Original Contributions

Clinical and Hemodynamic Aspects of Low-Flow Infarcts

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We used single-photon emission computed tomography to measure cerebral blood flow, cerebral blood volume, and cerebral perfusion reserve and transcranial Doppler sonography with CO₂ stimulation to assess hemispheric vasomotor reactivity in 37 patients and in normal controls. Computed tomography and magnetic resonance imaging were performed to differentiate morphologically low-flow infarcts (n=17) from territorial infarcts (n=20). In patients with either type of infarct, blood flow was decreased and blood volume was increased in the infarcted areas compared with the same areas in the controls. Perfusion reserve and vasomotor reactivity were significantly reduced in patients with territorial infarcts and carotid artery occlusions (n=12) and even more reduced in patients with low-flow infarcts (p<0.001). Both parameters were normal in patients with cardiac embolic territorial infarcts (n=8). In patients with territorial infarcts, blood flow and perfusion reserve changes were restricted to the infarcted areas, whereas in patients with low-flow infarcts, regions of decreased perfusion reserve considerably exceeded the area of the infarct. Low-flow infarcts are related to the hemodynamic effects of severe extracranial carotid artery disease. (Stroke 1991;22:1117–1123)

The identification of a subgroup of stroke patients with critically impaired cerebral hemodynamics may have a major impact on their management. The morphological appearance of low-flow–induced ischemic infarcts on computed tomography (CT) or magnetic resonance imaging (MRI) scans is different from that of thromboembolic ones. A thrombotic or embolic occlusion of a large basal cerebral artery or its branches leads to an infarct that is strictly related to its territory. Such infarcts have been called “territorial.” They are commonly associated with potential sources of emboli such as internal carotid artery (ICA) stenoses or cardiac pathology. Territorial infarcts are most often cortical, but there exists a subcortical variant, the large striatocapsular infarct, which is supposed to be due to the simultaneous occlusion of branches of the long, deep perforators by a temporary embolic middle cerebral artery (MCA) occlusion. Low-flow infarcts are considered to be the result of a critically reduced perfusion pressure distal to an occlusive lesion in the neck, whereas the brain artery directly supplying this territory is usually not affected. Such hemodynamic infarcts may occur between neighboring territories in the frontoparasagittal or temporoparieto-occipital watershed areas. More commonly, these infarcts are found in the terminal supply areas of the deep perforators in the supraganglionic periventricular white matter, strictly sparing the gray substance. Because both territorial infarcts and low-flow infarcts may be cortical or subcortical and both may be associated with ICA occlusion, it seemed reasonable to use a pathophysiological approach to differentiate between the two conditions.

The degree of hemodynamic compromise can be assessed by evaluating the compensatory responses to a decrease in perfusion pressure. Autoregulatory vasodilation leads to an increase in regional cerebral blood volume (rCBV) without a change in regional cerebral blood flow (rCBF) until vasodilation becomes maximal. Only thereafter will rCBF decline, with rCBV remaining at a maximum. The rCBF/rCBV ratio is a sensitive index of the hemodynamic reserve. Compensatory vasodilation can also be assessed by measuring the cerebral capacity to increase blood flow in response to hypercapnia. A loss of CO₂ reactivity indicates maximal vasodilation, which counterbalances reduced perfusion pressure. We wanted to find out whether low-flow infarcts compared with territorial infarcts occur in a hemisphere with chronically reduced hemodynamic reserve.
Subjects and Methods

We studied 37 patients with first stroke and documented infarction on CT along with 49 controls. Only patients with strictly unilateral brain infarcts and no other pathological findings on CT were included. Between October 1988 and September 1989, we selected 17 patients who were judged on the basis of CT patterns as having hemodynamically induced low-flow infarcts. All had ipsilateral ICA occlusion or, in one case, MCA occlusion but no obstructive lesion of the contralateral extracranial ICA. All patients were investigated ≤3 days after the onset of the stroke and were followed up clinically for 2 months to 2 years (median 4 months). Twenty patients, seven women and 13 men (mean age 56, range 42–79 years) with territorial infarcts were recruited for comparison. Eighteen had typical cortical infarcts in the MCA territory, and the other two patients had large (>3 cm in diameter) striatocapsular infarcts. In 12 patients the ipsilateral ICA was occluded. Eight patients had normal carotid arteries and a cardiac source of emboli demonstrated by transesophageal or transthoracic echocardiography. We studied 40 normal controls to define the normal range of CO₂-dependent vasomotor reactivity (for details see Reference 16). Nine normal subjects served as controls for single-photon emission computed tomography (SPECT) studies. Informed consent was obtained prior to each study.

