Effect of Chronic Middle Cerebral Artery Stenosis on the Local Cerebral Hemodynamics

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SUMMARY In 36 patients with angiographically proven middle cerebral artery (MCA) stenosis, local cerebral hemodynamics were studied employing angiography. $^{133}$Xe inhalation regional cerebral blood flow (rCBF) measurements and CT scans. They had transient ischemic attacks in 8 and completed stroke in 28. The patients with less than 50% stenosis ($n = 16$) had no hemodynamic abnormality in angiographical and rCBF examinations. The infarction in this group was small and located in the basal ganglia area. The patients with 50 to 74% stenosis ($n = 9$) often revealed a delayed filling of MCA branches in the angiography, however, they showed no significant rCBF reduction. The infarction in this group was also small and located in the basal ganglia area. The patients with 75 to 99% stenosis ($n = 11$) exhibited a significant flow depression both in angiographical and rCBF examinations. Three of them had large cerebral infarction in the watershed zone or the cerebral cortex. The results of the present study suggest that the hemodynamic effect of MCA stenosis begins to manifest at 50% in grade and becomes apparent at 75%. The danger of hemodynamic crisis as well as the risk of large cerebral infarction may increase when MCA stenosis exceeds 75% in grade.

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IT HAS BEEN WELL DOCUMENTED in the experimental literature that severe cerebral artery stenosis acutely produced in animals causes a drop in perfusion pressure and a reduction of blood flow in the distal regions. The critical point leading to such hemodynamic depression was reported to be 50 to 95% narrowing of the arterial lumen.1-4

In patients with ischemic stroke, stenotic lesions are often found in major cerebral arteries. During the past two decades, numerous studies have been performed on the significance of major cerebral artery stenosis, and it is now well understood that stenotic lesions play an important role in the occurrence of stroke as one origin of artery-to-artery embolism. However, insofar as the hemodynamic role of chronic cerebral artery stenosis is concerned, our knowledge remains limited.

The present authors therefore undertook a clinical investigation of the effect of chronic middle cerebral artery (MCA) stenosis on the local cerebral hemodynamics. In this study, 36 patients with angiographically proven MCA trunk stenosis were classified into 3 groups according to their grade of stenosis. The state of the peripheral circulation in the 3 groups was compared from three different viewpoints, employing angiography, $^{133}$Xe inhalation measurements of regional cerebral blood flow (rCBF) and computed tomography (CT). The data obtained may contribute to the better management of patients with major artery stenosis.

Case Materials

The study was performed in a retrograde manner. During the period from April 1, 1977 to December 31, 1982, 764 patients with ischemic cerebrovascular disease were admitted into our department for a treatment of acute stroke or for a neurological evaluation, and 511 underwent angiographical examinations. Among them, 49 cases had a noticeable MCA trunk stenosis. The angiograms of these patients were carefully reviewed by four of the authors. It was found that 36 had the MCA stenosis alone and no additional occlusive change in the ipsilateral carotid arterial system, except for small ulcerative plaques in the internal carotid artery (ICA) in 7. The other 13 had additional occlusive changes in the ipsilateral carotid arterial system, such as severe ICA stenosis ($n = 2$), occlusion of the anterior cerebral artery ($n = 1$) and occlusion of main MCA branches ($n = 7$), or no information concerning the extracranial part of the ipsilateral carotid artery ($n = 3$). These 13 cases were excluded from the following analyses.

The 36 patients with MCA stenosis suffered transient ischemic attacks (TIAs) in 8 and completed stroke in 28. There were 23 men and 13 women with ages ranging from 41 to 73 years. They were admitted into our institution within 1 week of ictus in 26 and after 1 week to 3 months of ictus in 10. The angiographical examinations were performed within 1 week of ictus in 14, during 2 to 3 weeks of ictus in 17 and more than 3 weeks of ictus in 5. Angiography was performed by transfemoral route in 17, by the combination of direct carotid artery puncture and brachial artery injection in 14, and by direct carotid artery puncture alone in 5. Two-vessel to four-vessel angiograms were obtained in 31 and single carotid artery angiograms in 5. All patients had a noticeable stenosis in the main stem of MCA. Stenosis occurred at the origin of MCA proximal to the lenticulostriate segments in 11, in the region of the lenticulostriate segments in 19 and in the region distal to those segments in 6. Four cases had 50% or greater stenosis in the contralateral ICA.
Methods

The patients were classified into 3 groups according to their grade of MCA stenosis: Group A (n = 16), cases with less than 50% stenosis; Group B (n = 9), cases with 50-74% stenosis; and Group C (n = 11), cases with 75-99% stenosis. The grade of stenosis was determined on the basis of angiographical findings by measuring the diameter of the MCA origin and that of the narrowest part of stenotic segments. In these 3 groups, the local cerebral hemodynamics in the area distal to the stenosis were compared from three different viewpoints by analyzing the results of angiography. $^{133}$Xe inhalation rCBF measurements and CT scans.

