Original Contributions

Changes in Cerebral Blood Flow and Recovery from Acute Stroke

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SUMMARY We prospectively studied 14 patients with acute cerebral infarctions using serial 133Xenon inhalation cerebral determination (133Xe-rCBF), scored neurological examinations, and neuropsychological testing. All patients underwent the same battery of tests at 3 days, 1 week, 2 weeks, and 4 weeks after cerebral infarction to determine the prognostic value of early rCBF studies and the chronological relationship of changes in rCBF to clinical status. Baseline rCBF within 3 days of symptoms of acute stroke did not correlate with clinical neurological outcome (r = −0.17, p < 0.30; r = −0.18, p < 0.28, for the two indices of rCBF used). Among the 11 patients demonstrating neurological recovery, 7 improved at 1 week, significantly before increases in rCBF (p < 0.05). We conclude that early baseline rCBF does not predict clinical outcome in patients with acute cerebral infarctions and that return of neurological function precedes rather than follows increases in rCBF.

AS VASCULAR OCCLUSION is the underlying cause of acute cerebral infarction, decreased regional cerebral blood flow (rCBF) would appear to be a predictable occurrence following acute stroke. Several reports indicate early rCBF determinations do correlate with magnitude of infarction and predict clinical outcome. These studies find that luxury perfusion indicates a good prognosis, and low initial rCBF bodies ill for the patient with acute stroke. 1,2 As lysis of a thrombus and/or opening of collaterals could be crucial in salvaging ischemic neurons, it seems reasonable that an increase in rCBF would accompany improvement in stroke patients. However, no study has examined the chronological relation between changes in rCBF and clinical changes in patients with acute stroke. In an attempt to assess this relationship and more precisely define the predictive value of early rCBF measurement in patients with acute stroke, we prospectively followed 14 patients with acute hemispheric infarctions by means of serial neurological exams, rCBF determinations, and neuropsychological testing.