All patients underwent intra-arterial selective arteriography or extracranial and transcranial Doppler sonography (TCD 2–64, EME, Ueberlingen, Germany). Vasomotor reactivity of the MCA was calculated from blood flow velocity changes measured by transcranial Doppler sonography in relation to changing end-tidal CO₂ concentrations (CO₂ Vol.%) for normal, hypercapnic, and hypocapnic conditions (for details see Reference 16). The CO₂ Vol.% was measured directly by an infrared CO₂ analyzer (Capnolog, Datex Instrumentation OY, Helsinki, Finland). Hypercapnia was achieved by breathing 6%, 5%, 4%, 3%, and 2% CO₂ in air, and hypocapnia was achieved by stepwise accelerated hyperventilation. The MCA blood flow velocity when breathing room air was set arbitrarily at 100%. The percentage changes in mean blood flow velocity during hypercapnia or hypocapnia were plotted against the corresponding CO₂ Vol.% and were analyzed by curve fitting. In normal individuals, the curve of best fit is a tangent hyperbolic function. The asymptotes represent blood flow velocity at maximum dilation (hypercapnic limb, high velocity) or maximum constriction (hypocapnic limb, low velocity). The perpendicular distance between the two asymptotes reflects the range of responsiveness of the cerebral vasculature to capnic stimuli, the so-called CO₂-induced cerebral vasomotor reactivity, calculated as the range of velocity changes divided by blood flow velocity at normal CO₂ Vol.%, expressed as a percentage. The CO₂ test was performed 5–6 weeks after the ischemic event. Investigators were blinded for the classification of infarcts.

A Somatom DRH (Siemens, Erlangen, Germany) was used for CT scanning within the first 3 days and after 3–4 weeks. All low-flow infarcts were entered into a standard grid model of brain slices, 17,18 which were derived from plates of the atlas of Matsui and Hirano. 19 SPECT was performed 23–28 days after the onset of symptoms with a rotating double-head gamma camera (Rota-Dual, Siemens-Gammasonics, Erlangen, Germany). The protocol for assessment of rCBF and cerebral perfusion reserve is described elsewhere. 20 First, rCBF was imaged directly after the injection of 370 MBq of technetium-99m-labeled hexamethylpropyleneamine oxime (⁹⁹ᵐTcHMPAO). Then rCBV was measured indirectly; a stannous pyrophosphate preparation with 740 MBq (⁹⁹ᵐTc) pertechnetate to label erythrocytes was injected immediately after the rCBF imaging with (⁹⁹ᵐTcHMPAO), without having changed the patient's position, resulting in a combined image (rCBF+rCBV). Subtraction of the rCBF image from the combined image yielded rCBV. Cerebral perfusion reserve 11 was calculated as a ratio image by dividing rCBF by rCBV pixel by pixel, in effect using the equation cerebral perfusion reserve=rCBF/rCBV=rCBF/[rCBF+rCBV]=rCBF/[(rCBF+rCBV)−rCBF]. MRI was performed on the same day as SPECT with a 1.5-T unit (Magnetom, Siemens).

To correlate rCBF with the morphological findings, an overlay technique was introduced (for details see Reference 21) to place regions of interest simultaneously on MRI and SPECT images. All SPECT values (rCBF and rCBF/rCBV) were obtained and compared as interhemispheric ratios (infarcted versus contralateral side), not as absolute values. Mean values of rCBF within the infarcted areas were calculated from three contiguous transaxial slices according to the extent of the infarct. The rCBF/ rCBV ratio was calculated from 18 contiguous blocks of noninfarcted tissue corresponding to the superficial and subcortical distributions of the MCA. The lowest values entered the group comparisons. Due to nonnormality of the data, the groups were compared using the Kruskal-Wallis test and subsequent pairwise U tests followed by a nonparametric discriminant analysis (using kernel density estimation, program ALLOCOSO 22 ) among all three groups simultaneously using perfusion reserve and vasomotor reactivity as variables. Cerebral blood flow was not used as a variable because its discriminating power is mainly due to the different sizes of the two types of infarcts. Perfusion reserve and vasomotor reactivity, however, as indices of the cerebral hemodynamic reserve add additional functional information. They provide information not obtainable from structural imaging. Probability values for pairwise group comparisons (controls, territorial infarcts, low-flow infarcts) of each measurement were separately interpreted according to the sequential multiple test procedure of Holm. 23
Results

