Local Relationships Between Restricted Water Diffusion and Oxygen Consumption in the Ischemic Human Brain

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Background and Purpose—MR is widely used to depict still ischemic but viable tissue in acute stroke. However, the relationship between the apparent diffusion coefficient (ADC) and energy failure from reduced oxygen supply are unknown in man.

Methods—Acute carotid-territory stroke patients were studied prospectively with both diffusion tensor–imaging and back-to-back steady-state $^{15}$O-PET. Substantial numbers of voxels with oxygen extraction fraction $>0.70$ (ie, significant ongoing hypoxia) were identified in 3 patients (imaged at 7, 16 and 21 hours after stroke onset). In this voxel population, the quantitative relationships between the ADC and cerebral metabolic rate of oxygen (CMRO$_2$), and ADC and cerebral blood flow (CBF), were assessed.

Results—The ADC remained essentially unchanged until CBF reached values $\leq 20$ mls/100g per min, beyond which it declined linearly. In contrast, except when severely reduced, the ADC was a poorer predictor of CMRO$_2$. For both CBF and CMRO$_2$, however, the relationship with ADC became steeper with longer times since onset, ie, the same ADC reflected lower perfusion and CMRO$_2$ with elapsed time.

Conclusions—Despite the small sample and late times from stroke onset, the findings indicate that the degree of restricted water diffusion reliably reflects the severity of oxygen deprivation below the penumbral threshold but is less strongly related to metabolic disruption, which may explain why the ADC does not reliably predict tissue outcome. However, the same degree of diffusion restriction may correspond to greater severity of tissue disruption with elapsing time, which has relevance for stroke therapy. Time elapsed since stroke onset should be taken into account when interpreting ADC declines and in voxel-based infarct prediction models. (Stroke. 2006;37:1741-1748.)

Key Words: cerebral blood flow ■ cerebral ischemia ■ diffusion magnetic resonance imaging ■ PET ■ stroke

Reduced oxygen supply, the hallmark of cerebral ischemia, translates with positron-emission tomography (PET) as increased oxygen extraction fraction (OEF), with 3 operationally-defined high OEF compartments being usually present at any one time after acute ischemic stroke, namely “benign” oligemia, penumbra and core.1–3 MR-based diffusion-weighted (DWI) and perfusion-weighted imaging are increasingly used in the clinical setting to identify the at-risk tissue in acute stroke and guide therapeutic decisions. The DWI lesion provides early evidence of cellular injury, whereas the significantly hypoperfused but DWI-intact tissue, so-called ‘mismatch’, points to the at-risk tissue4 and corresponds well to the high OEF area.5 The DWI lesion is attributable to a reduction of the apparent diffusion coefficient (ADC), related to a water shift from the extra- to the intracellular space caused by energy failure from reduced oxygen supply.4 However, the relationship between ADC changes and energy failure in human stroke is largely unknown. Establishing this relationship for the tissue with high OEF would be important as the level of oxygen consumption in ischemic stroke is a good marker of subsequent infarction.1,2,6–8