Methods and Materials

Fourteen patients admitted to the neurology service of the Hospital of the University of Pennsylvania with diagnoses of acute cerebral infarctions involving cerebral cortex in the distribution of the internal carotid artery constituted the group studied (see table 1). Within the first month each patient underwent four determinations of CBF, clinical neurological status, and neuropsychological function. No patient had a history of previous cerebral infarction; none had other uncontrolled systemic illness while studied; all patients had at least one CT within 24 hours of the first rCBF study. Patients underwent testing within the first 72 hours after onset of clinical symptoms of acute stroke, and at 1 week, 2 weeks, and 4 weeks. rCBF was determined by 133Xenon-inhalation technique (133Xe-rCBF) using Obrist’s two-compartment model. 10 Mean arterial blood pressures were recorded in all subjects. Hematocrit and hemoglobin were measured, and all rCBF values corrected to a pCO2 of 36.5 mm Hg. The two measures of CBF used in this study were the initial slope (IS) 10,11 and initial slope index (ISI).12,13 The former is a dimensionless measure of grey matter flow, and the latter is a dimensionless measure of grey matter flow and white matter flow. Both are reproducible and free of “slippage.”11 Studies in 14 normal controls who underwent two consecutive 133Xe-inhalation rCBF measurements in our laboratory in one session and 14 age-matched neurological controls with static deficits from chronic (more than 1 year prior to study) strokes or head trauma studied 1 to 8 weeks apart indicate that the standard deviation of hemispheric rCBF from test to test in one individual for IS is 5.7% and ISI 4.3%. Standard deviations for these two groups of controls were nearly identical (less than 1% different) and therefore averaged. Luxury perfusion was defined as a 2 standard deviation (SD) or more elevation of rCBF at 1 or more probe sites compared to hemispheric mean. Diaschisis was defined as a global decrease in CBF of 2 SD or more from one 133Xe-rCBF study to the next. A change of 2 SD of either IS or ISI for the affected...
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Description</th>
<th>Hemisphere with infarction</th>
<th>Initial rCBF of hemisphere involved (IS)</th>
<th>Initial rCBF of hemisphere involved (ISI)</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 year old man with dense left hemiparesis, left hemisensory deficit, left homonymous hemianopsia</td>
<td>Right</td>
<td>46.2</td>
<td>34.6</td>
<td>Improved</td>
</tr>
<tr>
<td>2</td>
<td>61 year old woman with anomic and conductive aphasia, weakness of right arm and face</td>
<td>Left</td>
<td>43.8</td>
<td>35.8</td>
<td>Unimproved</td>
</tr>
<tr>
<td>3</td>
<td>66 year old man with left hemiparesis, constructional apraxia</td>
<td>Right</td>
<td>44.8</td>
<td>33.5</td>
<td>Improved</td>
</tr>
<tr>
<td>4</td>
<td>74 year old man with Broca's aphasia, right hemiparesis and hemisensory deficit</td>
<td>Left</td>
<td>25.7</td>
<td>23.4</td>
<td>Improved</td>
</tr>
<tr>
<td>5</td>
<td>73 year old woman with Broca's aphasia, dense right hemiparesis, right hemisensory deficit</td>
<td>Left</td>
<td>25.5</td>
<td>23.1</td>
<td>Improved</td>
</tr>
<tr>
<td>6</td>
<td>62 year old man with right hemiparesis, right hemisensory deficit, conducton aphasia</td>
<td>Left</td>
<td>52.2</td>
<td>40.0</td>
<td>Improved</td>
</tr>
<tr>
<td>7</td>
<td>78 year old woman with atrial fibrillation, Wernicke's aphasia, right superior quadranopia</td>
<td>Right</td>
<td>27.9</td>
<td>24.8</td>
<td>Improved</td>
</tr>
<tr>
<td>8</td>
<td>74 year old woman with global aphasia, right hemiparesis (greatest in arm), and right hemisensory deficit</td>
<td>Left</td>
<td>36.2</td>
<td>32.0</td>
<td>Improved</td>
</tr>
<tr>
<td>9</td>
<td>47 year old woman with constructional apraxia, weakness of right arm and face, and right hemisensory deficit</td>
<td>Right</td>
<td>53.9</td>
<td>43.8</td>
<td>Improved</td>
</tr>
<tr>
<td>10</td>
<td>70 year old woman with global aphasia, dense right hemiparesis, right homonymous hemianopsia, right hemisensory deficit</td>
<td>Left</td>
<td>41.0</td>
<td>33.6</td>
<td>Improved</td>
</tr>
<tr>
<td>11</td>
<td>57 year old man with dysarthria and worsening right arm weakness, right arm sensory loss</td>
<td>Left</td>
<td>54.1</td>
<td>41.8</td>
<td>Improved</td>
</tr>
<tr>
<td>12</td>
<td>53 year old man with dense left hemiparesis, left neglect, denial of deficit, and left homonymous hemianopsia</td>
<td>Right</td>
<td>44.8</td>
<td>36.6</td>
<td>Unimproved</td>
</tr>
<tr>
<td>13</td>
<td>55 year old man with dysarthria, anoma, right facial and arm weakness</td>
<td>Left</td>
<td>53.6</td>
<td>42.1</td>
<td>Improved</td>
</tr>
<tr>
<td>14</td>
<td>79 year old man with Gertzman's syndrome, right hemiparesis, right hemisensory deficit, conducton aphasia</td>
<td>Left</td>
<td>46.9</td>
<td>34.7</td>
<td>Unimproved</td>
</tr>
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hemisphere between any two $^{133}$Xe-rCBF determinations in one subject was considered significant. Further, one of the authors (HG) reviewed CT scans and $^{133}$Xe-studies to determine which two probes best corresponded with the areas infarcted. These regional values were then compared with neurological exam scores and neuropsychological studies to determine whether focal rCBF values had prognostic significance which might be lost in analyzing over the entire hemisphere. In cases where the infarcted region covered more than the distribution of two probes, the lowest two rCBF values were used. Neurological examinations followed a standardized form including mental status, cranial nerves, cerebellar testing, sensory and motor exams. These were scored from 0 to 260 with the latter score being normal. Two of the authors (AB or MK) examined all the patients immediately before the subjects underwent each $^{133}$Xe-rCBF determination. These same authors had recently examined, independently and in random order, eight other patients not included in this study to determine reproducibility and significant change in the neurologic exam. A 15% change in the neurological exam score was required for a patient’s clinical status to be considered significantly changed.