Preceding ipsilateral transient ischemic attacks were noted in seven (41%) of the 17 patients with low-flow infarcts. The onset of stroke was acute in all patients. Symptoms resolved within 24 hours in three patients. Further clinical findings are presented in Table 1. One patient had a mainly crural hemiparesis; two had cortical monoparesis of the arm. Two patients were somnolent on admission, one with conjugate eye deviation, the other with hemianopia. Two thirds of the patients with lesions of the dominant hemisphere had aphasia. These included a left-handed woman who became aphasic after a right hemisphere stroke. One patient had spatial and visual neglect and disturbance of spatial orientation. At follow-up, seven patients had no focal signs; motor paresis was improved in another one. Two patients suffered a new infarction within 1 week (early stroke recurrence rate 12%).

Most low-flow infarcts were small (Figure 1). Size, extent, and location were identical on MRI and CT.

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Side</th>
<th>Presenting symptoms</th>
<th>Aphasia/neglect</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/59/M</td>
<td>R</td>
<td>HP 1</td>
<td>None</td>
<td>ICA</td>
</tr>
<tr>
<td>2/58/M</td>
<td>L</td>
<td>HP 1</td>
<td>None</td>
<td>Norm</td>
</tr>
<tr>
<td>3/76/F</td>
<td>L</td>
<td>HP, HS m</td>
<td>Trans-motor</td>
<td>Norm</td>
</tr>
<tr>
<td>4/54/M</td>
<td>R</td>
<td>HP, HS m</td>
<td>Trans-mixed</td>
<td>Norm</td>
</tr>
<tr>
<td>5/78/F</td>
<td>L</td>
<td>HP, HS 1</td>
<td>Trans-motor</td>
<td>Norm</td>
</tr>
<tr>
<td>6/78/M</td>
<td>L</td>
<td>HP, HS 1</td>
<td>Not class</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>7/38/F</td>
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<td>HP 1</td>
<td>Trans-motor</td>
<td>Ocl</td>
</tr>
<tr>
<td>8/60/F</td>
<td>R</td>
<td>HP 1</td>
<td>None</td>
<td>Ocl</td>
</tr>
<tr>
<td>9/59/F</td>
<td>R</td>
<td>HP, HS m</td>
<td>None</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>10/44/F</td>
<td>L</td>
<td>HP, HS s</td>
<td>Trans-motor</td>
<td>Norm</td>
</tr>
<tr>
<td>11/50/F</td>
<td>L</td>
<td>HP 1</td>
<td>None</td>
<td>Ocl</td>
</tr>
<tr>
<td>12/57/F</td>
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<td>HP, HS 1</td>
<td>Trans-sensory</td>
<td>&gt;90%</td>
</tr>
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<td>13/70/M</td>
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<td>HP 1</td>
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<td>None</td>
<td>Not class</td>
<td>Ocl</td>
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<tr>
<td>15/80/M</td>
<td>R</td>
<td>HP 1</td>
<td>None</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>16/73/F</td>
<td>L</td>
<td>HP, HS 1</td>
<td>Dysarthria</td>
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<tr>
<td>17/67/F</td>
<td>R</td>
<td>HP, HS m</td>
<td>Neglect</td>
<td>Norm</td>
</tr>
</tbody>
</table>

Pt, patient; M, male; F, female; R, right; L, left; HP, hemiparesis; HS, hemisensory loss; l, light; m, moderate; s, severe (paralysis of at least one limb); trans-motor, transcortical motor aphasia; trans-mixed, transcortical mixed aphasia; not class, unclassifiable aphasia; ICA, internal carotid artery; MCA, middle cerebral artery; trans-sensory, transcortical sensory aphasia; Ocl, occlusion; Norm, Normal.