1. Angiographical Evaluation of Local Cerebral Hemodynamics

Angiograms were reviewed by four of the authors, and the attention was focused on the following two points: 1) Whether a filling of MCA branches was delayed compared to that of the ipsilateral anterior cerebral artery (ACA) branches, and 2) whether a retrograde flow from the ACA or from the posterior cerebral circulation to the MCA territory was visualized. These findings were estimated to be the signs of circulatory abnormalities.

2. Measurements of rCBF

During the admission, 20 patients underwent rCBF measurements by $^{133}$Xe inhalation methods. Measurements were made during first 3 weeks of ictus in 3, after 3 weeks of ictus in 13 and both during acute and chronic stage in 4. In the present study, the rCBF data obtained during the chronic stage alone was analyzed.

The rCBF measurements were carried out according to the method of Obrist et al. in a dark and quiet room. During the measurements, the blood pressure was repeatedly monitored from the left upper arm, and the arterial blood gas was monitored from the right brachial artery. Sixteen probes were mounted over each cerebral hemisphere, and the rCBF (Initial Slope Index, ISI) was calculated as reported by Risberg et al. Although rCBF values were obtained from the 16 detectors in each hemisphere, only those from 8 detectors overlying the diseased MCA territory were analyzed in this study.

In our institution, more than 500 patients have undergone $^{133}$Xe inhalation rCBF measurements to date. Among these patients 17 cases with cerebral infarction who met the following criteria were selected as the controls: 1) Angiography was performed within 3 days of ictus, and no stenosis or occlusion was found in the carotid arterial system; 2) Infarcted lesions in CT were mainly in the basal ganglia area; and 3) rCBF was measured after 3 weeks of ictus. The rCBF values in each stenotic group were compared against these controls.

3. Size and Location of Infarction Estimated from CT Findings

After the admission, serial CT examinations were performed in all patients, except for 5, to clarify an existence of infarction and to see a development of ischemic cerebral edema. Five exceptional cases received only single CT study, because they were admitted more than 3 weeks after TIAs or stroke, and single CT study provided satisfactory information concerning ischemic lesions. The CT films were reviewed by three of the authors. If a low density area suggestive of infarction was found in the territory of the MCA, the size of the infarction was calculated as follows:

\[
\text{Infarction Size Index} = \frac{\text{Size of maximum low density area}}{\text{Maximum area extent of ipsilateral cerebral hemisphere}} \times 100\%
\]

In principle, the measurement of size of infarction was made using the CT films obtained more than 3 weeks after ictus, since CT findings in this stage are usually more definitive than those in the earlier stage.

The locations of the infarction on CT films were classified into 3 types: 1) mainly in the basal ganglia area; 2) mainly in the cortical area; and 3) in the watershed zone. Determination of the watershed zone in CT was based on the report of Wodarz although in the present study, the head of the caudate nucleus was not included in the watershed zone but in the basal ganglia area.

Results

The mean age of Groups A, B and C was 63.4 ± 9.9, 61.4 ± 10.1 and 60.4 ± 11.5 years, respectively. There was no significant age difference among them. In Group A, 5 cases had TIAs alone and 11 had completed stroke. In Group B, 1 had TIAs and 8 had completed stroke. In Group C, 2 had TIAs and 9 had completed stroke. Thus, completed stroke tended to occur less frequently in Group A than in the other two groups, yet, the difference was not statistically significant.

1. Angiographical Circulatory Condition

In all patients, main branches of the MCA were clearly visualized, and no occlusion was found in the peripheral branches. The table summarizes the angiographical circulatory condition of 3 groups. In Group A, none had angiographical circulatory abnormality. In Group B, 6 cases showed a delay in filling of MCA branches compared to that of ACA branches. The other 3 had normal filling of the branches. In this group, none showed a retrograde flow from the ACA or from the posterior cerebral artery (PCA). In Group C, all patients showed a remarkable delay in filling of the MCA branches. Four cases in this group had a retrograde flow from the ACA to the MCA territory through cortical anastomotic channels. One of these four had a retrograde flow also from the PCA. The retrograde flow was supplying the territory of the ascending branches in 3 cases and the territory of the angular branch in the other case. One of the former 3 patients had infarction in the watershed zone (tempororooccipital triangle), and the other 2 had no infarction.
The latter patient with the retrograde flow to the angular branch had a small infarction in the capsular region.