Neuropsychological testing consisted of a battery of standard tests designed to examine cognitive function in multiple regions of both hemispheres in a one hour period. These included: temporal orientation, Trails A and B, Wechsler memory scale, finger tapping, aphasia screening test, and judgement of line orientation. From these we calculated a general impairment index from 0 to 5, where 0 was above average, 1 was average, and 5 was severely impaired. A 15% change in
general impairment index defined significant change in neuropsychological status. CT scans were performed in the Department of Radiology of the Hospital of the University of Pennsylvania on either a Phillips 300 or an EMI 1005 Head Scanner. All patients had at least one CT scan before and after injection of intravenous contrast. Nonparametric statistical analyses, signed rank tests and rank correlations served to determine significant changes in rCBF, neurological examination, and neuropsychological testing, as well as correlation between initial values of rCBF and clinical course and neuropsychological outcome.¹⁴

Results

CT scans revealed unilateral cerebral infarctions in 13 patients in the appropriate hemispheres and lobes for the patients' histories and clinical findings. All were in the distribution of the internal carotid artery or its branches. No patient entered this study because of a lacune. No infarction was seen on CT scan in 1 patient (Patient 7) who had a lumbar puncture which revealed a protein of 68 mg % and no red cells or xanthochromia. The patient had recent onset of atrial fibrillation. She had presented with a Wernicke's aphasia, and the infarction was thought to be purely cortical secondary to a cardiac embolus. One other patient (Patient 4) had an asymptomatic lacune in the cerebellum in addition to an acute left cerebral hemisphere infarction. He gave no history of nor did he have exam findings consistent with previous stroke. None of the subjects had evidence of intracerebral or subarachnoid hemorrhage on CT or by analysis of cerebrospinal fluid.

No significant changes for the entire group were noted in mean arterial blood pressure, end-tidal CO₂, hemoglobin, or hematocrit. Hemispheric changes in CBF were parallel for the infarcted and unaffected side in 12 of 14 patients for all ¹³³Xe-rCBF studies. Among the other two patients, 4 of their 9 studies showed perfusion changes in different directions between the two hemispheres. The IS and ISI showed excellent correlation (r = 0.98). Focal regions of hypoperfusion corresponding with infarction on CT scan were seen in 13 of the patients in at least one ¹³³Xe-rCBF study but in only 6 on the first determination.

Eight of the 14 subjects had their highest rCBF value globally for the affected hemisphere within 72 hours of acute stroke. In another 3, the initial value was the second highest, and in two of these patients, the initial value was not surpassed until the 4th study (1 month after ictus). The lowest rCBF value was found at 1 week in 7 subjects, at 2 weeks in 3 subjects, at 72 hours in 1. The only statistically significant change of rCBF in the group was the decreased flow both globally and for the infarcted hemisphere found using the ISI and IS between 72 hours and 1 week (p < 0.05). The increase in rCBF between 1 and 4 weeks was not statistically significant (p < 0.20). Neurological examination score significantly improved for the group at 1 month (p < 0.01) but not neuropsychological function. The mean general impairment index was insignificantly changed from admission to 1 month (3.52 to 3.53).

