MR Perfusion Imaging in Moyamoya Syndrome
Potential Implications for Clinical Evaluation of Occlusive Cerebrovascular Disease

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Background and Purpose—Ischemic symptoms in patients with moyamoya syndrome (MMS) are usually due to hemodynamically mediated perfusion failure, and identification of abnormal tissue perfusion in these patients is therefore clinically important. Although dynamic susceptibility contrast (DSC) MRI can be used to study tissue perfusion, there are potential technical problems in MMS. This study investigates the scope and limitations of perfusion MRI in the clinical evaluation of such patients.

Methods—Thirteen patients with bilateral MMS were studied with the use of structural, diffusion, and perfusion MRI. The DSC MRI data were analyzed both visually and by a quantitative regional analysis, and the relationship between perfusion status and clinical symptoms was investigated.

Results—Extensive bilateral DSC MRI abnormalities were observed in all the patients. There was a very heterogeneous distribution of bolus arrival time. The areas of abnormality included the major arterial border zones in all cases, although these usually appeared normal on structural and diffusion MRI. Only the most clinically unstable patients had peak width (defined as time to peak minus bolus arrival time) >5 seconds on the quantitative regional analysis. Several technical limitations of perfusion quantification in MMS are described, as well as the implications of these limitations in patients with other forms of occlusive large-vessel disease.

Conclusions—The technical limitations of DSC MRI described in this study are important for the accurate interpretation of perfusion MRI in MMS. Despite these limitations, these preliminary findings suggest that the use of quantitative regional analysis of summary parameters may provide clinically useful information in patients with MMS. (Stroke. 2001;32:2810-2816.)

Key Words: cerebral ischemia ■ hypoperfusion ■ moyamoya disease ■ perfusion ■ stenosis

Moyamoya syndrome (MMS) is an angiographically defined cerebrovascular disorder with terminal internal carotid artery (ICA) occlusion and basal collateral vessels that may be idiopathic or may occur secondary to many disorders, including neurofibromatosis and sickle cell anemia. The most common presentation is with recurrent transient ischemic attacks (TIAs) or stroke in childhood, resulting in significant morbidity. Ischemic symptoms are usually due to hemodynamically mediated perfusion failure rather than thromboembolism. One possible treatment is surgical cerebral revascularization, which aims to increase the blood supply to hypoperfused tissue. Identification of abnormal tissue perfusion is therefore an important aspect of the evaluation of these patients. Although positron emission tomography and single-photon emission CT can delineate areas of cerebral hypoperfusion, they are not optimal for repeated examinations and do not provide information about the structural integrity of hypoperfused tissue.

Dynamic susceptibility contrast (DSC) MRI allows noninvasive investigation of the tissue perfusion4 and could therefore be useful in the clinical evaluation of patients with MMS. In addition, the ability to simultaneously perform structural and diffusion imaging means that there is potential to identify tissue with mismatch between areas of diffusion and perfusion abnormality. In patients with acute stroke, such areas are believed to represent tissue “at risk.” In patients with chronic cerebral ischemia, the presence of diffusion-perfusion mismatch could potentially identify areas of hypoperfused tissue that are not irreversibly damaged.

Although some studies using perfusion MRI in MMS have been reported, interpretation of DSC MRI data in these patients is not straightforward. The presence of collaterals can introduce delay and dispersion in the bolus of contrast agent, making quantification of perfusion MRI data less reliable.9 With the use of numerical simulations, it has been shown that a delay of only 1 to 2 seconds (with associated bolus

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dispersion) can introduce a large underestimation (>40%) of cerebral blood flow (CBF) and overestimation (>60%) of mean transit time (MTT), making these maps potentially misleading. Awareness of this possible source of error is important because of the increasingly widespread availability of the software and hardware for performing analysis of perfusion MRI.

The aim of this study is to explore the scope and limitations of perfusion MRI in the clinical evaluation of patients with MMS.

**Subjects and Methods**

All patients in this study had angiographically confirmed MMS and were being evaluated for surgical revascularization. We have used the term moyamoya “syndrome” in all cases, whether or not there was an associated diagnosis, to describe the angiographic syndrome of ICA occlusion with basal collaterals. The MR data were obtained as part of this clinical evaluation, and their analysis was approved by the local research ethics committee. Conventional cerebral arteriograms were reviewed to grade the severity of the MMS according to the classification of Suzuki. This classification describes angiographic stages of progressive ICA occlusion and appearance of basal collateral vessels from stage 1 (bilateral terminal ICA stenosis) to stage 6 (complete obliteration of the ICA circulation with supply of脑 derived entirely from the external carotid artery). Obliteration of the posterior cerebral arteries constitutes stage 4 in this classification. The patients were categorized according to their clinical symptoms into the following classifications: absent, patients who were cognitively and clinically stable (category A); moderate, patients with occasional (less than once a month) TIAs (category B); and severe, patients who had TIAs occurring more than once a month or recurrent stroke within the previous 12 months (category C).