### 2. Regional Cerebral Blood Flow

The rCBF in patients with ischemic stroke generally correlates with the size of infarction. This was true also in the present study. Of 17 patients who underwent rCBF measurements in chronic stage, 2 had infarction, the size of which was apparently larger compared to that of the others. These 2 cases had 75 to 99% MCA stenosis. The rCBF values in these 2 cases were 29.1 and 31.7 respectively which were markedly lower compared to those measured in the others (41.6 ± 5.3). These 2 were excluded from subsequent analyses, and the rCBF values were compared only among cases who had small infarction, with an infarction size index of 5% or below.

In 17 control patients with normal angiograms, the infarction size index was 5% or lower and was comparable to that of the patients with MCA stenosis. The rCBF values in these controls were calculated to be 44.8 ± 3.7. A comparison of the rCBF values between the controls and 3 stenotic groups is given in figure 1. The blood pressure as well as the PaCO₂ at the time of rCBF measurements was the same in all groups including the controls. The mean rCBF values were 43.0 ± 5.3 and 42.0 ± 7.2, respectively. There was no significant rCBF difference between these 2 groups and the controls. The mean rCBF in Group C was 38.1 ± 2.5. This value was significantly lower than that in the controls (p < 0.005).

### 3. Location and Size of Infarction

The location of infarction estimated by CT is listed in table 2. Ten patients revealed no abnormal low density lesion in CT, and the other 26 had low density lesions in the MCA territory. As shown in table 2, it was characteristic that the majority of patients in Groups A and B had infarction in the basal ganglia area. In these 2 groups, only 1 case had infarction in the cortical area and another one in the watershed zone. On the other hand, in Group C, 2 cases had infarction in the cortical area, and 2 others had infarction in the watershed zone. The other 4 had infarction in the basal ganglia area.

The size of infarction in the 3 groups is compared in figure 2. The infarction in all patients of Groups A and

### Table 1: Angiographical Circulatory Condition

<table>
<thead>
<tr>
<th>Angiographical findings</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No flow abnormality</td>
<td>16</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Delay in filling of MCA branches</td>
<td>0</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Retrograde flow</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

The latter patient with the retrograde flow to the angular branch had a small infarction in the capsular region.

### Table 2: Location of Infarction Estimated from CT Findings

<table>
<thead>
<tr>
<th>Infarction in CT</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infarction</td>
<td>6</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Basal ganglia area</td>
<td>8</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Cortical area</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Watershed zone</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

rCBF in Group C was 38.1 ± 2.5. This value was significantly lower than that in the controls (p < 0.005).
B was small, with the infarction size index never exceeding 5%. In 8 of Group C patients, the infarction size index was also 5% or lower, but in the other 3 of this group, the index was as high as 8%, 13% and 16%, respectively. These large infarctions were seen in the cortical area in 2 and in the watershed zone in 1.

Discussion

Cerebral artery stenosis is an important underlying factor of ischemic stroke. In Caucasian populations, stenotic lesions are most commonly seen in the extracranial carotid artery, while in Japanese populations, atherosclerotic stenosis is more frequently found in the intracranial cerebral arteries, particularly in the MCA. This led us to choose the MCA for investigation of the hemodynamic effects of major cerebral artery stenosis in this study.

Stenotic lesions may play two different roles in the pathophysiology of ischemic stroke: one as an origin of artery-to-artery embolism, and the other as a factor disturbing the cerebral circulation. The latter role has not yet been fully investigated. The hemodynamic effect of acute arterial stenosis was studied by several workers producing artificial narrowing of the carotid artery or the iliac artery in man as well as in animals. All these workers agreed that moderate stenosis had no hemodynamic effect but that stenosis above a certain grade caused a reduction in perfusion pressure and a decrease of blood flow in the distal regions. Above this threshold even a small increase in grade of stenosis led to a progressive reduction in blood flow, culminating eventually in zero flow at the level of complete occlusion. The critical grade causing such circulatory depression differed considerably according to each worker ranging from 50 to 95% as reported in the literature. This large variation can be probably explained on the basis that the hemodynamic effect of arterial stenosis is determined not only by the grade of narrowing but also by several other factors, such as the length of narrowing, flow velocity, shape of the inlet or outlet segments and existence of parallel collateral routes.