Eleven of the 14 patients showed clinical improvement during the period of study. Seven of these also showed increases in rCBF although rCBF did not change significantly in the other 4 (fig. 1 and 2). At 1 week, among these same 11 subjects, improvement in clinical status preceded increases in CBF in 7 and in only 1 did CBF increase before neurological examination score. This difference was statistically significant (p < 0.05). Of the 7 patients who significantly improved clinically at 1 week, 5 of them then had their lowest CBF values for the entire period of study, a time course consistent with previous data on bihemispheric depression of CBF, often called diaschisis, after acute infarction.¹⁵,¹⁶ Among the other 4 subjects who improved clinically, 3 showed increased neurological examination scores at 2 and another at 4 weeks but no significant change in CBF during the month of follow-up.

[Graph and figure 1]
Initial neuropsychological status, the general impairment index, did not correlate with clinical improvement at 1 week (r = 0.25) or at 1 month (r = 0.10). Among the 3 (Cases 2, 12, and 14) patients who showed no improvement in neurological exam, two (Cases 12 and 14) showed significant increases in rCBF during the period of study. Neither of these patients showed any significant change in neuropsychological testing. There was no correlation between initial hemispheric CBF values and neuropsychological score (r = 0.02).

Two of the patients received anticoagulants within 24 hours of admission (Cases 2 and 11). Both were placed on intravenous heparin for several days and then gradually switched to warfarin. Prothrombin times and activated partial thromboplastin times were appropriately in therapeutic ranges for all studies. Patient 2 showed no significant increase in CBF for the entire period of study, but at 4 weeks her neurological exam score increased 14%, just below the 15% limit of significance. Patient 11 showed significantly improved neurological exam and neuropsychological testing at the end of 1 week. His CBF increased only at the end of the month.

Initial involved hemispheric CBF had no predictive value for clinical outcome at 1 week or at 1 month (r = -0.17, r = -0.26, respectively for IS; r = -0.18, r = -0.25 respectively for ISI). No correlation existed of initial rCBF values in the regional probes best corresponding to infarction on CT (Patient 7 had localization by clinical exam) and clinical course at 1 week or 1 month (r = 0.02, r = 0.05, respectively for IS; r = 0.01, r = 0.06, respectively for ISI). These values are summarized in Table 2. The average hemispheric and global CBF values were significantly lower than those of age-matched controls in our laboratory (p < 0.001). However, of the 7 patients with initial lowest CBF values for the hemisphere involved and globally, all but one (Case 2) made significant recoveries (Cases 1, 4, 5, 7, 8, 10) and, as noted above, Case 2 showed improvement in neurological exam score which was just below significance. This group includes the patients with the 2 lowest initial rCBF measurements (Cases 4 and 5). Two of the patients who failed to improve (Cases 12, 14) were above the mean for the group for initial CBF value in the affected hemisphere.

Discussion

Our data indicate that initial rCBF is not predictive of clinical outcome in patients with acute cerebral infarction. Further, increases in rCBF following cerebral infarction appear to result from improved neuronal function rather than cause it. At the very best, the two measures are independent of one another. Our finding that rCBF is relatively high within 72 hours of acute stroke is consistent with the clinical data of Olsen et al and the experimental data of others indicating luxury perfusion to be a common, early, although transient, phenomenon following acute stroke only case 1 developed focal hyperemia at 2 weeks). Its frequency of occurrence may explain why early rCBF determinations are not predictive of clinical outcome. The low CBF seen at the end of 1 week in most subjects is consistent with the previously published data on diaschisis. The parallel courses of CBF in the two hemispheres supports the concept that some of these changes are neuronally mediated.

Multiple studies have demonstrated that brief periods of complete or partial ischemia can cause cerebral infarction in experimental animals. Thus, relatively rapid reperfusion may not salvage already necrotic neurons.

