Brain Circulation in Cerebral Transient Ischemic Attacks

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Summary

Cranial blood flow, mean cranial transit time and cranial blood volume were measured by the intravenous RISA technique in 10 patients with cerebral transient ischemic attacks (TIA) at the various time intervals from the onset of last attack. Cranial blood flow was subnormal in 5 out of 11 determinations and mean transit time trended to be prolonged in the diseased hemisphere in cases suggestive of the unilateral hemispheric lesion.

A decrease in cranial blood flow was observed in TIA with lowering of heart rate below 60/min, or with atrial fibrillation, whereas no obvious correlation was present between heart rate and cranial blood flow either in 94 patients with, or in 62 patients without cerebrovascular diseases.

Cardiac dysrhythmias including bradycardia, leading to reduce perfusion to the brain was discussed as a possible factor for producing TIA.

Additional Indexing Words:
Cranial blood flow, Cranial transit time, Heart rate, Cardiac dysrhythmia, Cerebrovascular disease

The pathogenesis of cerebral transient ischemic attacks (TIA) has not been fully understood. Atherosclerosis of the brain plus some other factors including circulatory alteration would be necessary for explaining the mechanism of development of TIA. They include vasospasm, transient hypotension such as orthostatic hypotension, kinking or external compression of neck arteries by cervical spondylosis or neoplasm, temporary hypoglycemia, and thrombosis or embolism. However, TIA was seen in a great number of patients without apparent narrowing or obstruction of the extra- or the intracranial vessels.

The authors have reported in the previous study that cardiac dysrhythmias such as sinus bradycardia and supraventricular premature beats were frequently observed in TIA, suggesting that slowing or irregularity of heart rate seems operative to cause transient ischemia of the brain. In the
present study, cranial blood flow was measured by the RISA technique in 10 patients with TIA to elucidate whether variation of heart rate may contribute to alter cerebral hemodynamics.

**Material and Method**

Ten patients with TIA, 7 males and 3 females, aged from 20 to 77 years old, were subjected to this study. Clinical diagnoses other than TIA were made as follows: hypertension in 5, coronary or arteriosclerotic heart disease in 2, latent syphilis in 2, atrial fibrillation of unknown cause, autonomic dysfunction, diabetes mellitus, cervical spondylosis, chronic hepatitis, and psychogenic polydipsia in each one patient.

Clinical findings are summarized in Table I. Three of all 10 patients had a single episode of TIA such as unilateral hemiparesis, speech disturbance, impair-

### Table I. Clinical Findings in 10 Patients with Cerebral Transient Ischemic Attacks

<table>
<thead>
<tr>
<th>Case</th>
<th>Age &amp; Sex</th>
<th>No. of Attacks</th>
<th>Lesion</th>
<th>Retinopathy*</th>
<th>ECG</th>
<th>EEG</th>
<th>CSFP (mm H₂O)</th>
<th>Cerebral Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. N. S.</td>
<td>20 F</td>
<td>multi</td>
<td>stem</td>
<td>0</td>
<td>WNL</td>
<td>sl (B)</td>
<td>120</td>
<td>narrowing of basilar artery, questionable occlusion of PCA</td>
</tr>
<tr>
<td>2. N. H.</td>
<td>73 M</td>
<td>multi</td>
<td>hemi (B)</td>
<td>I</td>
<td>SB &amp; flat-T</td>
<td>WNL</td>
<td>190</td>
<td>occlusion of rt ACA, narrowings of lt carotid, lt ACA and rt VA</td>
</tr>
<tr>
<td>3. M. M.</td>
<td>53 F</td>
<td>1</td>
<td>stem &amp; hemi (L)</td>
<td>Ha</td>
<td>AF</td>
<td>WNL</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4. T. S.</td>
<td>57 M</td>
<td>2</td>
<td>stem</td>
<td>I</td>
<td>SB</td>
<td>—</td>
<td>170</td>
<td>mild sclerosis</td>
</tr>
<tr>
<td>5. S. S.</td>
<td>53 M</td>
<td>multi</td>
<td>stem</td>
<td>1</td>
<td>WNL</td>
<td>sl (L)</td>
<td>70</td>
<td>negative</td>
</tr>
<tr>
<td>6. A. F.</td>
<td>49 M</td>
<td>multi</td>
<td>hemi (R)</td>
<td>IIb</td>
<td>SB &amp; LVH</td>
<td>ST-T</td>
<td>WNL</td>
<td>90</td>
</tr>
<tr>
<td>7. U. T.</td>
<td>68 F</td>
<td>multi</td>
<td>stem</td>
<td>Ha</td>
<td>SB</td>
<td>WNL</td>
<td>—</td>
<td>negative</td>
</tr>
<tr>
<td>8. I. Y.</td>
<td>77 M</td>
<td>5</td>
<td>stem &amp; hemi (L)</td>
<td>I</td>
<td>SB</td>
<td>LVH</td>
<td>sl (B)</td>
<td>180</td>
</tr>
<tr>
<td>9. S. S.</td>
<td>31 M</td>
<td>1</td>
<td>hemi (L)</td>
<td>I</td>
<td>LVH</td>
<td>flat-T</td>
<td>sl (B)</td>
<td>220</td>
</tr>
<tr>
<td>10. N. T.</td>
<td>76 M</td>
<td>1</td>
<td>hemi (L)</td>
<td>—</td>
<td>SB</td>
<td>WNL</td>
<td>175</td>
<td>sclerosis of rt carotid and both VAs, external compression of lt VA by cervical osteophyte</td>
</tr>
</tbody>
</table>