Experimental and human studies9–12 have shown that the ADC remains almost unchanged with decreasing cerebral blood flow (CBF) until a certain level of perfusion close to the penumbral threshold is reached, beyond which it declines steeply. However, the corresponding relationship between the ADC and oxidative metabolism has not been demonstrated. The potential normalization of even markedly decreased ADC with reperfusion in both the rat13 and man14–16 highlights the well-reported poor value of the ADC to predict final
infarction. In turn, because the cerebral metabolic rate of oxygen (CMRO₂) is a good marker of irreversible damage, it is suggested that the ADC may be less tightly related to the severity of oxidative metabolism impairment than it is to perfusion. One group only has directly studied the ADC-CMRO₂ relationship using PET during MCA occlusion in the anesthetized pig. They reported a linear relationship and concluded that the ADC is an indicator of tissue oxygen metabolism. However, extrapolation of this study to human stroke is uncertain. Two previous clinical articles have reported DWI-CMRO₂ comparisons in acute stroke, but neither systematically assessed the ADC-CMRO₂ relationship. Here, we aimed to study directly in humans and at the voxel level, the ADC-CMRO₂ relationship, as compared with the ADC-CBF relationship, in the hypoxic tissue. Based on the available literature, we hypothesize that in ongoing hypoxic tissue the ADC is closely related to CBF below the penumbra threshold but is less clearly predictive of CMRO₂. However, because it has been reported that for a given CBF value the ADC is lower with longer time since stroke onset, our secondary aim was to explore whether the ADC becomes more predictive of metabolic decline with increasing time since stroke onset. A (time X severity) dependence of the ADC would explain at least in part its inconsistent predictive value for subsequent infarction. We applied back-to-back PET to measure the CMRO₂ and high-field MR to implement full diffusion tensor (DTI) allowing calculation of mean diffusivity (<D>), a more robust index of water diffusion.

Materials and Methods

Subjects
Patients with first-ever carotid territory stroke within 21 hours of onset were prospectively enrolled. Main exclusion criteria were previous stroke, lacunar syndrome, hemorrhagic infarct on CT, anticoagulation or thrombolysis (as arterial cannulation was required for the PET study), inability to cooperate or organ failure. Patients were scored with the National Institutes of Health Stroke Scale (NIHSS). The Local Ethics Committee approved the study and informed consent was obtained.

MR
DTI was performed on a 3-T magnet (Med-spec s300, Bruker). The MR technique, parameters and calculation of <D> are detailed elsewhere. Briefly, data sets were calculated from 12 noncollinear gradient directions and 5 b values (range: 300 to 1570 seconds/mm²), which effectively characterizes fast water diffusion, avoids contamination by perfusion and reduces CSF artifacts. Except in patient 1 (see Figure 1) full-brain coverage was obtained (field of view 19×19, matrix size 100×100, 27 slices, thickness 5 mm). A T₂-weighted FSE sequence was also acquired.

PET
A fully quantitative steady-state ¹⁵O PET study using H₂¹⁵O, ¹⁵O₂ and C¹⁵O was performed according to published procedures on a GE Advance scanner with axial field of view=15.3 cm (General Electrics). Image reconstruction included ⁶⁸Ge correction for attenuation, scatter, randoms and dead time. Parametric maps of CBF, CMRO₂ and OEF were calculated using standard models including correction for cerebral blood volume using the software PETAN. In all patients transcranial Doppler was performed before and between MR and PET scanning.

Figure 1. Illustrative set of coregistered maps of <D>, High OEF voxels, CMRO₂, CBF and T₂-weighted MR The High OEF voxels, defined as explained in Methods, are shown here for illustration projected onto a binary mask derived from the <D> maps. The pseudo-color scale indicates the absolute CMRO₂ in μmol/100 mL per minute and CBF in ml/s/100 mL per minute. Because of the limited axial extent of the DTI sequence used for patient 1, the process of coregistration to the PET data set resulted in the <D> images appearing ‘cut’.
**Image Processing**

Using PETAN, the PET parametric maps were coregistered to the T1 sequence using SPM99 (www.fil.ion.ucl.ac.uk/spm). The average image from the b0 DTI preparation sequence was coregistered to the T1, using the normalized mutual information algorithm in vtk-CIGS software package (www.image-registration.com). The matrix transformation file was applied to the b945 images and coregistered against CBF and CMRO2 maps. We then plotted <D> against CBF and CMRO2, for the High OEF and mirror voxel populations for each patient, and compared the relationships between the 2 hemispheres. To allow formal comparison, linear regressions were computed across the entire voxel data sets, and differences in correlation slopes derived from the regression analysis. In addition, we assessed whether time influenced the <D>-values for the Core, Penumbra and Oligemia subsets of the High OEF voxel population, defined by voxels with CBF <8.4, 8.4 to 20 and >20 mls/100 g per minute, respectively. To this end, 1-way ANOVAs taking time from stroke onset (in hours) as the independent variable and <D> (normalized to the mean of the mirror voxels to account for potentially different gray/white mix) as the dependent variable were performed separately for the 3 voxel subsets. So as to verify the findings, the probabilistic voxel-based CMRO2 threshold for the Core of 39 μmoles/100 ml per minute was also applied, as this threshold yields a not entirely overlapping voxel population than with the above CBF threshold.

