Early spontaneous hyperperfusion after stroke
A marker of favourable tissue outcome?

Gilles Marchal,1,2 Mauro Furlan,1,2,5 Vincent Beaudouin,1,3 Patrice Rioux,2 Jean Louis Hauttement,4 Carlo Serrati,1,2,5 Vincent de la Sayette,2,4 François Le Doze,2,4 Fausto Viader,2,4 Jean Michel Derlon1,4 and Jean Claude Baron1,2

1Cyceron Centre, 2INSERM U320, 3CEA DSV/DRM, 4CHRU Côte de Nacre, University of Caen, Caen, France and the 5Clinica Neurologica Dell’Università di Genova, Italy

Correspondence to: Jean Claude Baron, INSERM U320, Centre Cyceron, Bd Becquerel, BP 5229, 14074 Caen Cedex, France

Summary
To clarify the relationships between early hyperperfusion (i.e. the hallmark of early, efficient recanalization in animal stroke models) and ultimate infarction, we have compared acute-stage perfusion PET images and chronic-stage CT scans in patients with middle cerebral artery (MCA) stroke. We used PET and the oxygen-15 ($^{15}$O) equilibrium method to obtain cerebral blood flow (CBF), cerebral blood volume (CBV), oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen consumption (CMRO$_2$) parametric images in 30 consecutive, still symptomatic, first-ever MCA territory stroke patients without sign of haemorrhage at admission CT scan. Each subject was studied twice, first within 5–18 h of stroke onset, and, in survivors, ~1 month later; a plain CT scan (co-registered with PET) was performed ~1 month after onset. Following initial screening based on acute-stage perfusion images, 10 survivors with focal hyperperfusion in the appropriate MCA territory confirmed by computer were declared eligible. In each patient, the topography and volume of both hyperperfusion and infarction (delineated on late CT scan) were recorded, and all PET parameters were obtained for both areas and both times. The hyperperfused areas affected the cortical MCA territory, often widely so and in a patchy fashion; they were topographically distinct from, and consistently larger than (P < 0.01, Wilcoxon sign test) the final infarcts, which were small and generally deep-seated. In none of the nine patients in whom it was successfully performed did transcranial Doppler reveal MCA stem occlusion. In the hyperperfused regions, the acute-stage perfusion, blood volume and oxygen consumption were significantly increased, and the OEF significantly reduced, while all these variables had significantly returned toward normality in the chronic-stage PET study. The ultimately infarcted area did not exhibit significant hyperperfusion in the acute stage. The areas with acute-stage hyperperfusion exhibited haemodynamic and metabolic abnormalities consistent with post-recanalization hyperperfusion, i.e. vasodilatation and 'luxury perfusion'. Increased oxidative metabolism, previously reported only in animals, presumably reflects an overshoot of protein synthesis. The fact that the areas with hyperperfusion, though extensive, were topographically distinct from the infarcted region, suggests that spontaneous non-haemorrhagic hyperperfusion, when documented 5–18 h after onset, is a harmless and even perhaps beneficial phenomenon. These results have implications for clinical trials.

Keywords: cerebral ischaemia; PET; cerebral blood flow; cerebral metabolism; oxygen-15

Abbreviations: CBF = cerebral blood flow; CBV = cerebral blood volume; CMRO$_2$ = cerebral metabolic rate of oxygen consumption; MCA = middle cerebral artery; $^{15}$O = oxygen-15; OEF = oxygen extraction fraction; rCBF = regional cerebral blood flow; RI = recovery index; SPECT = single photon emission tomography; $^{99m}$Tc-HMPAO = technetium-99m hexamethylpropyleneamine oxime
Introduction

