
ALTHOUGH INTENSIVELY STUDIED the quantitative relation between the two different causes of cerebral infarction (embolism and thrombosis) is not yet firmly established. Stroke registries like the Framingham study,\(^1\) the Rochester studies,\(^2,\) the National Survey of Stroke,\(^3\) the Manitoba study\(^4\) and others\(^5-11\) all emphasize atherosclerosis as being by far the most common cause of cerebral infarction accounting for 80-95% of the infarcts while embolic infarcts are considered to account only for about 5-20%. In contrast to these studies the Harvard Cooperative Stroke Registry\(^12\) reported as many as 37% of the infarcts to be embolic while Blackwood et al.\(^13\) and Jørgensen and Torvik\(^14\) in autopsy studies found 48% and 47% of the infarcts to be of embolic origin.

Clinically, the differentiation: hemorrhage/infarct...
and thrombosis/embolism can be extremely difficult and very often it is impossible. In clinicopathological studies the clinical diagnosis of cerebral hemorrhage, thrombotic or embolic infarction could not be confirmed in 20–40% of the strokes and in large stroke registries 30–50% of the strokes cannot be classified.4–8 Some investigators even avoid attempts to classify stroke on a clinical basis.17 Radiologically, the ratio MCA occlusion:ICA occlusion in a stroke population is influenced by timing of angiography as MCA occlusions in contrast to ICA occlusions tend to disappear within the first few weeks after the stroke.16–24 Late angiography therefore seriously underestimates the ratio MCA:ICA occlusion in a stroke population and the same must apply to autopsy studies.

The present study represents another attempt to investigate the cause of cerebral infarction in a stroke population and in particular its relation to the size and the location of the infarcts. To avoid the above mentioned difficulties in classifying the infarcts the cause of infarction was evaluated on the basis of cardiac examination, CT-scan and cerebral angiography performed within a fixed period early after the stroke while a classification based on a clinical evaluation was avoided.

Material

The study comprises 73 acute stroke patients, with symptoms and signs lasting for more than 24 hours, admitted to the Bispebjerg Hospital, Copenhagen, within a period of 15 months in 1979–1981. Bispebjerg Hospital is a municipal hospital which serves a population of about 200,000 citizens living in a well-defined area of Copenhagen. The study is prospective and consecutive with the modifications given below. The protocol has been approved by the medical faculty, University of Copenhagen.

Included in the study were: stroke patients below the age of 75 years admitted to the hospital within the first 3 days of onset of the stroke.

Excluded from the study were: 1) Patients with clinical symptoms and signs presumed to originate from lesions in the brain stem and in the cerebellum. 2) Patients with subarachnoid hemorrhage. 3) Patients who had had myocardial infarction within 3 months prior to the stroke. (Because of the increased risk of embolism to the brain in the first weeks after myocardial infarction cerebral angiography, in our clinic, is usually postponed to 3 months after the myocardial infarction). 4) Patients with insufficiency of the heart, lungs, kidneys and liver. 5) Patients with severe disabling diseases such as multiple sclerosis, advanced malignant diseases, severe dementia, previous disabling stroke. Thus, we excluded patients in whom another severe disease was present.

Excluded later on were the following 20 patients who primarily were included in the study: 1) 14 patients because CT-scan revealed an intracerebral hematoma. 2) 2 patients because CT-scan revealed infarcts in the cerebellum and in the brain stem. 3) 1 patient because CT-scan revealed a hematoma in a malignant glioma. 4) 3 patients who died before angiography and CT-scan were performed.

Age and sex of the 73 patients are shown in table 1.

Methods

The patients underwent a full clinical neurological examination on admission. Cerebral angiography was performed in all on the second day after admission (in average 2 ± 1 days post-stroke) and on the third day after admission CT-scan was performed also in all the patients (in average 3 ± 2 days post-stroke). To avoid overlooking an infarct in its full development the CT-scans were further repeated two weeks and six months later (in average 18 ± 4 days post-stroke and 207 ± 39 days post-stroke). The second CT-scan was performed in only 65 patients because 5 patients died within the first 2 weeks after the stroke and in 3 patients a CT-scan was not performed for various practical reasons. The third CT-scan was performed in only 56 patients because another 4 patients had died within the first 6 months after the stroke and in 8 patients the third CT-scan was not performed for various practical reasons.