**Data Analysis**

To assess the <D>-CMRO2 and <D>-CBF relationship in ischemic tissue on a voxel-by-voxel basis, we used high OEF as a marker of ischemia and selected all voxels with OEF >70% in the affected hemisphere, using Analyze. The High OEF voxel set was then ‘flopped’ onto the unaffected hemisphere, and the spatial coordinates of all the selected voxels were transferred to the coregistered <D>-values (thresholded at 1200×10^-6 mm^2/s^-1 to eliminate CSF). CBF and CMRO2 maps. We then plotted <D> against CBF and CMRO2 for the High OEF and mirror voxel populations for each patient, and compared the relationships between the 2 hemispheres. To allow formal comparison, linear regressions were computed across the entire voxel data sets, and differences in correlation strength between the affected and nonaffected hemispheres were assessed using standard methods, with P<0.05 being significant.

To assess the effects of time since stroke onset, the <D>-CMRO2 (as well as the <D>-CBF) relationship was compared among patients (scanned at different times), both visually and using the slopes derived from the regression analysis. In addition, we assessed whether time influenced the <D>-values for the Core, Penumbra and Oligemia subsets of the High OEF voxel population, defined by voxels with CBF <8.4, 8.4 to 20 and >20 mls/100 g per minute, respectively. To this end, 1-way ANOVAs taking time from stroke onset (in hours) as the independent variable and <D> (normalized to the mean of the mirror voxels to account for potentially different gray/white mix) as the dependent variable were performed separately for the 3 voxel subsets. So as to verify the findings, the probabilistic voxel-based CMRO2 threshold for the Core of 39 μmoles/100 ml per minute was also applied, as this threshold yields a not entirely overlapping voxel population than with the above CBF threshold.

**Results**

**Clinical Data**

Of a series of 6 consecutive patients who completed the imaging protocol, 3 (2 males; age 53 to 84 years; imaged 7, 16 and 21 hours after stroke onset) exhibited substantial numbers of High OEF voxels (1144, 468 and 976, respectively) and form the basis of this report. Their main clinical data are shown in Table 1. They all had extensive clinical deficits (NIHSS range: 10 to 16). In all, transcranial Doppler showed occluded MCA before MR scanning, unchanged between MR and PET. Patient 3 had a distal carotid occlusion with the stroke affecting both the MCA and posterior cerebral artery territories.

**Imaging Findings**

Figure 1 shows for each patient the coregistered <D>, High OEF voxels, CMRO2, CBF and T2-weighted maps for a subset of illustrative planes.

Table 2 shows the mean (and 1SD) for <D> and the PET variables for the High OEF and Mirror voxel populations in each patient. In addition to the increased OEF (expected), the <D>-CBF and CMRO2 were all significantly reduced in the High OEF as compared with Mirror voxel population for each patient.

The <D>-CBF and <D>-CMRO2 relationships within the High OEF and Mirror voxel populations for each patient are shown in Figure 2. In the Mirror voxel population, <D> was as expected essentially stable across the voxels, with the spread of CBF and CMRO2 values reflecting the fact that the data sets comprised a mix of gray and white matter voxels. Strikingly different relationships characterized the High OEF voxels not only relative to the Mirror population but also between CBF and CMRO2; these observations were consistent across patients, although with some differences. Regarding CBF, the relationship could be described as follows: (1) it

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**Table 1. Summary of Patient Data**

