Hypoxic tissue in ischaemic stroke: persistence and clinical consequences of spontaneous survival

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Summary
In ischaemic stroke, expansion of the infarct core occurs at the expense of surrounding hypoxic, metabolically compromised tissue over a period of 24 h or more in a considerable proportion of patients. It is uncertain whether hypoxic tissue observed at later times after stroke onset retains the potential for survival or whether such survival has an impact on functional outcome. These factors may determine the effectiveness of therapeutic strategies aimed at salvaging this tissue. We tested the hypotheses that metabolically compromised hypoxic tissue observed within 48 h after onset of ischaemic stroke retains the potential for spontaneous survival and that the impact of such survival on functional outcome is time dependent. Consecutive patients presenting within 48 h of ischaemic stroke were studied with [18F]fluoromisonidazole, a ligand binding to hypoxic but viable tissue, and PET. Subjects were grouped into two time epochs, <12 and >12 h, based on the interval from stroke onset to the time of tracer injection, and had infarct volumes measured on CT/MRI at 7 days (n = 60). The total ischaemic volume (TIV) and the proportion of the TIV that spontaneously survived (surviving hypoxic volume ratio, SHVR) were defined from the co-registered CT/MRI images. These volumetric measures were correlated with neurological outcome assessed at day 7–10 by percentage change in the National Institutes of Health Stroke Scale (ΔNIHSS), and at 3 months by Barthel Index (BI) and modified Rankin Score (mRS). Of 66 patients investigated, hypoxic tissue occurred in 33 and outcome data was available in 27. Hypoxic tissue constituted >20% of the TIV in 60% of studies <12 h and 16% >12 h. The spontaneously surviving proportion of the TIV (median 6.9%) or hypoxic tissue (median 45.9%) was not significantly different in patient subgroups studied ≤12 or >12 h after stroke onset. Spontaneous survival of hypoxic tissue (surviving hypoxic volume ratio) was associated with improved neurological outcome in both time epochs: ≤12 h, ΔNIHSS (r = 0.85, P < 0.01), day 90 BI (r = 0.86, P < 0.01) and day 90 mRS (r = −0.89, P < 0.01); >12 h, ΔNIHSS (r = 0.59, P < 0.01) and day 90 mRS (r = −0.46, P < 0.05). The finding that similar proportions of hypoxic tissue survived spontaneously within each time epoch suggests that its fate is not predetermined. The favourable neurological outcome associated with spontaneous survival of hypoxic tissue, even 12–48 h after stroke onset, suggests that the volume of hypoxic tissue that progressed to infarction may represent a valuable target for therapeutic intervention.

Keywords: [18F]fluoromisonidazole; hypoxia; ischaemic stroke; penumbra; PET

Abbreviations: BI = Barthel Index; FMISO = [18F]fluoromisonidazole; HV = hypoxic volume; IV = infarct volume; mRS = modified Rankin Score; ΔNIHSS = percentage change in the National Institutes of Health Stroke Scale; SHVR = surviving hypoxic volume ratio; TIV = total ischaemic volume


Introduction
In focal cerebral ischaemia, reduced delivery of oxygen and glucose results in energy failure that induces a time-dependent cascade of functional and metabolic changes in the hypoperfused region (Hossmann, 1994). Infarction occurs rapidly in the region of most severe ischaemia (Baron, 1999; Heiss, 2000) and the infarct core expands at the expense of
the surrounding hypoxic tissue from the centre to the periphery of the hypoperfused region over a variable period of time (Markus et al., 2003). The functionally impaired region that surrounds the infarct core and is threatened by necrosis has been termed the ischaemic penumbra (Astrup et al., 1981; Touzani et al., 2001). Survival of the ischaemic penumbra is one mechanism that underlies spontaneous neurological improvement after stroke (Furlan et al., 1996). Therapeutic strategies in acute stroke are based on the concept of arresting the transition of the penumbral region into infarction, thereby limiting ultimate infarct size and improving neurological and functional outcome (Fisher, 1997).