All patients underwent MR examination with the use of a 1.5-T Siemens Vision system that included structural MRI (T1- and T2-weighted imaging), time-of-flight MR angiography, and MR diffusion and perfusion imaging.

**MR Diffusion Imaging**

Diffusion imaging was performed with a fluid-attenuated inversion recovery (FLAIR) spin-echo-planar imaging (EPI) sequence, with a pair of diffusion gradients on either side of the refocusing pulse (echo time [TE]=86 ms; repetition time [TR]=8700 ms; inversion time [T1]=2100 ms). The diffusion parameters were as follows: diffusion gradient duration (δ)=15 ms; time interval between diffusion gradients (Δ)=40.2 ms; b values=0 and 617 s/mm². Maps of the apparent diffusion coefficient (ADC) were calculated in 3 orthogonal directions, which were combined to generate average ADC maps (ADCAV).

**MR Perfusion Imaging**

DSC MRI was performed with a spin-echo EPI sequence. The imaging parameters were TE=100 ms, TR=1500 ms. Six slices were acquired, with 1 of the slices including the middle cerebral artery to enable estimation of the arterial input function (AIF). A bolus of 0.15 mmol/kg body wt contrast agent (Gd-DTPA; Magnevist, Schering AG) was injected intravenously (rate ~4 mL/s) with the use of an MR-compatible power injector (Medrad Inc.), followed by a saline flush.

The DSC MRI data were analyzed in 2 different ways. The first method used deconvolution, which can, in principle, generate accurate measurements of CBF, cerebral blood volume (CBV), and MTT. In addition, because of the potential errors in the calculation of CBF and MTT associated with bolus delay and dispersion (see above), the data were also analyzed by calculating summary parameters (see below and Figure 1).

**Analysis of Perfusion Data Using Deconvolution**

The signal intensity–time course was converted to a concentration-time course, and the AIF was used to deconvolve the concentration-time curve by singular value decomposition. A 3×3 uniform smoothing kernel was applied to the raw image data before deconvolution. Maps of CBF, CBV, and MTT were calculated on a pixel-by-pixel basis. The data were assessed for the presence of bolus arrival delay and bolus dispersion.

**Analysis of Perfusion Data Using Summary Parameters**

Several summary parameters obtained directly from the concentration-time course profile can be used as indirect measures of perfusion (Figure 1). The most commonly used include time to peak (TTP), bolus arrival time (BAT), a measure of the peak width (PW), maximum peak concentration (MPC), and the peak area (PA, proportional to CBV). Fitting to an analytical function (eg, gamma-variate function) is usually used to eliminate the presence of recirculation at the end of the peak and to calculate the summary parameters more accurately. This fitting is difficult on a pixel-by-pixel basis because of the low signal-to-noise ratio and is particularly problematic with data from children because the peak is usually much narrower than that from adults. Nevertheless, TTP and MPC can be calculated in a fairly robust way for each pixel because they can be obtained with only the measurements around the maximum of the peak, without requiring the identification of the start and end of the peak. In this study TTP and MPC maps were calculated by fitting a second-order polynomial to the 10 points across the peak maximum. The same 3×3 smoothing kernel was used on the raw data before the fitting.

**Quantitative Regional Analysis of Summary Parameter Maps**

For a more accurate quantitative analysis of summary parameters in children, a regional analysis was also performed. It has been shown that summary parameters can show large variability due to differences in AIF. To minimize this effect and to allow a better comparison between patients, a region of interest in the cerebellum was used as a reference. The noninfarcted tissue was segmented into 3 categories: ΔTTP values from 0 to 5, 5 to 10, and 10 to 15 seconds, where ΔTTP=TTPTTPBAT. The signal intensities of the pixels in each category were averaged to increase signal-to-noise ratio and allow a more robust calculation of the various summary parameters. The averaged signal in each segmented region was fitted to a gamma-variate function to calculate mean values of TTP, BAT, PW (PW=TTP–BAT), MPC, and PA for each category (Figure 1). All these parameters were referenced to the corresponding values in the cerebellum. The resulting relative values and percentage of pixels in each segmented region were used to investigate the relationship between perfusion status and clinical symptoms.