Focal cerebral hyperperfusion after stroke in man has long been documented (Lassen, 1966) and is a frequent, yet poorly understood, phenomenon. Two-dimensional studies of regional cerebral blood flow (rCBF) with Xenon-133 have shown that hyperperfusion, early after stroke onset can be associated with reversible deficit (Hartmann, 1985), while lack of angiographically detectable occlusion is a consistent finding (Paulson et al., 1970). The latter would be consistent with animal experiments which show that following a period of ischaemia, restoration of cerebral perfusion pressure consistently results in a marked and variably prolonged hyperperfusion (Lassen, 1966; Tamura et al., 1980; Tasdemiroglu et al., 1992). Xenon-133 studies have also shown a frequent occurrence of focal hyperperfusion at later times, days to weeks after stroke onset; this kind of subacute hyperperfusion has been more often equated with infarction, though there appeared to be exceptions to this (Olsen et al., 1981; Olsen and Lassen, 1984; Sugiyama et al., 1986). In the classic studies of Olsen (Olsen et al., 1981; Olsen and Lassen, 1984), however, the relationships between hyperperfusion and infarction were make uncertain by the twodimensional and unilateral nature of the rCBF studies. PET is presently the method of reference to assess focal hyperperfusion after stroke because it allows quantitative, simultaneously bilateral and high-resolution tomographic imaging of both CBF and oxygen consumption (Baron, 1991). However, and despite these advantageous features, the relationships between hyperperfusion and tissue outcome have remained unclear. Several PET studies documented that subacute hyperperfusion was almost always associated with tissue necrosis (Baron et al., 1981; Lenzi et al., 1982; Baron, 1987; Hakim et al., 1987; Ackerman et al., 1989; Fink et al., 1993), while acute-stage hyperperfusion unassociated with extensive severe hypometabolism always heralded excellent clinical outcome (Marchal et al., 1993, 1995). These apparently conflicting findings would, however, be consistent with recent studies which show that the time of occurrence of reperfusion after MCA occlusion in the rat might be a critical factor for tissue outcome (Menezawa et al., 1992; Minematsu et al., 1993). As of today, no study has assessed in a three-dimensional way the topographical relationships between acute-stage hyperperfusion and ultimate brain infarction in man.

The aims of the present study were thus: (i) to establish, by means of combined PET and CT scanning, the relationships between early spontaneous hyperperfusion and tissue outcome; (ii) to analyse the pathophysiological basis of such relationships by measuring the combined alterations in cerebral haemodynamics and oxygen consumption in the hyperperfused and the infarcted brain regions.

Patients and methods

Patients

Patients, aged >18 years, with first-ever acute MCA territory ischaemia/infarction, diagnosed on clinical and CT grounds <18 h from onset, were selected among all stroke patients admitted in the Medical Emergency Department of the Caen University Hospital over the period between 1990 and 1993. All patients had a full neurological assessment by one of the authors (G.M.) at admission. Patients symptom-free at the time of PET study or with haemorrhage on admission CT scan or with marked obtundation of consciousness, typical lacunar syndrome, recent myocardial infarction, or other organ failure were excluded from the study. After informed consent was obtained from the patient or his/her nearest relatives, enrolled patients were not given cerebrovascular-directed therapies (e.g. calcium channel blockers); arterial hypertension was treated only if systolic blood pressure exceeded 220 mmHg. We used the Orgogozo’s MCA stroke scale (Orgogozo and Dartigues, 1991) to quantify the neurological deficits just before the PET study (day 0) and at 2 months (day 60) follow-up; this validated scale ranges from 0 to 100, with a score of 100 being normal neurological status. The percentage of neurological recovery was assessed using Martinez-Vila’s recovery index (RI): RI = (day 60–day 0)/(100–day 0) (Martinez-Vila et al., 1990). A cervical and a transcranial doppler ultrasound study was performed after PET and within the first 48 h after onset. Blood samples were withdrawn for usual blood tests, particularly blood sugar levels. In survivors, PET studies were repeated ~1 month later; a late CT scan was also performed (see below).

PET scanning procedure (for details, see Marchal et al., 1992)

Patients were scanned on a LETI TTV03 camera, which has a high physical spatial resolution (5.5×5.5×9 mm), and allows seven brain transversal slices. We used the classical ¹⁵O steady-state inhalation technique with C¹⁵O₂, C¹⁵O and C¹⁵O₂ to measure CBF, CBV, OEF and CMRO₂. Following noise filtering, the lateral (x, y) resolution in the reconstructed images was ~11 mm. Measured OEF was corrected for the unextracted label remaining in the vascular space, according to a published procedure (Baron et al., 1989). We used the Fox method (Fox et al., 1985) for head positioning (and repositioning) at both PET studies; this stereotaxic approach, based on the glabella–inion line seen on a lateral skull X-ray, was also used for late CT scanning procedures. The seven transverse slices cut the brain, parallel to the glabella–inion line at levels: -4, +8, +20, +32, +44, +56 and +68 mm from this line. A transmission scan with an external source of germanium-68 was performed before each study for attenuation correction. Arterial whole blood and plasma ¹⁵O activity, blood gases, haemoglobin and pH were measured with six arterial blood samples (1 ml each) for each acquisition period. Heart rate and blood pressure were monitored continuously. Studies were performed at rest with eyes closed, ears partially blocked and in a quiet environment with dimmed light. C¹⁵O₂, C¹⁵O₂ and C¹⁵O matrices were transformed pixel-
by-pixel into CBF, OEF, CMRO\textsubscript{2} and CBV images by means of well-validated equations (Frackowiak et al., 1980). Parametric images from both PET studies were exactly realigned and late CT was co-registered with PET. The PET procedure has been approved by the Ethics Committee of Caen.