In one-third of patients studied with serial MRI after ischaemic stroke, substantial enlargement of the infarct continued beyond the first 24 h (Baird et al., 1997). Metabolically compromised but viable penumbral tissue has been observed in regions that ultimately infarct as late as 48 h after stroke onset in patients studied with multitracer PET (Heiss et al., 1992). However, it has not been established whether the bulk of metabolically compromised tissue that is demonstrated at late time points represents mainly dying brain tissue or mainly viable brain tissue, the survival of which is associated with functional improvement. It is also uncertain whether this balance is time dependent. This has important implications for the likelihood of success of therapeutic strategies aimed at salvaging this tissue.

The ligand [18F]fluoromisonidazole (FMISO), a PET marker of hypoxic but viable tissue, identifies metabolically compromised tissue at risk of infarction following ischaemic stroke (Read et al., 1998, 2000). We prospectively evaluated patients presenting within 48 h of ischaemic stroke with FMISO PET and longitudinal clinical assessments to assess the effect of time since stroke onset on the prevalence, fate and functional outcome of this tissue. Specifically, we hypothesized that time since stroke onset has an effect on: (i) the proportion of hypoxic tissue that survives spontaneously; and (ii) the functional impact associated with spontaneous survival of hypoxic tissue.

Subjects and methods

Subjects

Consecutive patients aged over 18 years presenting to the Austin and Repatriation Medical Centre with an acute hemispheric ischaemic stroke in whom PET imaging with FMISO was possible were included in this study. Exclusion criteria included brainstem or cerebellar stroke, cerebral haemorrhage on admission CT head scan, medical instability and contraindications to PET scanning. The time of stroke onset was determined from the patient or witnesses. In the case of waking deficit the midpoint between the time of waking and the last time that the patient was known to be neurologically normal (e.g. time of going to bed) was used. The interval from stroke onset to the time of tracer injection was used to group subjects into two time epochs: ≤12 and >12 h.

The control group comprised approximately age-matched normal subjects with no prior history of stroke or transient ischaemic attack (TIA) and with normal brain CT scans. Written informed consent was obtained from the subjects or their next of kin. The Human Research Ethics Committee of the Austin and Repatriation Medical Center approved the study protocol.

The first 24 patients of this cohort have been reported previously testing different hypotheses (Read et al., 2000). At the time, the PET and CT scans were co-registered manually and regions of significant FMISO uptake were identified by comparison with the ‘normal’ contralateral hemisphere of the patients. Since then we have studied the distribution of this tracer in normal age-matched control subjects, described the application of automated image registration algorithms to align PET and CT images into standard coordinate space (Talairach and Tournoux, 1988) and validated a method of using statistical parametric mapping to identify regions of increased FMISO uptake by comparison of each patients with the group of normal control subjects (Markus et al., 2002). The cohort of 66 patients reported in this paper includes the initial 24 subjects who were re-analysed using this objective, reproducible and validated method of image analysis that is described in more detail below.

Patient assessment and neurological scores

All patients had standard clinical management at the discretion of the treating neurologist. None of the patients was treated with thrombolysis, as it had not been approved for use in Australia at the time of the study. The National Institutes of Health Stroke Scale (NIHSS) (Lyden et al., 1994) was measured at the time of PET tracer injection (initial NIHSS, NIHSSinit) and repeated at the time of the repeat CT or MRI performed to evaluate final infarct volume 7–10 days later (NIHSSday7). Early neurological outcome was assessed by the change in the NIHSS (ΔNIHSS), defined as:

\[ ΔNIHSS = \frac{NIHSS_{day7} - NIHSS_{init}}{NIHSS_{init}} \]

Late neurological outcome was evaluated by measuring the Barthel Index (BI) (Mahoney and Barthel, 1965) and modified Rankin Score (mRS) (Rankin, 1957; Bamford et al., 1989) performed ~90 days after stroke onset. All clinical assessments were performed by a neurologist or clinical nurse specialist certified in the administration of the stroke scales and blinded to the PET data. In patients who died, the worst score on the relevant scale was used for that assessment (i.e. 0 on BI and 6 on mRS).