ment of consciousness or vertigo lasting less than 24 hours. One patient experienced 2 episodes, and other 6 had more than 3 attacks. Three of 10 patients had symptoms suggestive of unilateral hemispheric lesion, 1 patient having bilateral hemispheric lesions, 4 had brain stem lesion, and 2 had symptoms of both hemispheric and brain stem lesions. The interval from the onset of last attack to blood flow measurement ranged from 1 day to 8 months, being within 1 month in 7 patients and later than that in 4, in one of which blood flow studies were repeated 21 and 34 days after each attack.

As comparative groups, 94 patients with cerebrovascular diseases (CVD) and 62 patients with non-CVD were selected. In the former, 71 cases were diagnosed as infarction, 10 as subarachnoid hemorrhage, and 13 as cerebral hemorrhage. In the latter, 23 were hypertensives, 7 diabetics and the remaining 32 had a variety of diseases such as liver, digestive, muscle or nervous diseases. Cerebral embolism of cardiac origin or subarachnoid hemorrhage with arteriovenous malformation was excluded from this study.

Cranial blood flow, mean cranial transit time, cranial blood volume, ratio of left-to-right cranial blood flow and arm-to-brain circulation time were measured by modification of the Oldendorf's original method. Two hundred microcurie of I-131 RISA was injected rapidly through the antecubital vein, and the radioactive dilution curves were traced on the 2 channels recorder by the NaI scintillation detectors collimating each hemisphere separately. The technical details of this method have been reported elsewhere.6)

RESULTS

1) Brain Circulation in TIA

Cranial blood flow decreased in 5 of all 11 determinations and remained normal in other 6 as shown in Table II. The lowest value was 860 ml/min, or 57% of the control value. Cranial blood volume trended to be lowered in all patients, in which 3 were below the normal range. Mean transit time was normal in 8, and prolonged bilaterally in 2, and unilaterally in 1. A mean transit time difference of one side to the other of 1 sec or more was observed in 4 patients, in whom the prolonged side was compatible with the clinical hemispheric lesion. In 5 patients with brain stem lesion, there was none of the difference of mean transit time longer than 1 sec. Although cranial blood flow decreased in 5, ratio of left-to-right cranial blood flow was normal in all patients.

2) Relation of Cranial Blood Flow to Clinical Findings

Either the severity of retinopathy or the level of blood pressure was not related with changes in cranial blood flow. There was a poor correlation between a degree of EEG abnormalities and a decrease in cranial blood flow. In 6 out of 9 cases studied, cerebral angiography showed a variety of vascular changes; a mild stenosis of the internal carotid and/or the vertebral artery was seen in 3, of which one case (#10) had the external compression of the
Table II. Brain Circulation in 10 Patients with Cerebral Transient Ischemic Attacks