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Interval to First Imaging Study, h</th>
<th>Interval Between MRI and PET, min</th>
<th>Stroke Hemisphere</th>
<th>Neurological Examination</th>
<th>NIHSS</th>
<th>Stroke Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>53</td>
<td>7</td>
<td>60</td>
<td>Left</td>
<td>Hemianopia, aphasia, hemiparesis, neglect, Horner’s</td>
<td>16</td>
<td>Carotid dissection</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>64</td>
<td>16</td>
<td>30</td>
<td>Right</td>
<td>Hemianopia, dysarthria, hemiplegia, neglect</td>
<td>12</td>
<td>Large artery embolism</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>84</td>
<td>21</td>
<td>50</td>
<td>Right</td>
<td>Hemianopia, hemiparesis, neglect</td>
<td>10</td>
<td>Cardio-embolic</td>
</tr>
</tbody>
</table>

**Table 2. High OEF Voxel Population**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Affected Hemisphere</th>
<th>Unaffected Mirror Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>501±135</td>
<td>631±132</td>
</tr>
<tr>
<td>2</td>
<td>585±170</td>
<td>785±113</td>
</tr>
<tr>
<td>3</td>
<td>619±190</td>
<td>798±128</td>
</tr>
</tbody>
</table>
was displaced leftward relative to Mirror voxels; (2) \(<D>\) started to substantially decline only below CBF values \(\approx 20\) mls/100 g per minute; and (3) the steepest slope was found in Patient 3, studied the latest. Regarding CMRO2, the relationship could be described as follows: (1) it was displaced not only leftward but also downward, ie, \(<D>\) values tended to be reduced across the whole dataset; (2) although they also showed a monotonic decline, the slope was much shallower than with CBF; (3) again the slope was steepest in Patient 3; and (4) in each patient, a marked decline in \(<D>\) occurred with lowest CMRO2 values. Thus, although severely reduced ADC consistently corresponded to markedly low CMRO2, moderately reduced \(<D>\) could correspond to unchanged as well as substantially reduced CMRO2 but was more likely to represent more reduced CMRO2 at later time points.

Analysis of the linear regressions confirmed these observations (Figure 3). In the unaffected hemisphere, all \(<D>\)-CBF and \(<D>\)-CMRO2 correlations were weak (explaining \(<10\%\) of the variance\(^{32}\)), whereas in the affected hemisphere they were all meaningful; significant between-hemisphere differences were found for both sets of relationships in all patients apart from a trend for the CBF relationship of Patient 1 \((P<0.10)\). Slopes of the regression lines were very weak in the unaffected hemisphere for both relationships. In the affected hemisphere, they were steeper for the \(<D>\)-CBF than for the \(<D>\)-CMRO2 relationship, and the slopes became gradually steeper with increasing time since stroke onset.

Table 3 shows the normalized CMRO2 and \(<D>\) values for the Oligemia, Penumbra and Core voxel subsets. For each subset, there was a highly significant decrease in normalized \(<D>\) with increasing time from ictus \((P<0.001, \text{ANOVA})\),
most pronounced for the Core. Similar results were obtained when using the CMRO$_2$ instead of the CBF Core threshold ($P<0.001$, ANOVA; data not shown).

**Discussion**

This is the first study to combine fully quantitative PET and mean diffusivity calculated from a DTI sequence in acute stroke to examine the relationships between the ADC and oxygen consumption in hypoxic tissue, ie, the target for reperfusion therapy. Although only 3 patients contributed to this study, they all had acute MCA stroke and exhibited high OEF at scanning time, so can be considered representative. The other 3 patients who completed this demanding imaging protocol exhibited spontaneous reperfusion.