Imaging protocol

The FMISO PET scans were performed on an ECAT 951/31R PET scanner (Siemens/CTI Inc., Knoxville, TN, USA), 2 h after the intravenous administration of FMISO at a dose of 0.05 mCi/kg. Acquisition in 3D mode yielded 31 image slices 3.37 mm apart, with pixel dimensions of 2.34 mm in the x and y planes, a transverse image resolution of 6.5 mm and an axial resolution of 4.5 mm. Tissue attenuation of 511 KeV γ-radiation was measured with a 10-min 2D transmission scan acquired with retractable 68Ga/68Ge sources.

The final infarct volume was assessed by CT or MRI, performed 7–10 days after stroke onset. CT scans comprising contiguous 5-mm thick slices were performed on a Picker PQ 2000 scanner (Picker, Cleveland, OH, USA). MRI scans were obtained with a 1.5 T echoplanar imaging-equipped whole-body scanner (Signa Horizon SR 120; General Electric, Waukesha, WI, USA). This included T2-
were used to compare dependent variables, unless they were normally distributed, in which case parametric tests were preferred. Spearman’s rank correlation was calculated to assess the strength of the association between volumetric measures and clinical outcome (NIHSS, ANIHSS, BI and mRS). The Mann–Whitney U-test was used to determine significant differences in lesion volumes and clinical measures between patient subgroups. Fisher’s exact test was used to assess differences between categorized groups. Multivariate analysis of covariance (ANCOVA) with the initial NIHSS score as the dependent variable, TIV subgroup as the main effect and TIV (ml) as the covariate was used to assess the effect of the volume of hypoxic tissue on the clinical deficit. A P value of <0.05 (two-tailed) was considered statistically significant.

**Effect of time since stroke onset on the fate of hypoxic tissue**

The effect of time on the fate of hypoxic tissue was examined by examined by two methods. First, we assessed the relationship between time since stroke onset and the proportion of the TIV and HV that survived spontaneously. Secondly, we compared the proportion of the TIV and HV that survived spontaneously in the patient subgroups studied <=12 or >12 h after stroke onset.

**Effect of time since stroke onset on the functional impact of spontaneous survival of hypoxic tissue**

The effect of time on the functional impact of spontaneous survival of hypoxic tissue was assessed by ANCOVA with ANIHSS as the dependent variable, time subgroup as the main effect and SHVR as the covariate in patients studied <=12 or >12 h after stroke onset.

### Results

Sixty-six patients (44 male and 22 female; mean age ± SD, 74.4 ± 11.6 years) presenting with acute ischaemic stroke were studied with FMISO PET. Fifteen subjects (eight males; mean age ± SD, 67.4 ± 10.7 years) with no prior history of stroke or TIA and with normal brain CT scans formed the control group. There was no significant difference in age between the patients and control subjects (P > 0.05, Student’s t-test).

Hypoxic potentially viable tissue was identified on acute PET in 33 patients (22 male and 11 female; Table 1) at a median of 16.5 h (range 3.9–47.5 h) after stroke onset. Of the patients who exhibited hypoxic tissue, 53% had hypertension, 9% had diabetes, 19% had hyperlipidaemia, 25% had ischaemic heart disease and 50% had atrial fibrillation. There was no significant difference in the incidence of these vascular risk factors between those with and without hypoxic tissue identified on acute PET (P > 0.05, Student’s t-test). Patient 4 had a second stroke on day 2 and was excluded from the clinical analysis. Patients 6, 11, 12 and 17 died, and patient 28 withdrew from the study before day 7. Results from these six patients are not included in the clinical outcome analysis but are included in all other analyses when possible.
Hence, 27 patients (19 male and eight female; mean age 73 years) had hypoxic tissue identified on acute PET, and had late CT/MRI and clinical outcome data. In these patients the median volume of hypoxic tissue was 22.3 ml (range 0.6–164 ml). A median of 27% (range 1–100%) of the TIV comprised hypoxic tissue. The median IV was 88 ml (range 0–341 ml). A significant correlation \( (r = 0.6, P < 0.01) \) was observed between the TIV and the severity of the initial clinical deficit measured by the NIHSSinit. ANCOVA showed that there was no interaction between the patient subgroups with hypoxic tissue comprising <20 or >20% of the TIV and the strength of the association between the TIV and NIHSSinit \( (P = 0.87) \).