Brain CT scan
We used a CGR CE 12-000 model scanner (Compagnie Générale de Radiologie, Buc, France; resolution: 1.5X1.5X5.0 mm, x, y, z). A CT scan was performed in each subject twice (both unenhanced), once at admission to exclude haemorrhage or other non-ischaemic brain disease, and then repeated in survivors 30–60 days later to evaluate tissue outcome and obtain an index of infarct volume, if present. At this second CT study, we used the same stereotaxic positioning procedure and studied the same seven planes as for both PET scanning sessions (see above).

Eligibility of patients
Among all consecutive patients evaluated by PET according to the above criteria and procedure, patients with early spontaneous hyperperfusion were selected according to the two following criteria: (i) early spontaneous hyperperfusion on CBF images; (ii) availability of late CT scan to assess tissue outcome. The former criterion entailed a selection of patients according to a two-step procedure, as follows. First, the sets of CBF images for all patients were displayed using a 17 level-colour scale (Fig. 1A), and three neurologists with experience in PET imaging (V.d.l.S., F.V. and J.C.B.), unaware of clinical and CT scan data, but aware of the clinically affected side, were asked independently to select those patients with possible hyperperfusion on any PET plane but within the clinically appropriate MCA territory, relative to the unaffected side. Then, the PET images from all patients with possible hyperperfusion identified by any one of these three observers were subjected to an objective image analysis procedure to establish or disprove the presence of hyperperfusion (see below); as a quality control, the patients not selected by the visual procedure were also subjected to the computerized analysis. Regarding the second criterion (i.e. the availability of a late CT scan), it implied that only stroke survivors would be potentially eligible in the final stage.

Parametric image analysis
The strategy for image analysis was specially designed for the following purposes: (i) to formally establish or disprove the presence of focal hyperperfusion on acute-stage CBF images by means of an objective method which entailed computer-delineation of the hyperperfused areas; (ii) to compare the topography and volume of these hyperperfused regions with those of the infarcted area, as defined on co-registered late CT scan (see below); (iii) to measure the PET parametric values in the acutely hyperperfused regions as well as in the ultimately infarcted region both in the acute and in the chronic stage. This procedure ran as follows.

Delineation of hyperperfused regions
The hyperperfused regions in the relevant MCA territory were delineated plane by plane by a computer-generated percentage isocontour routine. This was done on the five upper PET planes (i.e. glabella-inion +20 to glabella-inion +68 mm), which contain the MCA territory. The finally applied value (in percent of peak voxel value) was selected according to a trial-and-error, real-time user-interactive procedure, such that the CBF in all the 1X1X9 mm voxels included in each final isocontour lay above the maximum voxel value in the homologous contralateral isocontour(s) (Fig. 1B). This conservative procedure generated one or several ‘functional’ regions-of-interest, together with their mirror regions on the contralateral hemisphere (Fig. 1B). The integrated surface of all hyperperfusion regions of interest were then computed for each PET plane and summed across all PET slices to obtain an index of hyperperfused tissue volume (in square centimetres).

Delineation of the infarct region of interest
Using the same software, the contours of hypodensity were visually delineated plane-by-plane on day 30–60 plain CT scans, and, then, projected onto corresponding co-registered and matrix realigned PET cuts for topographical comparison to the hyperperfusion regions of interest. Infarct areas were calculated and summed as above to obtain an index of infarcted tissue volume (also in square centimetres).

Calculation of PET variables
For each variable (i.e. CBF, CMR\textsubscript{O2}, OEF, CBV and CBF/\textit{CBV}) the mean value for all the 1X1X9 mm voxels included in the regions of interest with hyperperfusion and their contralateral mirror regions of interest (defined on the CBF images) was calculated. This was also applied to the same regions of interest projected onto co-registered late PET images (Fig. 1C). The same procedure was used to obtain the parametric values for the infarct regions of interest.

Statistical analysis
The volume indices for the hyperperfusion and for the infarct regions of interest were compared, using the non-parametric Wilcoxon sign test for paired samples. The PET physiological values in these regions of interest were compared to those in their mirror regions of interest by means of the non-parametric Wilcoxon signed rank test (BMDP software). The values for each variable at the first PET study were compared with those in the same regions of interest at the second PET
study by means of the same test. Statistical significance was accepted if two-tailed \( P \) values were < 0.05.