In the present study, the hemodynamic effect of chronic MCA stenosis was assessed mainly on the basis of angiography and $^{133}$Xe inhalation rCBF measurements, and the following two facts were clearly exhibited: 1) The patients with less than 50% stenosis had neither angiographical flow abnormality nor rCBF reduction; and 2) the patients with 75 to 99% stenosis had both angiographical flow abnormalities and rCBF reduction. Although the cases examined in the present study are small and not all of them have received rCBF measurements, the results seem to clearly indicate that less than 50% stenosis has little hemodynamic effect and that 75% or greater stenosis causes a significant circulatory depression in the distal regions. Previously, Hinton et al. and Corston et al. performed similar hemodynamic studies in patients with MCA stenosis using angiography. They also documented that the angiographical flow abnormality was rarely seen in patients with less than 50% stenosis. In the study of Hinton et al., 4 patients had 75% or greater stenosis, and all of them had angiographical flow abnormalities. The results obtained in the present study well agree with those of previous angiographic studies. One of the interesting facts found in the present study was that 4 patients with 75% or greater stenosis had a retrograde flow from the anterior cerebral circulation or from the posterior cerebral circulation to the post-stenotic area, while none of the patients with lower grade stenosis had such retrograde flow. The retrograde flow is usually seen in complete occlusion of the MCA or its branches. The possibility that these 4 patients have small embolism in the peripheral branches cannot be excluded completely. However, their angiograms failed to show the existence of occlusion. This retrograde flow may represent a development of collaterals, which is facilitated by the substantial hemodynamic effects of severe MCA stenosis. Other angiographical workers also reported the existence of such retrograde flow in patients with severe MCA stenosis and estimated it to be an important sign suggesting the hemodynamic effects of severe MCA stenosis.

The results of rCBF measurements in the present study showed that the blood flow in the patients with 50 to 74% MCA stenosis was maintained well within a normal range. On the other hand, the angiographical examinations indicated that 6 of 9 patients in this group had a retardation of post-stenotic arterial circulation. Thus, the results of rCBF measurements and the angiographical findings in this group had some discrepancy. Insofar as an arterial circulatory condition is concerned, angiography provides more reliable information than rCBF measurements generally. It seems therefore unquestionable that 50 to 74% MCA stenosis causes some flow abnormalities at least in the poststenotic arterial segments. A delay of arterial blood circulation demonstrated by angiography, however, does not necessarily indicate a decrease of tissue perfusion in the peripheral regions. As described in circulation literature, tissue perfusion is regulated mainly by a dilatation or constriction of microvessels. Even if the circulation in post-stenotic arterial segments is retarded, the tissue perfusion may remain unchanged, provided the peripheral microvessels give a compensatory dilatation. rCBF measurements usually well estimate such state of tissue perfusion. Above mentioned discrepancy may be explained by the view that 50 to 74% MCA stenosis causes a retardation of post-stenotic arterial circulation but not a depression of peripheral tissue perfusion. Alternatively, the discrepancy may be explained by a methodological limitation of $^{133}$Xe inhalation rCBF measurements. $^{133}$Xe inhalation method permits some errors due to a contamination of the extracranial blood flow, and its accuracy is not as excellent as that of $^{133}$Xe arterial injection method. If the cerebral blood flow reduction in this group of patients is very small, such moderate changes may be dismissed in $^{133}$Xe inhalation rCBF measurements. Unfortunately, only 4 patients with 50 to 74% MCA stenosis underwent rCBF measurements in the present study. This small size in samples may be an additional...
factor contributing to the lack of rCBF reduction in this group. Thus, two possibilities can be considered for the explanation of the discrepancy. Both are related to the small grade in circulatory changes. Whichever the explanation, the hemodynamic effects of this middle grade MCA stenosis may be small.

According to the report of Hinton et al., the angiographical flow abnormalities were seen in 9 of 10 patients with 50 to 74% MCA stenosis. While in the report of Corston et al., the flow abnormalities were found only in 3 of 9 patients with 50 to 74% stenosis. As represented by these two different reports, the occurrence of hemodynamic abnormality in 50 to 74% MCA stenosis seems to be rather inconsistent. The authors have assumed that 50 to 74% narrowing may be probably the border-zone at which MCA stenosis begins to show the hemodynamic effects. In this middle grade MCA stenosis, the hemodynamic depression may occur depending upon the condition of additional factors, such as the length of narrowing, flow velocity and shape of the inlet or outlet segments.