Spontaneous survival of hypoxic tissue was associated with improved early and late clinical outcome measures. The correlations between SHVR and \( \Delta \)NIHSS \( (r = 0.7, P < 0.01) \), day 90 BI \( (r = 0.5, P < 0.01) \), and day 90 mRS \( (r = -0.6, P < 0.01) \) were significant. As expected, the volume of hypoxic tissue that survived spontaneously was also correlated with the absolute change in NIHSS scores \( (r = 0.4, P < 0.05) \).

**Effect of time since stroke onset on the fate of hypoxic tissue**

Overall, in the 27 patients with complete outcome data, a median of 6.9% of the TIV (interquartile range 1.3–31.7%) and a median of 45.9% of the HV (interquartile range 23.7–74.8%) survived spontaneously. The relationship between time and the fate of hypoxic tissue was analysed by two methods. First, in the whole group there was no significant correlation between time since stroke onset and the proportion of the TIV \( (r = 0.01, P = 0.98) \) and HV \( (r = 0.26, P = 0.2) \) that survived spontaneously. Secondly, the proportion of the TIV \( (P = 0.56, \text{Mann–Whitney } U\text{-test}) \) and HV \( (P = 0.2, \text{Mann–Whitney } U\text{-test}) \) that survived spontaneously was not significantly different in the patient subgroups studied ≤12 and >12 h after stroke onset. These findings indicate that hypoxic tissue has an extremely variable outcome that is not predetermined even when it is observed at later times after stroke onset.
Effect of time since stroke onset on the functional impact of spontaneous survival of hypoxic tissue

The subgroups studied ≤12 and >12 h after stroke onset by PET were similar with respect to initial NIHSS, TIV and IV (Table 2). Strong correlations were observed between SHVR and ΔNIHSS \((r = 0.85, P < 0.01)\), day 90 BI \((r = 0.86, P < 0.01)\) and day 90 mRS \((r = -0.89, P < 0.01)\) in the subgroup of patients studied with PET within 12 h of stroke onset (Table 3). In comparison, for the subgroup of patients studied >12 h after stroke onset, weaker, but still significant, correlations were observed between SHVR and ΔNIHSS \((r = 0.59, P < 0.01)\) and day 90 mRS \((r = -0.46, P < 0.05)\), but there was no significant correlation between SHVR and day 90 BI \((r = 0.37, P = 0.12)\). The relationship between SHVR and ΔNIHSS for patients studied in each time epoch is shown in Fig. 2. ANCOVA showed that there was no significant interaction between time since stroke onset and the association between SHVR and ΔNIHSS. The results for the clinical characteristics, volumetric measures, prevalence of hypoxic tissue within the TIV, proportions of the TIV and HV volumes that spontaneously survived, and the correlations between SHVR and clinical outcome measures were similar when we used the median time from onset to PET study (16.5 h) to dichotomize patients into time epochs.
Effect of time since stroke onset on prevalence of hypoxic tissue

Hypoxic tissue was observed in 11 out of 13 (84%) studies performed within 12 h of stroke onset and 22 out of 53 (41%) studied beyond 12 h after onset (\(P < 0.05\), Fisher’s exact test). All patients with waking deficits were in the 12–48 h category. In the 60 patients where late CT or MRI were obtained, the number of studies where >20% of the TIV comprised hypoxic tissue was six out of 10 (60%) within 12 h of stroke onset and eight out of 50 (16%) performed after 12 h (\(P < 0.05\), Fisher’s exact test). Figure 3 shows the prevalence of hypoxic tissue related to time of study.

Discussion

The principal findings of this study were two-fold. First, metabolically compromised hypoxic tissue retained the capacity for spontaneous survival up to 48 h after the onset of ischaemic stroke. Secondly, its spontaneous survival was associated with improved early (ΔNIHSS) and late (BI and mRS) neurological outcome measures. This association was observed for both ≤12 and >12 h post-stroke epochs. Together with our previous report of the spatial evolution of hypoxic tissue from the centre to the periphery of the ischaemic region (Markus et al., 2003), these findings indicate that irreversible injury following ischaemic stroke is a dynamic process, spatially and temporally, that may continue for up to 48 h after stroke onset. Most importantly, interruption of this process is associated with functional improvement. These findings have important implications for therapeutic strategies in ischaemic stroke.