Two sets of findings, both consistent with our working hypotheses, emerged. Firstly, $<D>$ remained essentially unchanged with declining perfusion until CBF reached critical values, below which it linearly declined, whereas it linearly declined with CMRO$_2$ but the relationship was shallow, ie, the ADC was a poorer predictor of CMRO$_2$ over a wide range of values except when severely reduced, where it consistently predicted very low oxygen consumption. Secondly, the relationship between $<D>$ and CMRO$_2$ (and $<D>$ and CBF) was more pronounced with time since stroke onset, ie, the same degree of water diffusion restriction corresponded to more reduced CMRO$_2$, and hence greater tissue disruption, with elapsing time.

Our findings regarding the $<D>$-CBF relationship are entirely consistent with previous studies, all using MR to assess perfusion. Although experimental and clinical studies have shown the general relationship, only few have done so in a quantitative and detailed way. In gerbils, the ADC declined only when CBF fell beyond 15 to 20 mL/100 g per minute. In stroke patients, Lin et al, using a voxel-based approach, reported an abrupt ADC drop below a mean CBF threshold of 21 mL/100 g per minute (range: 15 to 24), below which it declined continuously. We now confirm these earlier findings with more quantitative evidence.

![Figure 3](image-url)

**Table 3.** Mean ($\pm$1 SD) Normalized CMRO$_2$ and $<D>$ Values for the Three Subsets of High OEF Voxels for Each Patient

<table>
<thead>
<tr>
<th>Oligemia</th>
<th>Penumbra</th>
<th>Core</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMRO$_2$</td>
<td>$&lt;D&gt;$</td>
<td>CMRO$_2$</td>
</tr>
<tr>
<td>Patient 1 (7 h)</td>
<td>1.10±0.14</td>
<td>0.89±0.17</td>
</tr>
<tr>
<td>Patient 2 (16 h)</td>
<td>1.10±0.09</td>
<td>0.95±0.20</td>
</tr>
<tr>
<td>Patient 3 (21 h)</td>
<td>0.82±0.20</td>
<td>0.76±0.23</td>
</tr>
</tbody>
</table>

The effect of time since stroke onset on normalized $<D>$ is significant ($P<0.001$; ANOVA) for each voxel subset. See Methods for definition of the subsets.
results using gold-standard PET. Altogether, a reduced ADC reflects tissue that is hypoxic below the threshold that defines the penumbra—ie, at immediate risk of, or already affected by, irreversible damage.

One group only20 has directly studied the ADC-CMRO2 relationship. Using PET in a pig model, these authors reported a linear relationship between relative ADC and CMRO2 during MCA occlusion, and concluded that the ADC is a reliable indicator of tissue oxygen metabolism. Our results showing a linear relationship between absolute CMRO2 and \(<D\rangle\) would be consistent with this earlier report. However, in the present study the observed CMRO2 gradients were shallower, such that moderate ADC reductions were weakly predictive of concomitant CMRO2, whereas severe ADC reductions were predictive of marked CMRO2 reductions. Close inspection of Sakoh et al’s data (Figure 420) indicates that in fact the behavior of the ADC-CMRO2 relationship is largely consistent between the 2 studies, as their data also show linearity in the moderate levels of ischemia until relative CMRO2 \(\sim 50\%\) is reached (corresponding to a relative ADC \(\sim 75\%\)), whereas below this level the CMRO2 appeared to decline precipitously in the face of small changes in ADC, to reach baseline for ADC \(\sim 65\%\). Our data (Figure 2) also suggest a steeper ADC-CMRO2 relationship for markedly reduced CMRO2 values in each patient, and the analysis of the data according to the 3 hypoxic tissue compartments also suggests marked ADC declines in the Core (see Table 3). Apart from the species, additional differences between ours and this earlier study20 include (1) the anesthesia used, which reduces oxidative metabolism37; (2) the complex cerebrovascular anatomy of the pig36; and (3) the use of large region-of-interest based on CBF thresholds rather than on high OEF as here, potentially merging tissues with different physiological states.