Table 2. Comparison of Cerebral Blood Flow, Perfusion Reserve, and Vasomotor Reactivity in Patients and Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=9 or 40)*</th>
<th>Territorial infarcts</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow</td>
<td></td>
<td>Normal ICA (n=8)</td>
<td>Occluded ICA (n=12)</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.98±0.03</td>
<td>0.73±0.11</td>
<td>0.69±0.13</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.99 (0.12)</td>
<td>0.79 (0.30)†</td>
<td>0.73 (0.39)†</td>
</tr>
<tr>
<td>Perfusion reserve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.03±0.10</td>
<td>1.00±0.11</td>
<td>0.86±0.09</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.05 (0.34)‡†</td>
<td>1.00 (0.34)‡†</td>
<td>0.86 (0.32)</td>
</tr>
<tr>
<td>Vasomotor reactivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>87±15</td>
<td>80±18</td>
<td>50±24</td>
</tr>
<tr>
<td>Mean (range)</td>
<td>86 (68)§</td>
<td>80 (49)§</td>
<td>49 (82)§</td>
</tr>
</tbody>
</table>

Blood flow and perfusion reserve are interhemispheric ratios (infarcted versus contralateral side in patients, right versus left in controls). Vasomotor reactivity is relative changes of middle cerebral blood flow velocity during hypocapnia and hypercapnia compared with velocity at rest (100%). Groups were compared with Kruskal-Wallis test and subsequent pairwise $U$ tests. Probability values for pairwise comparisons are interpreted according to sequential multiple test procedure of Holm. Groups followed by same symbol do not differ at $a=5%$.

*Nine controls in assessment of blood flow and perfusion reserve, 40 in assessment of vasomotor reactivity. ICA, internal carotid artery.
Documentation of lesions in 17 patients with low-flow infarcts. Infarcted areas are derived from magnetic resonance imaging slices with largest extent of lesion and entered into computer-processible grid model of brain. Last three images on bottom row show cumulative frequencies of "lesioned" grids expressed by bars on darkness scale from 1 to 20. Maximum darkness denotes involvement of this area in all 17 cases. Vascular territories of basal ganglia and deep white matter are drawn on the right according to the literature.6

Infarcts are located in most distal parts of territories of lateral lenticulostriate group and of anterior choroidal artery.

In two patients, MRI showed a few additional small hyperintense lesions on T2-weighted images directly adjacent to the gross infarct. The infarcts did not cover the entire territories of the lenticulostriate and adjacent arteries but involved only the most superior part of their territories (i.e., the terminal supply area).

The rCBF was decreased most within the territorial infarcts; rCBF was decreased to a far lesser degree in low-flow infarcts (Table 2). In contrast, the lowest values of perfusion reserve assessed outside the infarcted areas were found in patients with low-flow infarcts, followed by patients with territorial infarcts associated with ICA occlusions. Almost the same perfusion reserve values were found in patients with territorial infarcts with normal ICAs and the controls. All 17 patients with low-flow infarcts showed a characteristic pattern on SPECT images, with a severely decreased perfusion reserve in an area that far exceeded the infarcted areas seen on MRI (Figures 2 and 3). However, in all but three of the 20 patients with territorial infarcts, perfusion reserve changes were almost exclusively restricted to the infarcted area itself. Vasomotor reactivity of the MCA of the infarcted side decreased significantly from controls to patients with territorial infarcts and occluded ICAs and patients with low-flow infarcts (Table 2).

In the stepwise nonparametric discriminant analysis using perfusion reserve and vasomotor reactivity as variables, perfusion reserve was the stronger discriminator among the three groups. This also held true for distinguishing low-flow infarcts from territorial infarcts with ICA occlusion. Correct and incorrect classifications are given in Table 3. Patients with territorial infarcts were the least well-defined group. Patients with lowered perfusion reserve and vasomotor reactivity predominantly had ICA occlusions. Six of the eight patients with territorial infarcts without ICA occlusion were allocated to the control group by the nonparametric discriminant analysis.