Cerebral Angiography

The patients were premedicated with diazepam 10 mg intramuscularly. Under local anaesthesia using 5 ml 1% Lidocaine® the common carotid artery was punctured on the relevant side and the angiography was performed. The neck arteries and the intracranial vessels were visualised in two projections, anterior-posterior and lateral.

CT-scan

CT-scan was performed with an EMI 1010 scanner using the 160 × 160 matrix. The first two examinations were performed with and without contrast while the third examination 6 months after stroke was performed only without contrast. 60 ml Isopaque® 440 infused intravenously in 5 minutes was used as contrast medium.

Cardiac Examinations

All patients were examined for atrial fibrillation and previous myocardial infarction. An electrocardiogram was obtained in all patients on admission.

Postmortem Examination

A postmortem examination of the extra- and intracranial arteries was performed in 11 of the patients who died later on and came to autopsy. The ICA and
the main trunk and the proximal branches of the MCA were searched for thromboembolic material and atherosclerotic/stenotic lesions.

Results

The Infarcts

Size. According to the size of the infarcts as revealed by CT-scan and calculated to actual size the patients could be divided in the following four groups:

1) Patients with large infarcts — 20 patients: Patients having infarcts with a largest diameter ≥3 cm. Mean of the largest diameter in these patients was 6.5 ± 1.0 cm.

2) Patients with medium sized infarcts — 25 patients. Patients having infarcts with a largest diameter ≥ 1.5 ≤ 3 cm. Mean of the largest diameter in these patients was 2.3 ± 0.7 cm.

3) Patients with small infarcts — 15 patients: Patients having infarcts with a largest diameter < 1.5 cm. Mean of largest diameter in these patients was 0.8 ± 0.2 cm.

4) Patients without infarcts on CT-scan — 13 patients.

Location (cortical or subcortical)

According to the location of the infarcts as revealed by CT-scan the patients could be divided in the following two groups:

1) Patients with infarcts involving cortical structures — 27 patients. Besides the involvement of the cortical structures these infarcts also involved deeper structures and several were transhemispheric. 20 patients had large infarcts while 7 had medium sized infarcts. Small infarcts were not seen in this group.

2) Patients with deep (subcortical) infarcts without involvement of cortical structures — 33 patients. Large infarcts were not seen in this group. 18 patients had medium sized infarcts and 15 had small infarcts.

The arterial lesions. According to the angiographic findings the patients could be divided in the following eight groups:

A) Patients with occlusion in the MCA territory — 21 patients.

B) Patients with occlusion in the MCA territory combined with severe ICA stenosis of more than 75% of the lumen and/or non-occluding intraluminal thrombus formation in the ICA — 5 patients. The lesions were extracranial in 4 patients and intracranial in 1 patient.

C) Patients with early filling veins and capillary blush as the only abnormality — 3 patients.

D) Patients with occlusion of the ICA — 9 patients.

E) Patients with severe ICA stenosis of more than 75% of the lumen as the only abnormality — 5 patients. All lesions were located in the extracranial part of the ICA.

F) Patients with slight to moderate stenosis of the ICA as the only abnormality — 9 patients.

G) Patients with non-stenosing atherosclerosis of the ICA as the only abnormality — 14 patients.

H) Patients without abnormalities on the angiograms — 7 patients.

MCA occlusions, early filling veins associated with capillary blush, ICA occlusions and severe ICA stenosis of more than 75% of the lumen are in the following termed and considered to be “significant” lesions which explain the cause of the strokes. Early filling veins and capillary blush are commonly seen after proven recanalisation of occluded arteries in the acute state of stroke. We take this to indicate a previous occlusion in the MCA territory. Early filling veins and capillary blush may also be seen in patients with cerebral tumors. However, based on the clinical course (these patients were seen clinically from 1 to 3 years after the stroke) and on CT-scans and Tc⁹⁹-pertechnetate scans obtained in the acute state and 6 months after the stroke we could rule out the presence of a tumor in these patients. Slight-moderate stenosis and non-stenosing atherosclerosis of the ICA are not considered to explain the cause of the strokes. Such lesions occurred also in the groups A and C. They are accounted for in a following section.