**Results**

**Clinical material**

From our sample of 30 consecutive MCA stroke patients (mean age ± SD: 73 ± 10 years), all studied with PET within 5–18 h after the onset of clinical signs, 13 patients with possible hyperperfusion in the appropriate MCA territory were selected based on the independent visual assessment of the three observers (full agreement for five patients, two out of three agreements for three patients, and one out of three for five patients). Of these 13 patients, three (all belonging to the latter group) were secondarily rejected, two in whom hyperperfusion could not be confirmed objectively with the computerized analysis, and one because early death from extensive infarction at day 10 prevented assessment of tissue outcome (an autopsy was refused; see Discussion for further description of this case); in none of the 17 patients not selected by the visual procedure did the computerized analysis document hyperperfusion. Thus, focal hyperperfusion was confirmed objectively in 10 patients in whom a late CT scan was available, and these 10 patients were declared eligible.

Their clinical and ultrasound data are summarized in Table 1 (they have been reported previously as 'pattern III'; Marchal et al., 1993, 1995). They did not differ from our general stroke population by either age (72 ± 9 years) or interval between clinical onset and PET study (mean ± SD: 10.1 ± 4.5 h); the gender ratio was 5:5. There was a possible cardiac source of embolism in five cases. The Doppler ultrasound examinations showed an unoccluded MCA stem in nine patients (no temporal bone window was found in one patient); MCA branch occlusion was suspected in two cases, while carotid artery stenosis or occlusion at the cervical level was found in three patients. In Patient 10, the study disclosed reduced distal vascular resistance and increased MCA branch systolic velocities on the affected side, suggesting 'vasoplegia' (see below). Overall, therefore, an embolic mechanism for stroke could be suspected in all 10 patients. They all had mild to moderate initial neurological impairment, with MCA scores ranging from 55 to 95. Nine subjects were still symptomatic after 24 h, but all 10 had an excellent outcome/recovery after 2 months follow-up (MCA score range: 95–100, RI > 88%). Admission CT scan was normal in all or showed trivial age-related mild atrophy.

**Biological and physiological data**

No patient was diabetic and admission blood sugar levels were within the normal physiological limits in all. Arterial \( \text{pCO}_2 \), assessed at both PET studies remained within normal limits in all patients.

**Late CT scan**

Chronic-stage CT scans, performed according to the procedure described in Patients and methods, were unremarkable in two patients (1 and 2) and showed small infarcts in the remaining eight (<4 cm, in largest diameter); in seven of these eight cases, the hypodensity was deep-seated in the MCA territory, while it affected the parietal cortex in the last case (Patient 8) (see Figs 2 and 3).

**Topography of the hyperperfusion regions of interest and comparison to the infarct regions of interest**

The topography of the hyperperfusion and the infarct regions of interest are illustrated for one patient in Fig. 2 and sketched for all 10 patients in Fig. 3. In contrast to the infarcts, the regions with hyperperfusion were often extensive and widespread, generally patchy, and clearly predominantly

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**Fig. 1** (A) Illustrative parametric CBF image (obtained parallel to and 44 mm above the glabella–inion line) showing clearcut areas of hyperperfusion (arrows) in the right middle cerebral artery (MCA) territory, as compared to the left MCA territory. The colour scaling was adapted by a non-observer (G.M.) such that patches of maximum pixel values were displayed in white for all patients. In this case (Patient 9), disjointed hyperperfused areas are distributed throughout most of the affected MCA territory; the white patches visible outside the MCA territory near the midline represent normal findings and were considered neither for the visual nor for the computerized image analysis. (B) Areas of hyperperfusion were delineated with computer-generated isocontours based on a percentage of the peak voxel value. The latter was adjusted interactively so that all the final isocontour(s) in the MCA territory included only voxels with CBF values above the maximum pixel value in the contralateral homologous regions (see Patients and methods). Once defined, these isocontour(s) were registered one by one as regions-of-interest, and were then copied by symmetry onto the contralateral hemisphere. Note that this method is conservative, as the final isocontours tend to underestimate the extent of hyperperfusion as apparent visually.

(C) The regions-of-interest defined on both hemispheres on the acute-stage PET images were then projected upon the corresponding co-registered PET planes obtained in the chronic stage. This case (Patient 9) illustrates the disappearance of acute-stage hyperperfusion at the chronic stage, with return to essentially symmetrical CBF (within normal noise limits).