<table>
<thead>
<tr>
<th>Case</th>
<th>Interval from Last TIA (day)</th>
<th>MAP (mmHg)</th>
<th>Heart Rate (min)</th>
<th>Cr. BF (ml/min)</th>
<th>L-mean TT (sec)</th>
<th>R-mean TT (sec)</th>
<th>Cr. BV (ml)</th>
<th>L/R-Cr. BF</th>
<th>Cr. VR (mmHg/ml/min × 100)</th>
<th>ABCT (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-a</td>
<td>34</td>
<td>109</td>
<td>78</td>
<td>1,230</td>
<td>8.7</td>
<td>8.5</td>
<td>176</td>
<td>1.06</td>
<td>8.86</td>
<td>10.5</td>
</tr>
<tr>
<td>1-b</td>
<td>21</td>
<td>121</td>
<td>88</td>
<td>1,540</td>
<td>6.3</td>
<td>6.0</td>
<td>158</td>
<td>0.88</td>
<td>7.86</td>
<td>9.0</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>91</td>
<td>52</td>
<td>1,060</td>
<td>8.3</td>
<td>8.5</td>
<td>149</td>
<td>0.98</td>
<td>8.58</td>
<td>13.9</td>
</tr>
<tr>
<td>3</td>
<td>240</td>
<td>81</td>
<td>62</td>
<td>870</td>
<td>11.5</td>
<td>11.6</td>
<td>167</td>
<td>0.97</td>
<td>9.32</td>
<td>17.7</td>
</tr>
<tr>
<td>4</td>
<td>110</td>
<td>106</td>
<td>49</td>
<td>1,130</td>
<td>10.3</td>
<td>9.6</td>
<td>187</td>
<td>0.89</td>
<td>9.38</td>
<td>15.0</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>88</td>
<td>71</td>
<td>1,140</td>
<td>8.0</td>
<td>7.8</td>
<td>150</td>
<td>1.08</td>
<td>7.72</td>
<td>13.4</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>122</td>
<td>57</td>
<td>1,020</td>
<td>8.4</td>
<td>11.7</td>
<td>171</td>
<td>1.18</td>
<td>11.95</td>
<td>15.9</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>83</td>
<td>57</td>
<td>1,120</td>
<td>9.5</td>
<td>9.0</td>
<td>172</td>
<td>0.94</td>
<td>7.41</td>
<td>15.5</td>
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<tr>
<td>8</td>
<td>59</td>
<td>137</td>
<td>53</td>
<td>930</td>
<td>12.9</td>
<td>11.5</td>
<td>188</td>
<td>0.89</td>
<td>14.73</td>
<td>20.8</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>119</td>
<td>63</td>
<td>1,440</td>
<td>8.3</td>
<td>7.3</td>
<td>187</td>
<td>0.84</td>
<td>8.27</td>
<td>12.7</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>90</td>
<td>54</td>
<td>860</td>
<td>11.1</td>
<td>10.0</td>
<td>151</td>
<td>1.06</td>
<td>10.47</td>
<td>22.2</td>
</tr>
<tr>
<td></td>
<td>±66</td>
<td>±18</td>
<td>±12</td>
<td>±207</td>
<td>±1.8</td>
<td>±1.8</td>
<td>±14</td>
<td>±0.10</td>
<td>±2.07</td>
<td>±3.8</td>
</tr>
</tbody>
</table>

Young Control (28 yrs, n = 15) | 1,569 | 8.2 | 8.2 | 214 | 1.01 | 5.57 | 13.0
| Aged Control (56 yrs, n = 19) | 1,504 | 9.1 | 8.9 | 223 | 1.00 | 6.13 | 13.9
|                                | ±200  | ±1.3| ±1.2| ±29 | ±0.10| ±0.93| ±3.3

* atrial fibrillation, MAP: mean arterial pressure, Cr. BF: cranial blood flow, L-, R-mean TT: left, right mean transit time, Cr. BV: cranial blood volume, L/R-Cr. BF: left-to-right cranial blood flow ratio, Cr. VR: cranial vascular resistance, ABCT: arm-to-brain circulation time, values are mean±SD

Unilateral vertebral artery by osteophytes of the cervical vertebrae, and another case (#8) had concomitant spasms of both the anterior and the middle cerebral artery. These 3 cases had a slight to moderate decrease in cranial blood flow, although cerebral vascular changes seemed relatively mild.

Cranial blood flow decreased below the normal range in one (#2) with a marked stenosis of the intra- and the extracranial arteries, in whom weakness of both legs and a fluctuating rise of blood pressure had developed by compressing the right carotid artery. In other case (#6) with frequent attacks, 4 neck vessels study revealed complete occlusion of the right middle cerebral as well as the left anterior cerebral artery. Of this patient, cranial blood flow decreased slightly and mean transit time prolonged greater on the right hemisphere than that on the left. Narrowing of the basilar artery with questionable occlusion of the right posterior cerebral artery was seen in 1 (#1), of which cranial blood flow was normal on the repeated measurements.
In 3 cases having negative angiographic findings, cranial blood flow was within normal range.