Oclusions of the anterior cerebral artery (ACA) were not observed in this series. One patient with a small deep infarct had a severe stenosis of the ACA. Causal relation between the stenosis and the infarct could be excluded, however. Stenosing lesions in the MCA as a possible cause of stroke were not identified on the angiograms in this series.

Type of Vascular Lesion in Relation to the Size and the Location of the Infarct (table 2)

The 29 patients with angiographic evidence of MCA occlusion group (ABC) had relatively large lesions on the CT-scan. Fourteen were classified as large, another 14 as medium sized. One patient had no identifiable lesion on the CT-scan. Small infarcts were not present in that group. Cortex was involved in 18 infarcts.

The 14 patients with significant ICA lesion without identifiable MCA occlusion (groups DE) had also relatively large lesions. Six were classified as large, another six as medium sized. One patient had a small infarct and one had no infarct on CT-scan. Cortex was involved in 9 infarcts.

The 30 patients without "significant" lesions on the angiography (groups FGH) had relatively small lesions. Five were medium-sized, 14 were small and 11 patients had no identifiable lesion on the CT-scans. Large lesions were not seen in that group of patients. All infarcts in this group were subcortical. Large lesions on the CT-scans were always associated with MCA occlusion or "significant" ICA lesion. In patients with medium sized lesions on CT-scan this was the case in 80%. But, in patients with small or no lesion on the CT-scans MCA occlusion or "significant" ICA lesion were present in only 10% and 13% respectively.

Early filling veins were observed in 11 patients. In 3 patients they were the only abnormal angiographic finding (table 2) while they were seen in association with occlusions in the MCA territory in the remaining 8 patients.

 Intracranial atherosclerosis was seen in 13 of the 29 patients (45%) with angiographic evidence of MCA.
occlusion (groups ABC) and in 22 of the 30 patients (73%) without MCA occlusion or "significant" ICA lesion (groups FGH). The difference is statistically significant (Fisher's exact test, p < 0.05). Intracranial filling was insufficient for an evaluation in 12 of the 14 patients in groups DE.

The ICA lesions classified according to the size of the infarcts appear from table 3. "Significant" ICA lesions were seen in 2 of the 28 patients (7%) with small/no infarcts while they were seen in 17 of the 45 patients with large/medium sized infarcts (38%). The difference is statistically significant (Fisher's exact test, p < 0.002).

Cardiac Disease (table 4)

Nine patients had atrial fibrillation, 3 patients had both atrial fibrillation and previous myocardial infarction and 9 patients had previous myocardial infarction. Atrial fibrillation occurred in 8 of the 24 patients (33%) with angiographic evidence of MCA occlusion in whom embolism from the heart might be a possible explanation of the infarcts (i.e. the patients without "significant" ICA lesions, groups A, C). In the similar groups without evidence of MCA occlusion (groups FGH) atrial fibrillation occurred in only 3 of the 30 patients (10%). The difference is not significant at the 95% level most likely because the material is too small (Fisher's exact test, p = 0.075). Atrial fibrillation occurred in only 1 of the 19 patients (5%) with "significant" ICA lesion (groups BDE, i.e. patients in whom the heart is a less likely embolic source). Compared to groups AC this is also insignificant at the 95% level most likely because the material is too small (Fisher's exact test, p = 0.09). The frequency of atrial fibrillation in groups AC is, however, significantly different from that in the remaining 6 groups i.e. patients in whom thrombosis is the most likely cause of stroke, see discussion (Fisher's exact test p = 0.025).