Our findings add to growing evidence from clinical studies in humans and experimental research that infarct expansion occurs even beyond 24 h after onset of ischaemic stroke. The results indicate that this expansion is at the expense of hypoxic but potentially viable tissue and that even at late time points, the transition of hypoxic tissue to infarction is not inevitable. Investigators using sequential multitracer PET scans to document the evolution of hypometabolic tissue following middle cerebral artery (MCA) occlusion in baboons showed that the volume of this tissue increased progressively until it reached a maximum >24 h after onset and equated with the volume of infarction on histology (Touzani et al., 1995). Similar observations were reported after experimental MCA occlusion in cats studied with sequential multitracer PET (Heiss et al., 1994) and rats studied with multimodal MRI (Quast et al., 1993). In humans studied with sequential MRI, Baird et al. (1997) reported an increase in infarct volume of >20% in one-third of patients with ischaemic stroke beyond 24 h after onset. Heiss et al. (1992) observed metabolically active tissue in the peri-infarct region in patients studied with multitracer PET up to 48 h of

### Table 2

<table>
<thead>
<tr>
<th>Measure</th>
<th>≤12 h [mean (SD)]</th>
<th>&gt;12 h [mean (SD)]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>8</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>NIHSSinit</td>
<td>13 (6.6)</td>
<td>15 (7.1)</td>
<td>0.47*</td>
</tr>
<tr>
<td>TIV (ml)</td>
<td>129.6 (122.8)</td>
<td>141.3 (99.7)</td>
<td>0.79*</td>
</tr>
<tr>
<td>IV (ml)</td>
<td>111.9 (123.7)</td>
<td>127.5 (100.4)</td>
<td>0.56*</td>
</tr>
<tr>
<td>HV/TIV (%)</td>
<td>39.2 (36.1)</td>
<td>53.8 (24.8)</td>
<td>0.16*</td>
</tr>
<tr>
<td>HV/TIV (%)</td>
<td>57.8 (34.6)</td>
<td>24.9 (26)</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

*Mann-Whitney U-test adjusted for unequal sample sizes. NIHSS = National Institutes of Health Stroke Scale; HV = hypoxic volume; IV = infarct volume; HV S = spontaneously surviving hypoxic tissue volume; TIV = total ischaemic volume (IV + HV S).

### Table 3

<table>
<thead>
<tr>
<th>Measure</th>
<th>Correlation with SHVR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤12 h</td>
</tr>
<tr>
<td></td>
<td>(r^*)</td>
</tr>
<tr>
<td>ΔNIHSS</td>
<td>0.85</td>
</tr>
<tr>
<td>Day 90 mRS</td>
<td>-0.89</td>
</tr>
<tr>
<td>Day 90 BI</td>
<td>0.86</td>
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</table>

*Spearman’s rank correlation coefficient. SHVR = surviving hypoxic volume ratio; NIHSS = National Institutes of Health Stroke Scale; BI = Barthel Index; mRS = modified Rankin Score.
stroke onset. Infarction of this tissue had occurred in nine out of 16 patients when the study was repeated 13–25 days later.

We observed that spontaneous survival of hypoxic but viable tissue correlated significantly with functional improvement on a number of widely used clinical outcome measures at both 1 week and 3 months in patients studied both before 12 h and between 12 and 48 h from stroke onset. There was a trend towards greater benefit in patients studied earlier. Our study thus provides evidence that spontaneous survival of hypoxic tissue confers functional benefit and may be an important mechanism underlying recovery from stroke.

Furlan et al. (1996) have previously shown that spontaneous survival of penumbral tissue identified by multitracer PET within 7–16 h (mean 10 h) of stroke onset was associated with significant functional improvement measured by relative change in the Mathew and Orgogoza stroke scales at 2 months (both scales) and at 21 days (Mathew scale only), but not at 1 week. In our study, spontaneous survival of metabolically compromised tissue improved both early and late functional outcome irrespective of the clinical rating scale used and this association was observed even up to 48 h after stroke onset. In both studies the proportion of threatened tissue that survived spontaneously was similar, with a mean of 49% of hypoxic tissue surviving in our study and a mean survival rate of 52% of non-infarcted penumbral voxels being reported by Furlan et al. (1996). Four patients in the group had small total ischaemic volumes (<6 ml) but had substantial neurological impairment, with initial NIHSS scores of 7, 13, 12 and 3.