In all of 10 cases was increased cranial vascular resistance, calculated by mean arterial blood pressure and cranial blood flow. In 3 cases (#6, 8, 10) having a marked increase in vascular resistance beyond 10 mmHg/ml/min, or 163% of the mean control value, angiography revealed a narrowing or occlusion of the brain vessels, whereas of another 3 cases (#5, 7, 9) having normal angiographic findings, cranial vascular resistance was normal in 2, and slightly increased in 1. Arm-to-brain circulation time as partial indicator of systemic hemodynamics, was prolonged in 2 cases, of which cranial blood flow decreased significantly.

3) Relation of Heart Rate to Cranial Blood Flow in TIA, CDV and Non-CVD

Heart rate in each case was obtained by as follows; counting of heart rate from ECG traced on the day close to blood flow study, averaging the values for pulse rate obtained during 2 days before and after blood flow study, or direct counting of pulse rate at the time of blood flow measurement.

As depicted in Fig. 1, cranial blood flow decreased below the normal range in 5 out of 11 determinations in 10 patients with TIA, of which 4 cases had bradycardia at rate of less than 60/min and the remaining 1 had a normal heart rate but atrial fibrillation on ECG. In these 5 cases with subnormal cranial blood flow, 2 (40%) were hypertensives but the other 3 were normotensives. On the other hand, cranial blood flow remained normal
in 4 determinations of 3 cases who had regular cardiac rhythm with heart rate between 60 and 100/min, although 2 cases were hypertensives.

Fig. 2 shows the relationship between 2 parameters in CVD excluding TIA. Cranial blood flow decreased below the normal range in 54 of 94 patients, of whom 31 (57%) were hypertensives. There was no obvious correlation between 2 parameters, namely in cases with bradycardia below 60/min cranial blood flow decreased as much extent as in those with a normal

![Graph](image)

Fig. 2. Relation of heart rate to cranial blood flow in various cerebrovascular diseases.

There is no obvious relationship between 2 parameters in these patients accompanied with or without hypertension.

![Graph](image)

Fig. 3. Relation of heart rate to cranial blood flow in patients with diseases other than cerebrovascular disease.

Cranial blood flow in hypertensives is relatively lower than that in normotensives, although there is no correlation between heart rate and blood flow in each group.
heart rate.

As shown in Fig. 3, a subnormal cranial blood flow was obtained in 15 of 62 patients with non-CVD, of whom 10 (67%) had hypertension and other 5 had diabetes mellitus, liver disease, digestive disease or cervical tumor. Of these 10 hypertensives, cranial blood flow decreased to a moderate degree below 1,000 ml/min in 4 cases, of which 2 were diagnosed as malignant hypertension.

DISCUSSION

It has been uncertain whether thrombo-embolic event\(^1\) or purely hemodynamic derangement\(^7,8\) is a major factor of causes of TIA. The possibility of thrombo-embolic event could not be excluded from the present results showing that 6 out of 9 cases studied had more or less the angiographic changes of the intra- or the extra-cranial vessels. In the remaining 3 cases having normal angiographic findings, however, it is controversial to this concept. Although vascular changes are present or not, the major problem in TIA seems to be a failure of perfusion to the brain, which may be focal or generalized.

The hemodynamics of TIA have been studied by Skinhoj et al\(^9\) and Rees et al.\(^10\) The former found no abnormalities in cerebral blood flow in 12 patients after two and a half days of the onset, whereas the latter observed a focal decrease in cerebral blood flow or changes in the proportion of tissue flow to be persistent for many days, in 1 case as long as 90 days, after last attack. A persistent decrease in cerebral blood flow, despite neurological deficits lasting less than 24 hours, suggests that the vascular changes of the brain might be existent on basis leading to reduced cerebral blood flow. In the present study, cranial blood flow was subnormal in 5 out of 10 patients, in which the lowest value was 860 ml/min, or 57% of the control, being compatible with observations made by Rees et al.\(^10\)