Six patients in groups AC, 1 patient in group BDE and 5 patients in groups FGH had previously had myo-

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### Table 2: The 73 Stroke Patients Classified According to the Size of the Infarcts on CT-Scan and to the Underlying Vascular Lesions Seen on the Angiograms

<table>
<thead>
<tr>
<th></th>
<th>A MCA occlusion</th>
<th>B MCA occlusion + severe ICA stenosis and/or intraluminal ICA thrombosis</th>
<th>C Early filling veins + capillary blush</th>
<th>D ICA occlusion</th>
<th>E Severe ICA stenosis</th>
<th>F Slight-moderate ICA stenosis</th>
<th>G Non stenosing ICA atherosclerosis</th>
<th>H Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large infarcts n = 20</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Medium sized infarcts n = 25</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Small infarcts n = 15</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>No infarcts on CT-scan n = 13</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total n = 73</td>
<td>21</td>
<td>5</td>
<td>3</td>
<td>9</td>
<td>5</td>
<td>9</td>
<td>14</td>
<td>7</td>
</tr>
</tbody>
</table>

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### Table 3: The ICA Lesions Classified According to the Size of the Infarcts

<table>
<thead>
<tr>
<th></th>
<th>MCA occlusion + severe ICA stenosis and/or intraluminal ICA thrombosis</th>
<th>ICA occlusion</th>
<th>Severe ICA stenosis</th>
<th>Slight-moderate ICA stenosis</th>
<th>Non stenosing ICA atherosclerosis</th>
<th>Normal</th>
</tr>
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<tr>
<td>Large infarcts n = 20</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Medium sized infarcts n = 25</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Small infarcts n = 15</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>No infarcts on CT-scan n = 13</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total n = 73</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>13</td>
<td>27</td>
<td>14</td>
</tr>
</tbody>
</table>
Cardiac infarction. There is no significant difference between the frequency of previous myocardial infarction in these 3 groups.

Postmortem Examinations

Postmortem examinations of the intracranial arteries were performed in 8 of the patients with angiographically verified MCA occlusion who died within a period of 3 years after the stroke. The main trunk and the proximal part of the major branches were searched for thromboembolic material. In only one patient, who died one week after the stroke, the occluding material was found at a site corresponding to the occlusion on the angiogram. In the remaining 7 patients who died 1 week, 6 weeks, 3 months, 3 months, 20 months, 23 months and 34 months after the stroke the occluded artery was found to be patent on autopsy. Stenotic lesions corresponding to the angiographical site of occlusion were not observed at autopsy in these 8 patients.

Postmortem examinations of the internal carotid arteries were also performed in 3 patients with “significant” ICA lesions who died within 2 weeks after the stroke. Two patients had large infarcts. One patient had no infarct either at autopsy nor on the CT-scan. In accordance with the angiographical findings two patients had severe ICA stenosis and one patient had ICA occlusion — all due to atherosclerosis in the sinus of the ICA.

Operative Examinations

Operative examinations of the ICA during carotid endarterectomy about 3 months after the stroke confirmed the angiographic findings of stenoses severely restricting flow in two patients and intraluminal thrombus formation in another two patients — all on the basis of atherosclerosis in the sinus of the ICA.

Discussion

This prospective hospital study is not an epidemiological study and cannot be considered consecutive in a strict sense. The material is relatively small and comprises only patients below 75 years of age with stroke in the carotid territory. Patients in whom another severe disease was present were excluded because angiography was considered to be without diagnostic and/or therapeutic relevance. Apart from this exception, however, cerebral angiography in our clinic is nearly always performed in patients below the age of 75 years with acute stroke in the carotid territory; the attitude to cerebral stroke traditionally is an active one in the clinic. Carotid endarterectomy, anticoagulation therapy and surgical evacuation of a hematoma are considered in all stroke patients in the age group mentioned above. Secondly, as a CT-scanner is not available in our hospital cerebral angiography is considered to be an important diagnostic tool (the CT-scans performed in this series were possible only because of a special arrangement with a neighbouring hospital). It should also be noted that our hospital is a municipal hospital serving as the only hospital a population of 200,000 citizens living in a well-defined area of Copenhagen and that more than 90% of the stroke patients in the age group mentioned above become hospitalized in this area of Copenhagen.27 We therefore consider major sampling bias to be unlikely.