In the patients with multiple MRI scans, all the studies were analyzed with the use of deconvolution and by visual inspection of the summary parameter maps. For the quantitative analysis of summary parameters, only the most recent scan was analyzed, except in patients who had had scans before and after revascularization, for whom the latest preoperative scan was used.
For the remainder of this report, a region will be considered to have a hemodynamic abnormality if there was any abnormality on DSC MRI (either in a summary parameter or in a map obtained from the deconvolution analysis).

**Results**

Thirteen children and young adults (aged 22 months to 18.5 years; median age, 11.5 years) were studied; 6 patients were scanned more than once. Seven of 13 patients had had surgical revascularization involving a total of 12 hemispheres before their first MR examination. All patients had bilateral MMS, which was Suzuki stage 3 in 9 cases and stage 4 in 4 cases. Eleven of 13 had areas of established cerebral infarction. Five patients were in category A (symptoms absent), 3 in category B (moderate), and 5 in category C (severe).

**General Findings**

Bilateral hemodynamic abnormalities were observed in all the patients, including those who had had revascularization. There was a very heterogeneous distribution of BAT, with some areas displaying a delay in bolus arrival (ΔBAT, relative to the cerebellum) of >5 seconds (Table). The severity of the abnormality varied within the population despite the similarity of the angiographic severity of MMS. On visual inspection of the DSC MRI maps, the areas of abnormality included the major arterial border zones in all cases, although these appeared normal on structural and diffusion imaging in all but 1 case in which there had been a previous infarct.

**Deconvolution Analysis**

The observed heterogeneous pattern of very long delays (and likely dispersion due to the presence of collaterals) makes quantification of CBF very unreliable. This is illustrated in the data from 2 children with MMS shown in Figure 2. The patient in Figure 2A is a 6-year-old boy (patient 6 in the Table), who had had recurrent headaches and TIA’s affecting the left leg. The T2/diffusion data showed some small nonacute infarcts in the right caudate (not shown). However, there was an extensive hemodynamic abnormality in both hemispheres, with reduced CBF and prolonged MTT in noninfarcted regions bilaterally. The CBF ratio of 2 regions of interest in the right side (the anterior with relatively lower signal intensity in the CBF map; see inset in Figure 2A) was 0.50. The gamma-variate fitting to the regional concentration-time course indicated that the bolus arrived at both regions at approximately the same time. Therefore, the 0.50 ratio is likely to reflect (in the absence of significant dispersion) a true ~50% CBF reduction in the anterior region compared with the posterior region. On the other hand, Figure 2B shows data from a 12-year-old girl (patient 5 in the Table) in whom the deconvolution analysis gives misleading information. Although no abnormality was observed in the occipital areas on structural/diffusion MRI, these areas have an apparent perfusion abnormality (arrows). The CBF ratios of 2 occipital regions to a “normal” region in the basal ganglia were both ~0.45 (the occipital regions also show increased MTT). A regional analysis of the concentration-time course for the 3 regions showed that the bolus arrived at approximately the same time in the occipital regions but was delayed

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The cerebellum was used as reference. Category indicates clinical category of the patient; Region, segmented regions from the ΔTTP maps; REL, relative (ie, ratio) to the value in the cerebellum; % Pixels, number of pixels in the corresponding segmented region as a percentage of the total number of pixels. The reminder of the pixels (from 100%) consist of negative ΔTTP (ie, TTP shorter than that in the cerebellum) pixels (not included in the Table).

~2 seconds compared with the basal ganglia. This delay will introduce an underestimation in the calculated CBF in the occipital regions of ~40%. and the perfusion maps in Figure 2B are therefore misleading. Although both patients show maps with very similar relative decreases in CBF, the actual
tissue perfusion status is very different; the CBF could in fact be normal in patient 5.

Analysis Using Summary Parameters: Visual Inspection
Bilateral abnormalities were seen on visual inspection of the TTP and MPC maps in all patients. Most of these abnormalities comprised prolonged TTP with normal or reduced MPC relative to the cerebellum. Some patients also showed focal areas with reduced TTP and increased MPC after revascularization in cortical areas close to the operative site (eg, see Figure 3, bottom row). There were no abnormalities detected in the cerebellum, even in those patients with posterior circulation involvement. All but 1 patient (patient 3 in category A) had at least 1 hemisphere in which the abnormality affected more than half the middle cerebral artery territory. Although very extensive bilateral abnormalities were seen in all the children in category C, these were also observed in some patients in categories A and B. Therefore, there was no clear relationship between the extent of abnormality on the TTP and MPC maps and the clinical symptoms.