**Fig. 2** Illustrative co-registered PET CBF and corresponding CT images obtained in Patient 9, 13 h and 30 days after stroke onset, respectively. The PET CBF image is presented according to a pseudo-colour scale with pixel values ranging from 0–70 ml 100 ml \(^{-1}\) min \(^{-1}\). Hyperperfused areas (delineated by white isocontours—see Patients and methods and Fig. 1B) are patchy and widely distributed over the entire cortical MCA territory, and show virtually no overlap with the infarct (shown on the CT images), which is small and restricted to the deep MCA territory (a questionable area of periventricular hypodensity on plane +44 mm was not considered evidence of infarction; note also the dilated sylvian fissure overlying the subcortical cavitary infarct).
Table 1 Clinical and ultrasound data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/gender</th>
<th>Stroke to PET Interval (h)</th>
<th>Past medical history</th>
<th>Symptoms</th>
<th>MCA score*</th>
<th>Doppler</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Day 0)</td>
</tr>
<tr>
<td>1</td>
<td>67/F</td>
<td>8</td>
<td>MI</td>
<td>Aphasia, apraxia</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>85/F</td>
<td>5</td>
<td>MI</td>
<td>Aphasia, R hemiparesis R hemisensory deficit</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>64/F</td>
<td>5</td>
<td>HBP</td>
<td>95</td>
<td>100</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>69/F</td>
<td>15</td>
<td>HBP</td>
<td>90</td>
<td>100</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>73/F</td>
<td>18</td>
<td>L hemiparesis, visual neglect</td>
<td>90</td>
<td>100</td>
<td>R carotid stenosis</td>
</tr>
<tr>
<td>6</td>
<td>89/M</td>
<td>8</td>
<td>Pace-maker HBP</td>
<td>90</td>
<td>100</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>61/M</td>
<td>14</td>
<td>AF</td>
<td>Aphasia, L hemiparesis, L hemianopia Aphasia</td>
<td>55</td>
<td>100</td>
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<td>MI</td>
<td>95</td>
<td>100</td>
<td>L carotid stenosis</td>
</tr>
<tr>
<td>9</td>
<td>67/M</td>
<td>13</td>
<td>HBP, MI</td>
<td>L hemiparesis, visual neglect</td>
<td>55</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>71/M</td>
<td>8</td>
<td>HBP, dyslipemia</td>
<td>75</td>
<td>100</td>
<td>R MCA 'vasoplegia'</td>
</tr>
</tbody>
</table>

F = female; M = male; MI = myocardial infarction; R = right; L = left; HBP = high blood pressure; AF = atrial fibrillation; TCD not feasible in patient 5. *Score on the middle cerebral artery (MCA) scale of Orgogozo et al. (1991).

Table 2 Volume indexes (summed surfaces across all relevant tomographic planes, see Methods) for the hyperperfused areas at acute-stage PET and the hypodense areas at late brain CT-scanning

<table>
<thead>
<tr>
<th>Patient</th>
<th>Summed surfaces (cm²)</th>
<th>Hypperfused areas</th>
<th>Infarcted areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.85</td>
<td>0.85</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3.27</td>
<td>3.27</td>
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</tr>
<tr>
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<td>8.90</td>
<td>8.90</td>
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</tr>
<tr>
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<td>13.21</td>
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</tr>
<tr>
<td>5</td>
<td>3.45</td>
<td>3.45</td>
<td>0.66</td>
</tr>
<tr>
<td>6</td>
<td>3.04</td>
<td>3.04</td>
<td>1.51</td>
</tr>
<tr>
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</tr>
<tr>
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<td>25.21</td>
<td>5.38</td>
</tr>
<tr>
<td>10</td>
<td>14.68</td>
<td>14.68</td>
<td>11.50</td>
</tr>
</tbody>
</table>

cortical. Strikingly, there was virtually no overlap between the hyperperfusion and the infarct regions of interest (a very small overlap was questionable in Patients 4 and 9). Computerized-delineated hyperperfused areas were found in 35 of the 50 PET planes analysed (i.e. five planes per patient); their summed surfaces ranged from 0.85 to 25.21 cm² (see Table 2). Furthermore, the hyperperfused areas were often seated in parts of the MCA territory far remote from the infarct itself (see Figs 2 and 3).

The computerized analysis detected hyperperfused areas in four out of the 17 patients not selected by the visual procedure. However, this was only in one PET plane per patient (i.e. four planes out of 85 analysed), and the hyperperfused areas consisted in only one island per plane, for a summed surface ranging from 0.14 to 0.60 cm², which could therefore represent statistical noise in CBF images. Furthermore, these islands of hyperperfusion were remote from the infarct in each case.