Discussion

Two types of low-flow infarcts can be differentiated. Low-flow infarcts in the cortical border zones (i.e., true watershed infarcts) are rare,4 have been ascribed to thromboangiitis obliterans25 or showers of microemboli,26 and have been found bilaterally after prolonged systemic hypotension.27,28 Unilateral watershed infarcts are most often associated with ICA occlusion.1,29,30 The other, more common, type of low-flow infarcts lie subcortically and are called terminal supply-area infarcts1 or subcortical watershed infarcts.2 These infarcts are not related to any vascular territory but are located at the distal part of territories perfused by the deep perforators, sometimes at the border with the territory of a superficial perforator. In our study, perfusion reserve and vasomotor reactivity demonstrated a much higher degree of hemodynamic compromise in patients with low-flow infarcts than in patients with territorial infarcts. No low-flow infarct occurred in a hemodynamically intact hemisphere. Thus, this type of low-flow infarct can be related to the distant hemodynamic effects of severe extracranial occlusive disease.
FIGURE 2. Corresponding computed tomogram (left), magnetic resonance image (MRI) (center), and single-photon emission computed tomogram (SPECT) (right) of patient with small right-sided low-flow infarct in centrum semiovale. MRI shows additional, even smaller, infarct more anteriorly. SPECT shows decreased cerebral perfusion of nearly entire right middle cerebral artery (MCA) territory and smaller defect on left side. (Extracranial occlusion of right internal carotid artery [ICA]; vasomotor reactivity of right MCA 22%; abnormality of circle of Willis: both anterior cerebral arteries originating from left ICA, which is itself severely stenosed at Cl segment.)
In addition to the occlusive extracranial lesion, there must be an additional factor for the decrease in perfusion pressure that causes the low-flow infarct. Some authors have attributed low-flow infarcts to hemodynamic effects in sudden systemic hypotension. However, more chronic hemodynamic compromise due to an inadequate intracranial collateral blood supply caused by either contralateral ICA occlusion or abnormalities of the circle of Willis may be prerequisite. This is indicated by the hemodynamic changes we found during the chronic state after a stroke and may explain the comparatively high frequency of low-flow infarcts in persons with moyamoya disease or ICA dissection. In persons with moyamoya disease, the collateralizing capacity of the circle of Willis is severely reduced due to occlusions of the basal arteries. In persons with ICA dissection, an ICA occlusion may develop so rapidly that time is too short for the recruitment of sufficient collateral pathways.

Localization and hemodynamics clearly distinguish low-flow infarcts from territorial infarcts. In persons with cardiac embolic territorial infarcts, hemodynamics normalize rapidly after an initial vasoparalytic phase and a subsequent hyperperfusion phase. In persons with territorial infarcts due to artery-to-artery embolism in ICA occlusion, however, cerebral hemodynamics may not necessarily differ from those in persons with low-flow infarction, possibly depending on the anatomy or pathology of the circle of Willis. Why should cerebral embolism be impossible in a hemodynamically altered hemisphere?

Low-flow infarcts are commonly seen on CT or MRI images, however, representing only the small visible tip of an iceberg of decreased perfusion reserve. This is reflected by severe clinical symptoms, such as aphasia or neglect, which are more typical of larger hemispheric strokes. These patients are at risk for further strokes as reflected in the high early stroke recurrence rate in our study. However, all of our patients survived at least 2 months. This may be due to the fact that we included only patients who survived for at least 5 weeks to perform our hemodynamic tests adequately. However, there was no excluded patient with a low-flow infarct who died within this period. To ascertain rapid and effective diagnostic and therapeutic strategies, low-flow infarctions must be differentiated from other subcortical stroke types such as lacunar infarction and large striatocapsular infarction. Lacunes are normally located in the basal ganglia and internal capsule, but such lesions may have the same size and site as low-flow infarcts. Large striatocapsular infarcts may also be similar in size to low-flow infarcts. The striatocapsular infarcts are, however, strictly related to the territories of the deep perforators and involve the proximal as well as the distal parts of the vessels' territories. For differentiation, pathophysiological methods should be used to evaluate cerebral hemodynamic reserve, which is normal in persons with lacunes due to cerebral microangiopathy and in persons with typically cardiac embolic striatocapsular infarcts but is severely reduced in persons with hemodynamically produced low-flow infarcts.

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References


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