Patients with MCA Occlusion

Twenty-nine patients (40%) had angiographic evidence of MCA occlusion. Five of these had a "significant" ICA lesion from which an embolus might originate and 8 of the remaining 24 patients had atrial fibrillation. Thus, a probable embolic source either from the heart or from the ICA was found in 45% of the patients with MCA occlusion. This is significantly more than in the groups without MCA occlusion. Postmortem studies in 8 patients from this group were characterized by the absence of atherosclerotic/stenotic lesions at the angiographic site of occlusion and by the absence of occluding material at this site in 7 of these patients in whom the occluded artery thus had become patent. If the occlusions, seen on angiography, were of thrombotic nature an atherosclerotic/stenotic lesion should be found at the site of occlusion in most cases. Early filling veins are commonly seen after proven recanalisation of occluded arteries in the acute state of stroke.24 In the case of recanalisation the atherosclerotic/stenotic lesion would still be identifi-
able on the angiograms in most cases. Such lesions were neither identified on the angiograms in the patients with early filling veins nor at autopsy. The majority of occlusions in this series thus seems to be embolic and thrombosis must play a minor role. Five patients probably had emboli from the ICA and 8 patients probably had emboli from the heart. The embolic source was impossible to determine in the remaining 16 patients.

The findings which indicate an embolic genesis of the MCA occlusions in this series accord with neuropathological experience that occlusive atherosclerotic thrombosis in the MCA is a rarity.\textsuperscript{13, 14, 26-31} In a study of 178 postmortem cases supposed to have a high incidence of brain disease Fisher et al. 1954\textsuperscript{30} found no thrombotic occlusions of major intracranial arteries while ICA thrombosis was found in 15 cases. In 47 postmortem cases with infarction in the MCA territory Lhermitte et al. 1970\textsuperscript{31} found only 2 cases with thrombotic MCA occlusion and in another series of 122 cases of ischemic accidents in the MCA territory the same investigators\textsuperscript{32} found only 5 cases with evidence of thrombotic MCA occlusion. Of 25 consecutive postmortem cases with recent MCA occlusion Jørgensen & Torvik 1969\textsuperscript{14} found only 3 cases of thrombotic occlusion. Thus, the incidence of thrombotic MCA occlusions is probably no more than 10–20% while 80–90% of the MCA occlusions probably are of embolic origin.

Patients with “Significant” ICA Lesions

The 19 patients with “significant” ICA lesions (group BDE) had atrial fibrillation very infrequently (5% compared to 38% in groups A with MCA occlusion). Postmortem studies in three of these patients confirmed the angiographic finding of severe flow-restricting stenosis or total occlusion of the ICA due to severe atherosclerosis. Operative examinations of the ICA during carotid endarterectomy confirmed the angiographic finding of severe flow restricting stenoses in two patients and intraluminal thrombus formation in another two patients — all on atherosclerotic basis.

We interpret these findings to indicate that the ICA lesions in this series were primary non-embolic lesions and not secondary lesions due to embolism from the heart. On the other hand, ICA lesions seem to be important embolic sources. Five of the 19 patients in this group (28%) had also MCA occlusion. MCA occlusions might occur in even more than these patients as visualisation of the intracranial arteries was either insufficient or impossible in 12 of the remaining 14 patients. MCA occlusions are well-known sources of embolism.\textsuperscript{33-36} For example Castaigne et al. 1970\textsuperscript{36} found evidence of recent emboli in 25 of 60 postmortem cases with ICA occlusion.

The findings which indicate a thrombotic genesis of ICA occlusions accord with neuropathological experience that ICA occlusions mainly are due to thrombosis.\textsuperscript{13, 36-38} In postmortem studies of ICA occlusions Torvik & Jørgensen 1964\textsuperscript{18} found 75% to be thrombotic and 25% to be embolic; Castaigne et al. 1970\textsuperscript{36} found 68% thrombotic occlusions and 23% embolic while Blackwood et al. 1969\textsuperscript{33} found 84% thrombotic occlusions and 16% embolic.