As discussed above, it seems that chronic MCA stenosis begins to exert a moderate hemodynamic effect at 50 to 74% and causes a significant circulatory disturbance at 75% or above. In the respect that the hemodynamic effects begin to manifest at a certain grade, chronic MCA stenosis and acute experimental arterial stenosis seem to be the same. However, these two have a large difference in the degree of resultant circulatory disturbance as follows: In acute arterial stenosis, severe blood flow reduction usually occurs, when the narrowing reaches a high level. On the other hand, in chronic MCA stenosis, blood flow reduction is small, even if the narrowing reaches a high level. For example, the rCBF reduction seen in the patients with 75% or greater stenosis was only 15% compared to the values of the controls. This small change may result, probably because in chronic MCA stenosis, a dilatation of peripheral micro-vessels and/or development of collaterals occurs gradually compensating the hemodynamic effects.

Such moderate circulatory disturbance would exert little influence on the cerebral metabolism and function, and may be of little importance from a clinical viewpoint. However, it should be noted that above described results were obtained in a normotensive state or in a hypertensive state. A circulatory condition supported by collaterals or by dilated micro-vessels is known to be vulnerable to a decrease of blood pressure. Meyer and Denny-Brown in their experimental study of MCA occlusion using monkeys showed that a retrograde collateral flow from the anterior cerebral circulation to the occluded area disappeared when the systolic blood pressure fell to 85 mmHg. Thus, if the blood pressure drops, a grave circulatory disturbance may ensue in the area distal to the stenosis. Several clinical workers emphasized that a drop in blood pressure may lead to a manifestation of ischemic symptoms in patients with severe ICA stenosis. In the present study, 2 of 11 patients with 75% or greater stenosis showed cerebral infarction in the watershed zone. The occurrence of infarction in these 2 patients may be related to hypotension, since watershed infarction is often caused by a hemodynamic mechanism as pointed out by Adams et al. Another 2 patients with 75% or greater stenosis had large cerebral infarction in the cortical area. Such large infarction was never found in the patients with lower grade stenosis. Whether hypotension had participated in the development of such infarction was unclear. Yet, it is reasonable to assume that the large cortical infarction would not have formed, unless severe MCA stenosis existed in these patients.

In conclusion, it can be said that the hemodynamic effects of chronic MCA stenosis are rather small, provided the blood pressure is maintained in the physiological range. Nevertheless, the hemodynamic effects may be amplified, if hypotension does occur. For this reason, patients with 50% or greater MCA stenosis, particularly those with 75% or 99% stenosis, are in danger of hemodynamic crisis as well as at risk of large cerebral infarction. A long term prognosis of patients with MCA stenosis was reported to be benign in several clinical studies, where the anticoagulant therapy well prevented the occurrence of new stroke. However, recently Corston et al. provided a contradictive report showing that 4 of 21 patients with MCA stenosis died because of recurrent stroke during the follow-up period of 3 months to 16 years, in spite of the anticoagulant therapy. Three of them had 50% or greater stenosis at the beginning of the follow-up period. The results of their study seem to suggest that more aggressive treatment, such as the extracranial-intracranial (EC/IC) bypass surgery, is needed in some patients with MCA stenosis. Although an efficacy of EC/IC bypass surgery is still under debate, this surgical treatment is likely to decrease a danger of hemodynamic crisis as well as a risk of large cerebral infarction. The authors consider that EC/IC bypass may be useful for improving a prognosis of patients with MCA stenosis, provided they have 50% or greater stenosis.

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Cerebral Ischemic Attacks As A Complication Of Aortic And Mitral Valve Prolapse

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SUMMARY The high incidence of mitral valve prolapse (MVP) in patients with ischemic attacks is puzzling when compared with the very low incidence of cerebrovascular attacks observed in individuals known to have MVP. Our aim was to determine if it is possible to identify a patient subset with MVP at the highest risk of embolization on the basis of 2D-echocardiographic findings.

We compared the echocardiographic picture of a group of 39 patients with MVP and cerebral ischemic attacks (29 TIAs, 10 strokes) in the carotid territory, without any pathological lesions at angiography, with that of a control group of 111 patients with MVP without neurological complications. The two groups were not different for age or sex.

Patients with MVP and neurological complications showed a higher prevalence of aortic valve prolapse (62% vs 34%, p < 0.01), of an association between valvular diffuse thickening and aortic valve prolapse (54% vs 23%, p = 0.001), and of multiple valve prolapse with valvular diffuse thickening (26% vs 7%, p < 0.01) than those of the control group.

This study suggests that in young people cerebral ischemic events could be related to the presence of a combined valve prolapse and to an echocardiographic picture of valve diffuse thickening. These data suggest that in this selected group with multiple valve prolapse and valvar diffuse thickening prophylaxis against embolic events by pharmacological preventive measures should be considered.

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