Analysis Using Summary Parameters: Quantitative Regional Analysis
The Table shows the summary of the results obtained after segmenting the tissue according to its \( \Delta TTP \) value (eg, see Figure 4). Although most of the patients showed large abnormalities in various summary parameters, the patients in category C (severe) tended to have more severe hemodynamic abnormalities. The general pattern in the children from category C was that of the following: very prolonged \( \Delta BAT \) (including segments with \( \Delta BAT > 5 \) seconds in 2 of 5 children, exclusively seen in this category); very prolonged \( \Delta TTP \) (including segments with \( \Delta TTP > 7 \) seconds in 4 of 5 children, exclusively seen in this category); very prolonged \( \Delta PW \) (including segments with \( \Delta PW > 5 \) seconds in 5 of 5 children, exclusively seen in this category); decreased relative...
MPC; increased relative PA; and segmented regions with $\Delta$TTP between 10 and 15 seconds (in 3 of 5 children, exclusively seen in this category). However, some of these characteristics were not exclusive to patients in category C. Some other patients (1 of 3 in category B and 2 of 5 in category A; see patient 4 in the Table for the worst case) also showed some of these abnormalities, but none had $\Delta$PW >5 seconds.

This quantitative regional analysis suggests that a threshold value of 5 seconds for PW differentiated the most clinically unstable patients (category C) from the rest. Despite the lack of relationship between the extent of the hemodynamic abnormality and the clinical symptoms, only the patients in category C had segmented areas of the brain with $\Delta$PW >5 seconds.

Discussion

Extensive areas of abnormality on the DSC MRI data were observed in all the patients with MMS. This is consistent with previous studies of MMS. The abnormalities observed were most evident in the arterial border zones and persisted even after surgical revascularization. The abnormalities tended to be more extensive in the most clinically unstable patients, although they were also observed in less clinically severe patients. The distribution of the abnormalities, involving the major arterial border zones, is consistent with a hemodynamic mechanism for ischemia in MMS.

The main dilemma in the management of patients with MMS is the identification of individuals likely to benefit from surgical revascularization, who are most likely to be those with symptomatic cerebral hypoperfusion. However, as found here, the angiographic severity of cerebrovascular disease does not appear to predict the hemodynamic status of tissue. These issues may also be relevant to adults with severe carotid stenosis or occlusion due to atheroma since there is an active debate in the literature regarding any potential benefit from surgical revascularization. Delineation of areas of abnormal tissue perfusion, in combination with clinical symptomatology, may direct the target for revascularization and provide a means of evaluating the efficacy of treatment. As shown in Figure 3, DSC MRI can detect hemodynamic changes after revascularization, indicating which areas have been affected by the surgery. However, interpretation of these findings in terms of true tissue perfusion status is not straightforward since direct comparison of quantitative measures on 2 separate occasions may be misleading (see below).

MMS presents a considerable challenge for measurement of perfusion with MRI. The presence of collateral vessels introduces very large delays ($\Delta$TTP in some of the patients in this study) and likely dispersion to the bolus of contrast agent. These effects are not accounted for in the kinetic model used in the quantification of perfusion, and therefore the maps generated with the use of deconvolution can be very misleading in that they will tend to underestimate the CBF and overestimate the MTT. The main problem is the impossibility of measuring the true AIF, which is generally estimated from a large artery (e.g., middle cerebral artery or ICA) that, in practice, may be relatively distant from the tissue that is being studied. For MMS, this estimation will be an inaccurate representation of the true AIF. Until a correction for this effect is found (which will require modeling of the vascular bed and generalization of the kinetic model), any maps generated with the use of deconvolution should be
inspected for the presence of significant delay and dispersion before interpretation is attempted. This study has shown that delays as long as 7 seconds are possible in MMS. A continuous range of shorter delays is expected to be possible in other forms of cerebrovascular disease. Therefore, these limitations should also be considered in patients with other forms of occlusive large-vessel disease, such as occlusive carotid artery disease due to atheroma, since these patients may also have significant delay and dispersion of the bolus.\textsuperscript{16,17}

It should be noted that many of these limitations also affect the MR techniques for measuring perfusion with the use of arterial spin labeling.\textsuperscript{4} In particular, the long transit times due to the presence of collaterals is one of the fundamental limitations of arterial spin labeling techniques. Because of the loss of labeling during these long transit times (due to $T_1$ decay), the arterial spin labeling techniques have the potential problem of not being able to differentiate between no flow ($CBF=0$, no signal in the arterial spin labeling image) and very long transit times (full relaxation of the labeled blood, no signal in the arterial spin labeling image regardless of $CBF$). Although DSC MRI cannot measure $CBF$ accurately in these situations, it can at least differentiate these cases, which have different clinical implications.