Patients without MCA Occlusions or “Significant” ICA Lesions

These 30 patients had a much lower rate of atrial fibrillation (10%) than the patients with MCA occlusion (33%). The infarcts, when identifiable, were localized deep in the hemisphere and they were of relatively small size. “Significant” ICA lesions (i.e. embolic sources) were much less frequent in the patients with small or no infarcts (7%) than in patients with large or medium sized infarcts (38%). Finally, intracranial atherosclerosis was significantly more frequent in this group (73% against 45% in patients with MCA occlusion).

The infarcts discussed here had all the characteristics of the so-called lacunar infarcts.\textsuperscript{39} They were of small size, located deep in the hemisphere in areas supplied by penetrating arteries, the occlusions were not identifiable on the angiograms and the majority seemed to be of non-embolic origin. This is in accordance with findings from neuropathological studies performed by CM Fisher.\textsuperscript{39} In a postmortem series of 50 consecutive lacunes 45 cases had occlusion of the relevant artery and 44 were of non-embolic origin. Only one occlusion was supposed to be embolic.

The Ratio Embolic: Thrombotic Stroke

MCA occlusion was identified as the cause of stroke in 40% of the patients in this series. Most of these occlusions (80–90%) are, as discussed before, due to emboli either from the heart or from extracranial arteries. A few lacunar infarcts and a few infarcts with occlusion or severe stenosis of the ICA are probably of embolic origin although the majority are thrombotic. The frequency of embolic strokes in this series therefore seems to be close to 40% and the embolic:thrombotic ratio 2:3. A similar embolic:thrombotic ratio was reported from the Harvard Cooperative Stroke Registry.\textsuperscript{12} The criterias for differentiating between embolic and thrombotic stroke were, however, different from those used in this study. The results, therefore, are not directly comparable.

The ratio is considerably higher than that reported in epidemiological studies: The Framingham study 1:4;\textsuperscript{41} the Rochester studies 1:25;\textsuperscript{42} and 1:6;\textsuperscript{43} the National Survey of Stroke 1:15;\textsuperscript{44} the Manitoba study 1:6.\textsuperscript{45} Most of these and other reports\textsuperscript{5-11} emphasize that the frequency of embolic stroke is underestimated because of great difficulties in differentiating between embolic and thrombotic stroke on clinical grounds. The finding that MCA occlusion nearly always is embolic while thrombotic MCA occlusion is rare is, however, based on strong neuropathological evidence.\textsuperscript{13, 14, 30, 31} We therefore consider a differentiation based on the angiographical and the CT-scan findings to be more reliable than a differentiation on clinical grounds. The present study thus suggests that the frequency of strokes due to
embolism is higher than indicated by epidemiological studies.

Lacunes comprise a surprisingly high percentage of the infarcts in the series. The 15 small infarcts had a size and a location typical for lacunar infarcts and 14 of these had (also typically for lacunar infarcts) no “significant” ICA or MCA lesion on angiography. Thus at least 19% of the strokes in this series were due to lacunes. Five medium sized deep infarcts without “significant” ICA or MCA lesions were most likely large lacunes while most of the 11 cases without CT lesion or “significant” ICA or MCA lesion probably represent the smallest lacunes. The percentage of lacunar infarcts in the present series is therefore between 19% and 41% and probably closest to the latter figure. Small vessel thrombosis therefore was a much more common cause of stroke than large vessel thrombosis. In the Framingham study only 6% of the ischemic strokes were considered to be due to lacunes while 23% of the infarcts in the Harvard Cooperative Stroke Registry (having CT-scan at their disposal) were considered to be lacunar. Like this registry the present series suggests that lacunar infarction is a much more common cause of stroke than hitherto accepted.

MCA occlusion was responsible for 62% of the large or medium sized infarcts i.e. major strokes. In this series therefore, emboli from the heart and extra-cranial arteries gave rise to twice as many major strokes as did thromboses. In the Framingham study only 6% of the ischemic strokes were considered to be due to lacunes while 23% of the infarcts in the Harvard Cooperative Stroke Registry (having CT-scan at their disposal) were considered to be lacunar. Like this registry the present series suggests that lacunar infarction is a much more common cause of stroke than hitherto accepted.