An inadequate cerebral circulation might be caused by a variety of systemic disorders such as hypotension, cardiac arrhythmias, and polycythemia. From many observations reported, it is very likely that cardiac dysrhythmias are one of the most important factors to cause TIA. In our previous study,\(^5\) 27 out of 30 patients with TIA between attacks had the ECG abnormalities such as bradycardia, supraventricular premature beats, atrial fibrillation, atrioventricular blocks, and changes in ST-T waves. Walter et al.\(^11\) found that 10 out of 39 cases with TIA had episodic cardiac dysrhythmias detected by a continuous ECG monitoring. Furthermore, Fowler et al.\(^12\) reported that the occurrences of symptoms of TIA were related to cardiac
slowing or arrest in 3 of 6 cases with sino-atrial bradycardia. In the series reported by Walter et al\textsuperscript{11}) and Fowler et al,\textsuperscript{12}) symptoms subsided or improved by the specific anti-arrhythmic treatment. Lavy and Stern\textsuperscript{13}) also studied that transitory symptoms of cerebral dysfunction occurred as a result of temporary impairment of cardiac rate and rhythm. Very recently, McAllen and Marshall\textsuperscript{14}) reported 9 cases with TIA in association with episodic cardiac arrhythmias of 16 cases referred for the insertion of a permanent cardiac pacemaker, suggesting the possibilities of a cardiac dysrhythmia as a cause of TIA. Despite the contradictory observations to be reported,\textsuperscript{15}) it is evident from these studies\textsuperscript{5,11)-14}) that episodes of TIA are frequently associated with temporary cardiac dysrhythmias, raising the question whether or not cardiac dysrhythmia could cause a reduction of cerebral blood flow.

On the relationship between heart rate and cranial blood flow, the present study demonstrated that in patients with TIA, cranial blood flow trended to decrease as related with slowing of heart rate, whereas no obvious correlation was observed between 2 parameters in CVD or in non-CVD patients. In hypertensives of non-CVD group, however, cranial blood flow was generally lowered comparing with that in normotensives, but it was not related to heart rate. These results indicate that the lowering of cranial blood flow is extremely rare or hardly occurs in normotensive subjects without CVD even when their heart rates reduce below 60/min, but it may happen in patients with TIA.

Corday and Irving\textsuperscript{16}) demonstrated in dogs that most cardiac arrhythmias induced cause a reduction of cerebral blood flow and an increase in cerebrovascular resistance; frequent premature ventricular beats cause a reduction of the internal carotid flow of 12\%, and atrial fibrillation of 23\%. Held and Gottstein\textsuperscript{17}) found in patients with an extreme bradycardia that cerebral blood flow decreased markedly and recovered to normal when heart rate was raised to the normal level by a pacemaker. In complete heart block, Shapiro and Chawla\textsuperscript{18}) observed that a resting cerebral blood flow to be lowered at heart rate of 30 to 40/min rose to 118\% of the resting value with pacing at 60/min or over. Furthermore, Sulg et al\textsuperscript{19}) demonstrated that an artificial pacing leads a decreased cerebral blood flow to increase with a concomitant improvement of EEG abnormalities in patients with complete atrioventricular block and that correction of the cardiac dysrhythmia relieves focal neurological symptoms. Similarly, the continuous measurement of brachial artery flow has shown a marked fall in peak flow during extrasystoles, atrial fibrillation, or high and slow ventricular rates, and the degree of fall in flow to depend upon the cardiac rate.
In addition to cardiac dysrhythmia, transient hypotension might be suggested as a cause of TIA by Denny-Brown,7) and Meyer et al8) as well as Shanbrom et al.20) Even a small reduction of systolic blood pressure has caused an insufficient blood supply to the brain in 2 cases with arteriosclerotic diseases of the carotid and the basilar system, in one of which a minimum blood pressure of 160 mmHg was necessary to prevent producing neurological symptoms.20) Meyer et al8) observed that an induced fall of blood pressure by tilting may cause focal cerebral dysfunction, whereas others21),22) described that acutely induced hypotension did not cause focal neurological symptoms.

There is no doubt that in pathologic states like the acute stage of CVD,23) a marked influence occurs in autoregulation of cerebral blood flow. Cerebral perfusion is maintained in response to falling blood pressure by means of vascular dilatation in normal subjects, although a process is not adequate in presence of rigid atherosclerotic vessels. Skinhøj et al9) demonstrated the impairment of autoregulation during few days after attack in TIA. It is possible but still open question that cerebral autoregulation per se is already impaired prior to the episode of TIA, or that the critical level of autoregulatory blood pressure range is shifted to the higher in TIA as shown in the severe hypertensives, in whom the lower limit of autoregulation rose to 120 mmHg of mean arterial pressure comparing with that of 60–70 mmHg in the normotensives.24)

In TIA, there were cases having the lowered cranial blood flow even during the state free from symptoms between attacks, and this phenomenon seemed to be related with slowing or irregularities of heart rate. Cardiac dysrhythmias are frequently observed not only during period between attacks5) but also more frequently during episode of TIA.11)–14) Considering these observations together, it comes to conclusion that a major factor for developing TIA is a transient lowering of perfusion to the brain, related with a seeming occurrence of episodic cardiac dysrhythmias, although the possibility can not be excluded that other factors such as sclerotic vascular changes might have participated as a basic cause.

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