Interestingly, even in this group of patients with small total ischaemic volumes the degree of clinical improvement was closely related to the proportion of the TIV that spontaneously survived. In particular, patient 2, who had 3 ml of hypoxic tissue and an initial NIHSS of 7 when examined 4.5 h after stroke onset, had no infarct on delayed CT and an NIHSS of 1 at day 7. This emphasizes that even small lesions in the eloquent areas of the brain can result in substantial clinical deficits, and that salvage of small volumes of potentially viable tissue may confer benefit in this situation.
Markers of tissue hypoxia have the advantage of being able to distinguish viable but metabolically compromised ischaemic regions independent of time and variations in blood flow since the vascular insult. Baron (1999) proposed three operational criteria to define penumbral tissue in the living human brain, which have been modified recently to be applicable to other modalities of functional neuroimaging (Doman and Davis, 2002): (i) the tissue should have physiological characteristics consistent with cellular dysfunction but not death; (ii) it should have an undetermined outcome; and (iii) the initial neurological deficit should be proportional to the volume of the tissue and the volume of surviving tissue should correlate with clinical outcome. These criteria were previously applied to multitracer PET (Furlan et al., 1996; Baron, 1999), and now it has been shown that tissue with FMISO uptake also fulfills these criteria. Findings in animal stroke models indicate that tracer retention only occurs in tissue that is at risk of infarction (Hoffman et al., 1987; Di Rocco et al., 1993; Lythgoe et al., 1997, 1999). Initial human studies showed that FMISO uptake identified peri-infarct hypoxic tissue that had an undetermined outcome (Read et al., 1998) and contributed to the initial neurological deficit (Read et al., 2000). The finding of the present study confirms these results in a larger sample of patients, and shows a significant correlation between survival of tissue with tracer uptake and improved clinical outcomes. The observation that infarct expansion at the expense of hypoxic tissue progresses from the centre to the periphery of the ischaemic region (Markus et al., 2003), in a manner similar to that seen in animal stroke models (Heiss et al., 1994; Touzani et al., 1995), lends further support. The relative inaccessibility of PET, however, limits the use of this tracer to research studies.

A number of methodological issues should be considered. Clinical outcome was assessed prospectively at 1 week and 3 months post-stroke. We observed an improvement in the NIHSS score at 1 week, which was comparable to the results of an earlier study of serial NIHSS change in patients with acute stroke who did not undergo thrombolysis (Wityk et al., 1994). The percentage change in NIHSS score has been used to monitor neurological outcome in other studies (Wintermark et al., 2002). We used manual identification of the infarct volume on CT, a method previously shown to have low intra-observer and inter-observer variability (van der Worp et al., 2001). Although CT scans performed 7–10 days after stroke onset maybe susceptible to the ‘fogging’ effect, the infarct contour outlined on day 7–10 CT was similar to that on later CT performed at 30 days in a subset that survived, suggesting that the effect was minimal. We used a 12 h threshold to dichotomize patients. Similar results, however, were obtained when the median time from onset to PET study was used to dichotomize patients into time epochs.

In combination, the observations that infarct expansion occurs at the expense of hypoxic tissue and that spontaneous survival of hypoxic tissue is associated with functional improvement have important clinical implications. Hypoxic tissue that spontaneously underwent transition to infarction is...
likely to be a valuable target for therapeutic intervention. However, the relationship between therapy-related salvage of hypoxic tissue and outcome was not directly examined in this study. The volume of hypoxic tissue was significantly higher in the subgroup studied within 12 h of stroke onset, and is presumably greatest immediately after stroke onset, suggesting that intervention is likely to be most efficacious when initiated early. However, the observation of substantial volumes of threatened, potentially viable tissue at later times, and that its spontaneous survival was associated with improved functional outcome, suggests that some patients may benefit even at later stages. With modern neuroimaging tools, it may be possible to achieve the goal of individualized stroke therapy based on an assessment of the pathophysiological state and the potential for neurological recovery of each patient.

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