The use of summary parameters as an alternative to the deconvolution analysis of DSC MRI also presents some difficulties in MMS. First, delay and dispersion of the bolus can also affect many of the summary parameters (eg, TTP). Second, none of the summary parameters gives a direct measure of $CBF$,\textsuperscript{18} which makes it difficult to infer the status of the tissue from any of these measures. Therefore, their relative clinical importance remains to be determined. While BAT provides information about the delay in bolus arrival and PA about CBV, all the other parameters can be influenced by many factors (such as AIF, CBF, MTT, and dispersion) in an unknown way. A multivariate analysis (including all the parameters) could indicate which parameters are most clinically useful. This was not possible in the present study because of the relatively small number of children and large number of parameters. Third, they do not take account of differences in AIF between patients and in follow-up studies,\textsuperscript{12} and any analysis involving setting up thresholds to differentiate tissue states or compare between maps should be performed with caution. For example, in this study a relatively broad interval was chosen for segmenting the $\Delta TTP$ maps (5-second intervals) to reduce the possibility of misclassification of tissue types (Perthen et al\textsuperscript{12} reported a $\Delta TTP$ variability of $\approx 2$ seconds for a range of AIFs characteristic of children). Fourth, since all the summary parameters only provide relative information about cerebral hemodynamics, there is an additional difficulty in MMS, in which the abnormalities are often bilateral. For the quantitative analysis performed in this study, a region of interest in the cerebellum was selected as a reference. It should be noted that 4 patients (those with Suzuki stage 4) had posterior circulation involvement. Although there were no abnormalities in the cerebellum detectable on visual inspection of their DSC MRI maps, we cannot discount the possibility of a global reduction in CBF. Therefore, these patients may not have had normal perfusion in the cerebellum, and, as a result, it is possible that any hemodynamic abnormality in the cerebral hemispheres may have been underestimated. This emphasizes the need for techniques that measure absolute perfusion in bilateral MMS.

Despite these limitations, the quantitative regional analysis performed in this study suggests that the most clinically unstable patients (category C) showed more severe DSC MRI abnormalities. A $\Delta PW$ threshold value of 5 seconds appeared to differentiate this group of patients from those in the other categories. A recent study in patients with acute stroke has shown a correlation between the volume of tissue with $TTP >4$ seconds and the clinical status.\textsuperscript{19} However, that study is not directly comparable to our study because ours was concerned with chronic hypoperfusion rather than the functional effects of acute ischemia. Although our data suggest that $\Delta PW$ is a good discriminator, sample size was not sufficient to determine the sensitivity and specificity of this classification, and the threshold criterion may need refinement. Furthermore, the ability of perfusion MRI to predict the future clinical course in individual patients remains to be shown.

Apart from the problems with quantification of DSC MRI data in MMS previously discussed, there are a number of other potential issues to be taken into account. The clinical classification that we used categorized patients with frequent TIAs and those with recurrent stroke in the same group. However, these groups of patients may be different in terms of their cerebral hemodynamic status. An important factor not considered in this study is cerebrovascular reserve.\textsuperscript{20} This may distinguish patients who respond to hemodynamic stress with less severe and more transient symptoms (ie, TIA) from those who are unable to maintain an adequate level of CBF and who develop cerebral infarction under conditions of hemodynamic stress. This suggestion is supported by comparing patient 13, who had 3 cerebral infarcts within a 6-month period, with patient 10, who has TIAs several times each week but has never had any cerebral infarcts. Despite the more aggressive clinical course of patient 13, the DSC MRI data suggest that patient 10 has more extensive and more severe hemodynamic abnormality in the “resting” state. Perfusion MRI could be used to explore this issue by measuring cerebrovascular reactivity in response to carbon dioxide or acetazolamide.\textsuperscript{20} However, this is not straightforward in MMS because these studies require serial measurements of perfusion (before and after challenge), and all the aforementioned problems of quantification and comparison of perfusion data will also apply.

In conclusion, DSC MRI provides a noninvasive method for the evaluation of regional cerebral perfusion in patients with MMS, with useful clinical applications. However, the technical limitations of DSC MRI described in this study are important for the accurate interpretation of perfusion MRI in MMS. If these issues are not taken into account, misleading results can be obtained, which may lead to erroneous decisions about future treatment. These limitations should also be considered in patients with other forms of occlusive large-vessel disease, such as occlusive carotid artery disease due to atheroma, since these patients may also have significant delay and dispersion of the bolus. It is therefore essential that DSC MRI data are checked for the presence of delays to avoid...
misinterpretation of the perfusion maps. Despite these limitations, the findings in this study suggest that the use of quantitative regional analysis of summary parameters can provide clinically useful information in patients with MMS.

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