Our results regarding the ADC-CMRO2 relationship are also consistent with a recent PET-MR comparison study in human stroke.7 Although these authors did not systematically study this relationship, they report relative preservation of the ADC in the penumbra despite substantial decrements in relative CMRO2 (absolute values were not measured) within 6 hours of onset; however, marked ADC declines were found for relative CMRO2 values below \(\sim 0.45\) which corresponded to the infarction threshold. Like these authors, we find that the ADC can be well preserved in hypoxic tissue unless there is markedly reduced CMRO2 and/or irreversible damage (see Figure 2 and Table 3). Over and above this earlier study,7 we show here that the ADC declines become more reliably associated with marked reductions in oxygen metabolism with times since onset >6 hours. Also, we show these relationships at the voxel level rather than with region-of-interest, and with absolute rather than relative CMRO2.

Our results suggest that the degree of water diffusion restriction in the penumbra is a good reflection of the severity of oxygen deprivation from reduced blood supply, but is much less dependent on the actual level of current metabolic disruption. It is well established that in hypoxic conditions the oxygen metabolism starts to become disrupted only beyond a certain point of reduced oxygen supply (ie, for CBF <20 mls), whereas it is maintained with less reduced oxygen supply (ie, CBF between 20 and 50 mls).39,40 Within the penumbral range (ie, CBF between 8 to 20 mls/100 mls per minute), the OEF reaches maximal values and the CMRO2 is initially relatively preserved but declines markedly in the lower penumbral range and with elapsed time.3,7 This may explain why even moderately severe ADC reductions do not consistently predict irreversible tissue damage, and can be permanently reversed.14–16 That the ADC can be substantially restricted in hypoxic tissue despite only mild reductions in CMRO2 is intriguing and may reflect the fact that in the initial stages of brain hypoxia (ie, oligemia and moderate penumbra) anaerobic glycolysis is triggered, resulting in intracellular lactic acidosis that causes a change in water diffusion.41 Conversely, in the more severe penumbra range the CMRO2 decreases rapidly but the ADC remains almost stable probably because of the relative preservation of ATP function maintaining membrane homeostasis.7 Finally, the CMRO2 declines precipitously in the core because of failure of ATP production, leading to cell depolarization and marked ADC declines.

With elapsing time since stroke onset the \(<D\rangle\)-CMRO2 relationship became steeper, ie, \(<D\rangle\) more reliably predicted metabolic impairment. There is no previous comparable data. There was a similar effect on the \(<D\rangle\)-CBF relationship, entirely consistent with Lin et al.11 To tease out further this effect, we determined the \(<D\rangle\) values for the core, penumbra and oligemia subsets of the High OEF voxels. Acknowledging the small sample, the results suggest that \(<D\rangle\) significantly declines with elapsing time, particularly so for the core. These findings are consistent with previous animal work22,42,43 which led to the hypothesis that the ADC threshold of ischemic tissue viability may be time-dependent.29 For instance, Rohl22 demonstrated in the pig that the ADC significantly decreased over time in the caudate-putamen, taken to represent the core. In humans, it is well established that across patients the ADC within the DWI lesion declines with elapsing time.44,45 Consistent with our findings, a recent study16 found that the ADC of tissue rescued by reperfusion increased with elapsing time, suggesting the viability threshold of the ADC is time-dependent. Such a dependence on time of the relationship between the ADC and tissue damage provides a plausible explanation for the discrepancies among studies attempting to identify an ADC threshold for infarction.14–18

Although the number of patients studied was small, limiting generalized conclusions, the data suggest that interpretation of ADC declines after stroke should take into account not only the degree of ischemia but also time elapsed since onset, which has clear clinical implications. Accordingly, duration might be worth adding to ADC and/or perfusion data in infarct prediction models.46,47

A limitation of our study is the late imaging times from stroke onset, beyond most current therapeutic time windows. However, the study provides valuable insight into some of the fundamentals of the water diffusion/energy failure relationship in acute human stroke. This may have relevance in the design of future therapy trials using imaging-based patient selection, currently being extended beyond the classic 3- to 6-hour time window.48

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Disclosures
None.

References


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