Volume indices for hyperperfusion and infarct (Table 2)
The volume indices of hyperperfusion and of infarct (if any) for each patient are reported in Table 2. The former were consistently larger than the latter, and this was highly significant across the whole sample (P= 0.005, Wilcoxon sign test). Because all 10 patients had an excellent outcome/recovery, quantitative correlations between these volume indices and final MCA score or RI could not be assessed. There was no significant correlation between the volume indices of hyperperfused areas and stroke-to-PET interval.

Haemodynamic and metabolic data (Fig. 4)
Hyperperfusion regions of interest
The mean (± 1 SD) parametric values for the hyperperfusion regions of interest and their contralateral mirror regions of
Fig. 3 Summary graph of the PET and CT data in the 10 patients studied. Only the relevant slices, i.e. with either hyperperfusion or infarct, or both, are represented. For each subject, the contours of the two hemispheres are outlined in black in a schematized fashion. Isocontours of hyperperfusion appear in red colour and contours of infarcts in blue. Infarcts affected the parietal cortex (Patient 8), the centrum ovale (Patients 3 and 6), the striatum and anterior limb of internal capsule (Patients 9 and 10), the stratum only (Patients 5 and 7) and the external capsule (Patient 4). This graph illustrates the main findings from this study, namely that the hyperperfused areas were extensive, mainly cortical and patchy, and distinct topographically from the infarcts, which were small and generally deep-seated.

Interest for the acute phase PET study are shown in Fig. 4A. As expected, the CBF was significantly higher in the former (P = 0.005; on average +74%). The CBV values were also significantly higher than values in the mirror regions (P = 0.013; on average +20%), as were the ratio CBF/CBV (P = 0.005; on average +48%), and the CMRO₂ values (P = 0.005; on average +34%). Finally, the mean OEF was significantly reduced (P = 0.005; on average -22%).

At second PET study (available in seven patients due to refusal or technical failure in three), performed on average 1 month later (26±12 days post-onset), the CBF, the OEF and the CMRO₂ had returned to symmetrical values in the regions with initial hyperperfusion and did not differ significantly from contralateral values; the CBV values were slightly decreased (P < 0.02; -14%). As compared with the acute-stage PET, there had been a significant decrease in absolute CBF, CBV, CBF/CBV and CMRO₂ values in the initially hyperperfused areas (P < 0.02 for each parameter), and a significant increase in absolute OEF values (P < 0.03).

Infarct regions of interest
At the first PET study, the infarct CBF was not significantly different from, though more variable than, the contralateral mirror region CBF (29.1±7.2 and 32.4±4.6 ml 100 ml⁻¹ min⁻¹, mean±SD, respectively). There was a tendency for a decrease in infarct CBF from the acute to the chronic stage (P = 0.07). The CBV values and the ratio CBF/CBV were not significantly changed either between sides or from one study to the next. The CMRO₂ and OEF values were not significantly affected in the acute-stage, but were significantly lower in the infarct than in the contralateral regions of interest in the chronic stage (P < 0.05); the infarct CMRO₂ significantly declined from the first to the second PET study (P < 0.05) (data not shown).

Discussion

Patient eligibility
The classification of patients into the 'hyperperfusion' category was based on a two-step procedure. In the first, three independent observers assessed parametric, pseudo-colour CBF images to select all possible cases with focal
areas of hyperperfusion; this visual approach was designed to mimic the clinical setting. In the second step, all areas markedly hyperperfused relative to the contralateral MCA territory were objectively screened for by means of computer-generated isocontours (Fig. 1A and B). We elected to use this procedure, rather than screen for hyperperfusion with respect to an absolute CBF threshold, because the latter would be dependent on the well-known intersubject variability in global CBF (Wise et al., 1986; Marchal et al., 1992). Also, taking each subject's unaffected hemisphere as control was judged valid as acute-stage changes in contralateral CBF have not been convincingly documented in humans (Andrews, 1991), nor in baboons (Pappata et al., 1993); accordingly, in the present study, the mean CBF in the mirror regions did not significantly differ from the mean value measured in whole neocortex in aged healthy volunteers (n = 5; age range 62–7 years). That this procedure did select truly hyperperfused areas is supported not only by the comparison with contralateral CBF values (see Results), but also by the fact that the average value in the hyperperfused tissue individually exceeded the upper 95% confidence limit for normal neocortical CBF (calculated as 47.8 ml 100 ml⁻¹ min⁻¹) in eight out of 10 eligible patients.