These findings are at odds with those of several previous studies. In four of these only one rCBF determination was performed or several were performed on

<table>
<thead>
<tr>
<th>Correlation of initial hemispheric CBF and neurological exam score</th>
<th>At 1 week</th>
<th>At 1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation of initial rCBF in infarcted regions and neurological exam score</td>
<td>r = 0.02 (IS)</td>
<td>r = 0.05 (IS)</td>
</tr>
<tr>
<td>Correlation of initial neuropsychological score and neurological exam</td>
<td>r = 0.25</td>
<td>r = 0.10</td>
</tr>
</tbody>
</table>
one day after inducing changes in arterial blood gases.6, 18 Other included patients with transient ischemic attacks (TIAs) who underwent a single rCBF determination between the first and twelfth weeks after the ischemic event.1, 3 Rao also included patients with TIAs and had few follow-ups beyond 5 days after the acute insult.9 Another related rCBF to survival rate during 7 years in patients with strokes 1 to 6 months prior to study.2 Olsen observed patients with postischemic hyperperfusion generally improved clinically but did not find absence of hyperemia to indicate poor prognosis.7 Another involved patients with hypertensive hemorrhage.4 Risberg, using the ISI, noted a direct correlation between decreases in rCBF and worsening clinical course, but did not remark which, if either, occurred first, demonstrated no change in rCBF thereafter, and included one patient with a subarachnoid hemorrhage and another with a basilar artery aneurysm.53

Tolonen et al noted no significant changes in rCBF over the 3 months after acute stroke.25 However, they noted a trend for lower rCBF to correlate with more severe infarction although at least one patient with a large stroke and neurological deficit developed luxury perfusion. Their studies also involved only two 133Xe-rCBF determinations in the first month after acute stroke. Demeurisse et al using 133Xe-rCBF noted no correlation between the early rCBF and clinical prognoses and between the evolution of rCBF over 3 months and clinical course in patients with acute infarction.24 Their first rCBF determination was 15 days after the acute ictus. However, their conclusions fully agree with ours. As we did not manipulate blood gases during CBF studies it is possible that such additional maneuvers might furnish prognostic data which our studies did not.

None of our subjects was unconscious at the time of study and none had complete hemiplegia (Patient 5 had only minimal voluntary movement of her left toes on admission), and rCBF theoretically could be more significantly reduced in such patients than in those in our study. Although the “no-reflow” phenomenon has been postulated from experimental studies as a cause of ischemic damage,25 this condition occurs most often after global ischemic insults,6, 26-28 does not occur in all (or even the majority of focal ischemic events),29, 30 and, as most laboratory studies indicate, need not develop for ischemic injury to occur.15, 31, 32 Postischemic hyperperfusion32 seen in experimental animals does not appear to correlate with diaschisis, as the former is strictly unilateral, occurs much sooner after infarction than the latter, and we found functional neurological recovery to begin most often during maximal diaschisis. This pattern is hyperemia followed by hyperperfusion with associated clinical improvement parallels that seen in patients sustaining head trauma.33

Several investigators have noted that massive reductions in perfusion pressure and rCBF are required to induce metabolic derangement or critical limitations of glucose delivery to neurons in experimental animals.34-36, 38 By comparison, the reductions in rCBF in our subjects were small. Recent experimental work involving focal ischemia fully supports our conclusion that after infarction, rCBF is determined by neuronal deficit, not the reverse, and that postischemic hyperperfusion may endanger neuronal recovery.19, 20 Olsen suggested postischemic hyperperfusion may have several different origins.20 Using positron emission tomography in patients with recent cerebral infarctions, Baron observed “misery perfusion,” regions with normal oxygen metabolism but reduced perfusion. He suggested this state to be clinically favorable.29 Using positron emission tomography, Wise noted cerebral oxygen metabolism correlated better with clinical status after acute cerebral infarction than did cerebral blood flow.40 Although the 133Xe-rCBF has limited spatial resolution and problems with inter-hemispheric cross-talk, the latter positron emission studies indicate that our data are not due to technical artifact.

Finally, the data presented here indicate that the level of neuronal function following acute ischemic insults may be more important than rCBF. If this be the case, agents directed at preserving neuronal function (calcium blockers, barbiturates, free radical scavengers) may be more efficacious in promoting favorable recovery from strokes than those directed at increasing perfusion.

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