References

Graded Focal Cerebral Ischemia in the Rat by Unilateral Carotid Artery Occlusion and Elevated Intracranial Pressure: Hemodynamic and Biochemical Characterization

RAUL BUSTO, B.S., AND MYRON D. GINSBERG, M.D.

SUMMARY Graded transient cerebral hemispheral ischemia was produced in nitrous oxide-anesthetized Wistar rats by a procedure combining unilateral common carotid artery occlusion; elevation of intracranial pressure to 40–45 mm Hg by infusion of mock cerebrospinal fluid; and maintenance of arterial blood pressure at 100–110 mm Hg by controlled hemorrhage. Cerebral perfusion pressure was thus reduced into the ischemic range ipsilaterally to carotid occlusion but remained 55–70 mm Hg contralaterally. Regional cerebral blood flow, measured autoradiographically, fell by 85–90% in the ischemic dorsolateral and lateral neocortex, hippocampus and lateral striatum, but remained at 71% of control or higher contralaterally. Metabolite assay revealed a gradient of energy depletion, with profound reductions in ATP and phosphocreatine and marked elevations of lactate in lateral neocortex, lateral striatum, hippocampus and lateral thalamus. Importantly, dorsolateral neocortex proved to be a penumbral zone, with marked lactate elevation comparable to that of lateral cortex, yet only intermediate degrees of ATP and PCR reduction. Contralateral structures were metabolically unaffected apart from mild increases in lactate. The advantages of this focal ischemia model include the consistent topographic distribution of ischemia and its regional gradations of intensity; the avoidance of painstaking intracranial microsurgery and of systemic complications; preservation of intact energy state of the contralateral hemisphere; ease of reversibility of ischemia; and lack of seizures. The consistent metabolic penumbral zone is a unique feature of the model.

THE PAST DECADE has witnessed a dramatic increment in our understanding of the pathophysiology of ischemic brain injury, acquired in large measure from experiments conducted on small, readily available laboratory animals (for overview, see ref. 1). Although well-validated models of global brain ischemia exist in the rat,23 the development of satisfactory models of focal ischemia in this species has nonetheless remained somewhat more elusive. We have undertaken the development of a model of transient cerebral hemispheral ischemia in the rat which would satisfy the following criteria: 1) ease of production without the need for painstaking microsurgery; 2) minimal perturbation of systemic physiology; 3) preservation of intact energy state of the contralateral cerebral hemisphere, which could serve as a control; 4) consistent localization, extent and severity of the resulting ischemic lesion; and 5) ready reversibility of the ischemic insult, permitting assessment of regional metabolite recovery following transient ischemia. In the present study, we describe the methods of procedure and the biochemical and hemodynamic characterization of a model which in large measure meets the above requirements. A preliminary account has been reported.*

Methods

Studies were carried out on fasted as well as nonfasted male Wistar rats weighing 250–350 g. Anesthesia was induced with diethyl ether in a closed jar, following which the rats were quickly removed, given d-tubocurarine, 5 mg/kg intraperitoneally, and rapidly tracheostimized before the cessation of spontaneous respirations. Animals were then ventilated with a constant-volume rodent respirator (Harvard Apparatus Co.) on a gas mixture consisting of 1–1.5% halothane, 30% oxygen, and a balance of nitrous oxide. Femoral arteries and veins were cannulated with PE-50 polyethylene tubing. All incisions were then infiltrated with 1% xylocaine and closed. Arterial blood pressure was monitored via an arterial catheter connected to a pressure transducer (Statham). Rectal temperature was measured with a mercury thermometer and maintained at 37 ± 0.5 degrees C by a heating lamp. The right common carotid artery was isolated with an atraumatic ligature fashioned from a loop of PE 10 polyethylene tubing contained within a double-lumen...
Cause of cerebral infarction in the carotid territory. Its relation to the size and the location of the infarct and to the underlying vascular lesion.

T S Olsen, E B Skriver and M Herning

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