In the patient with early hyperperfusion who died early from brain herniation and thus was ineligible, the hyperperfused area lay in the anterior part of the MCA territory, bordering an extensive area of near-zero CBF and CMRO₂ which presumably caused the poor clinical outcome (Marchal et al., 1993). Furthermore, the CMRO₂ in the hyperperfused zone in this patient was essentially preserved (2.01 and 2.32 ml 100 ml⁻¹ min⁻¹ in the hyperperfused and contralateral mirror regions, respectively), which indicates a potential for ultimate tissue integrity (Baron, 1991). Overall, therefore, the data available in this case would be compatible with, though do not prove, peri-infarct hyperperfusion from partial MCA branch recanalization.

Relationships with tissue outcome

Our study, which is based on a detailed analysis at the individual level, revealed areas of hyperperfusion that were both highly significantly larger than, and topographically distinct from, the final infarct, if any, and this rule applied without exception. Although this finding stems from a seemingly small-scale study of 10 patients, this sample of eligible subjects was actually extracted from a series of 30 consecutive patients all studied within 18 h of stroke onset, i.e. the largest available sample of acute-stage MCA territory stroke PET studies, prospectively collected according to strict entry criteria. This optimal homogeneity likely underlies the internal consistency of our findings.

To further ascertain that the ultimately infarcted area was indeed distinct from the hyperperfused areas, we directly assessed early CBF in the infarct; although we acknowledge the possible partial volume effects in these often small regions of interest, the data do not indicate hyperperfusion (there was a small CBF increase or decrease in three and five patients, respectively, which could represent statistical noise). Thus, although earlier on, the hyperperfused area may have been more extensive to engulf the ultimately infarcted area, it remains that the latter did not exhibit hyperperfusion at time of PET; the essentially symmetrical infarct CBF would be consistent with partial arteriolar recanalization and/or patchy no-reflow phenomenon as a consequence of already established necrosis (Hallenbeck and Dutka, 1990).

The consistent lack of noticeable overlap between hyperperfused regions and infarcted areas in our series of acute MCA stroke is a new finding. Previously, Olsen et al. (1981, 1984) mentioned this occurrence in a subgroup of their subjects, but these authors used a two-dimensional technique measuring CBF on one side only, making the assessment of hyperperfusion and its relationships with infarction uncertain; furthermore, not all their studies were done in the acute stage. Shimosegawa et al. (1994) reported three patients in whom single photon emission tomography (SPECT) within 6 h of stroke revealed focally increased technetium-99m hexamethylpropyleneamine oxime (⁹⁹mTc-HMPAO) uptake in apparently damaged areas on CT, but the latter was neither done in the chronic stage nor co-registered with SPECT, while increased ⁹⁹mTc-HMPAO uptake may not consistently reflect hyperperfusion (Sperling and Lassen, 1993a; Steinling et al., 1994). Other investigators noted that increased ⁹⁹mTc-HMPAO uptake within the first 48 h tended to occur in non-infarcted regions (Baird and Donnan, 1993; Sperling and Lassen, 1993b; Baird et al., 1995).

Finally, although early hyperperfused areas were distinct from the CT hypodense lesion (which would represent ‘pannecrosis’; Garcia et al., 1995), we may have missed a ‘selective neuronal loss’ (inapparent on chronic-stage CT (Lassen et al., 1983; Torvik and Svindland, 1986, Weiller et al., 1993). However, neuropathologically demonstrated perifocal neuronal loss is rare in humans (Lassen et al., 1983; Torvik and Svindland, 1986), especially with small infarcts and no occlusion (Nedergaard et al., 1986). The MRI studies of Weiller et al. (1993) and Shimizu et al. (1995) lacked neuropathological correlation but suggested laminar necrosis or incomplete infarction restricted to the overlying cortex as a non-rare event after deep MCA stroke; however, acute-stage hyperperfusion was not documented in their cases. Although we cannot exclude that delayed MRI scans, if performed, may have revealed changes in the early hyperperfused areas, the latter often spread over remote cortical areas in our series and, at variance with both previous investigations, there was no significant reductions in chronic-stage CBF or CMRO₂, suggesting preserved integrity. Furthermore, the amount of isolated dead neurons, if any, would be presumably minimal in our patients since all but one made a full clinical recovery. Further studies combining subacute-stage gadolinium-enhanced MRI and ¹¹C-Flumazenil PET or ¹²³I-Iomazenil SPECT as possible markers.
of neuronal death (Sette et al., 1993; Nakagawara et al., 1995) may clarify this issue.

