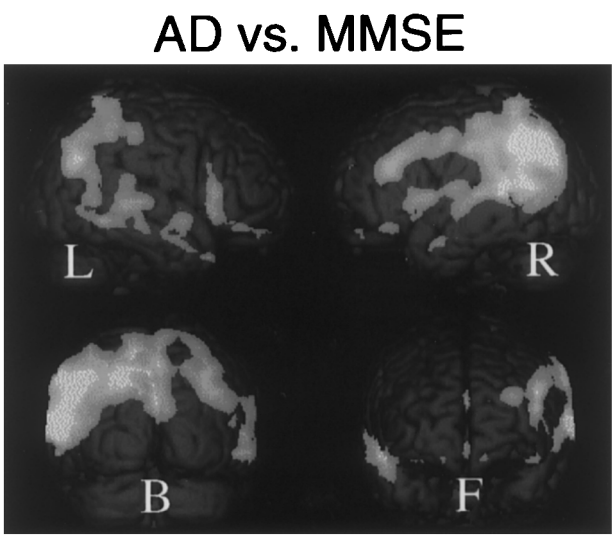

Fig. 9. Correlation of CBF changes with task performance on the mini-mental status examination (MMSE) in patients with Alzheimer's disease. Left hemispheric changes correlate prominently with poor performance on the MMSE, which is primarily a verbally based test.

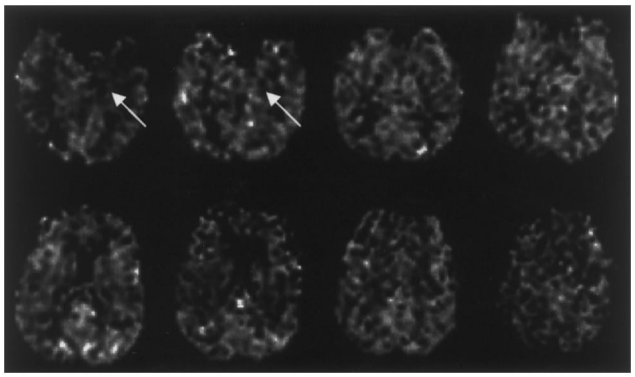

Fig. 10. CASL perfusion MRI in a patient with left temporal lobe epilepsy, showing subtle hypoperfusion in left mesial temporal structures (arrows). Images are in radiological orientation.

lates with the extent of resection as well as abnormalities in functional activity in this tissue.

Lateralization of TLE is predicted by interictal hypometabolism using fluorodeoxyglucose PET (FDG-PET) [47]. The presence of interictal abnormalities on PET or SPECT scanning [48,49] has also been associated with an improved outcome from epilepsy surgery. In some studies, uncoupling of CBF and metabolism has been demonstrated in the resting state [50,51], with FDG-PET showing better lateralization than ^{15}O PET measurements of CBF.

CASL perfusion MRI can successfully detect interictal asymmetries in mesial temporal lobe (mTL) perfusion in patients with TLE. It is readily combined with routine structural assessment and offers an inexpensive and completely non-invasive means of screening for asymmetries in interictal mesial temporal lobe (mTL) function, providing information using magnetic resonance which is complementary to structural imaging and metabolite levels measured by ^{31}P and ^{1}H NMR spectroscopy. In our preliminary experience in patients with TLE, there was reasonably good agreement between lateralized temporal lobe hypoperfusion observed using CASL perfusion MRI and both clinical laterality and PET hypometabolism. Lateralization by CASL and FDG-PET showed complete agreement in nine of ten patients studied in our initial series, based on a region of interest analysis of mTL structures. An example of left mTL hypoperfusion demonstrated by CASL perfusion MRI is shown in Fig. 10.

4. Conclusions

Over the past several years, the technical and theoretical foundations of CASL perfusion MRI techniques have evolved from feasibility studies into practical usage. Future technical improvements should further reduce the acquisition times for CASL perfusion MRI, while increasing the slice coverage, resolution, and stability of the images. However, currently existing methodologies are sufficient to make reliable and clinically relevant observations which complement structural assessment using MRI. Because tissue perfusion is a fundamental physiological process and is affected in a broad range of pathophysiological disorders, these techniques have a broad range of potential applications in clinical and basic research of brain physiology, as well as in other organs.

THEME

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