**Pathophysiological considerations**

In his classic CBF studies with angiographic data, Paulson (Paulson, 1970; Paulson et al., 1970) found that early hyperperfusion always correlated with normal carotid angiograms, while MCA occlusion was always associated with reduced flow in the early stage (within 24 h of onset). Consistent with this, in none of our cases was there evidence of MCA main stem occlusion on early post-PET transcranial Doppler studies (successful in nine of 10 patients; as we studied essentially elderly subjects with mild to moderate neurological deficit, an angiogram was not clinically indicated). There are several suggestions from our data in favour of spontaneous MCA recanalization which occurred at some undefined point in time before the PET study, early after stroke onset, and caused the observed hyperperfusion (thus far, other mechanisms for early hyperperfusion, e.g. inflammation, have not been documented). First, embolism was the clinically suspected stroke mechanism in each of our 10 patients, and embolic occlusions are especially prone to early recanalization (Fieschi et al., 1989). Secondly, our incidence of early hyperperfusion (about one in three) corresponds well to the known rate of occurrence of angiographically proven spontaneous recanalization (Hakim et al., 1987; Fieschi et al., 1989). Thirdly, the small size and deep location of the infarct in seven out of eight patients would be consistent with lenticulostriate artery mouth occlusion during transient MCA embolism (Minematsu et al., 1992; Ringelstein et al., 1992; Baird et al., 1995). Fourthly, the often widespread extent of hyperperfusion over the entire lateral cortical ribbon would be consistent with prior MCA stem occlusion. This interpretation would also be consistent with classic studies in animals, which have long documented that recirculation after a period of arterial occlusion induces an abrupt tissue hyperperfusion (Tamura et al., 1980; Tasdemiroglu et al., 1992), whose amplitude and duration are proportional to both the severity and length of prior ischaemia (Gourley and Heistad, 1984) and can exceed a two-fold increase from normal level and last several hours (Tamura et al., 1980). Two additional pieces of evidence from the PET variables further support the idea that we observed the equivalent of such early post-ischaemic hyperperfusion: (i) the finding of a significant increase in CBV, consistent with abnormal vasodilatation in the face of restored perfusion pressure (‘vasoplegia’; Lassen, 1966; Paulson et al., 1970), a phenomenon previously only documented in animal stroke models (Tasdemiroglu et al., 1992), and in which several biochemical processes triggered by ischaemia and/or reperfusion have been implicated (Macfarlane et al., 1991; Dawson et al., 1992; Nelson et al., 1992); (ii) the finding of a significant decrease in the OEF (‘luxury perfusion’; Lassen, 1966).

A paradoxical finding was that, while the OEF was low, the CMRO\textsubscript{2} was significantly increased in the hyperperfused regions. This enhanced oxidative metabolism may have contributed to the development of hyperperfusion, superimposed on the ‘vasoparalysis’ mechanism. A prolonged overshoot of energy metabolism and brain oxygen consumption after recirculation has been previously reported in gerbils (Levy and Duffy, 1977) and cats (Hossmann et al., 1976; Nemoto et al., 1981). Thus, the increased CMRO\textsubscript{2} may reflect a stimulation of protein synthesis and protein phosphorylation, shown in animals to follow ischaemia-induced inhibition and to be associated with tissue viability (Bergstedt et al., 1993). This process mainly affects the cerebral cortex (Bergstedt et al., 1993) and may be triggered by increased transcripts of growth factors, stress proteins or protooncogene products during reperfusion (Bergstedt et al., 1993; Krause and Tiffany, 1993). Consistent with this hypothesis, Heiss et al. (1993), using PET in five acute stroke patients, reported an increased \(^{13}\)C-aminoacid (l-methionine) uptake in ‘penumbral’ tissue surrounding infarction and experiencing reversible ischaemia.

At follow-up PET study, ~1 month later, the CBV, the CBV, the OEF and the CMRO\textsubscript{2} of previously hyperperfused areas, had all largely returned to normal values, consistent with a transient (post-ischaemic) event; the slight reduction in mean CBV and CMRO\textsubscript{2} presumably reflects cortical deafferentation due to small deep infarct (Baron, 1991).

**Clinical implications**

If our interpretation that the observed hyperperfusion reflects a post-ischaemic phenomenon is indeed correct, then our findings would agree with the concept of the ischaemic ‘penumbra’ (Jones et al., 1981), according to which, up to a certain time point which counts in hours, reperfusion is harmless, and actually beneficial. Independent from this interpretation, however, our findings indicate that, when observed 5–18 h after stroke onset, early hyperperfusion (especially if associated with increased CMRO\textsubscript{2}) is a marker of favourable tissue outcome. This may have practical implications in future management, notably for therapeutic trials of acute stroke, where more readily available perfusion imaging techniques could be used to depict hyperperfusion.

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