Reactivity of Cerebral Blood Flow to CO₂ in Patients With Transient Cerebral Ischemic Attacks

BY STEPHEN W. THOMPSON, M.D.

Abstract: Reactivity of Cerebral Blood Flow to CO₂ in Patients With Transient Cerebral Ischemic Attacks

Cerebral blood flow and its ability to increase in response to inhalation of 6% CO₂ was measured in six patients with a history of transient ischemic attacks in the internal carotid distribution and in ten normal control subjects. Flow was measured with a method which uses time concentration curves made with intravenously injected radioactive indicator and externally placed radiation detectors. It permits measurement of flow, expressed in arbitrary units as a flow index, within the range of a detector placed against the side of the head.

Resting flow indices and the increases in flow indices in response to CO₂ inhalation did not differ significantly between the TIA patients and the normal control subjects. These results are discussed in terms of possible mechanisms of TIA, and it is concluded that the preserved CO₂ responsiveness of the flow indices in these six patients is in support of the theory that intermittent platelet microembolization is an important cause of TIA.

ADDITIONAL KEY WORDS
hemodynamic instability
autoregulation
cerebral infarction
platelet microemboli

The most common clinical manifestation of cerebral atherosclerosis is a focal neurological deficit which may be permanent if due to infarction, or brief, as in transient cerebral ischemic attacks (TIA). The pathogenesis of both disorders is not completely understood. Characteristically, both are of rapid onset, and both probably are due to the rapid development of focal brain ischemia. However, the slow pathogenesis and relatively fixed nature of the underlying lesion seems to indicate that such ischemia is based on a long-existing, relatively fixed abnormality of the cerebral circulation. If so, and if cerebral infarction and TIA are based on the same predisposing abnormality, this is not necessarily a reduction of cerebral blood flow per se. Although low cerebral blood flow has been found in patients with completed cerebral infarction,4-8 there is evidence that patients who have experienced TIA and who have no deficit often have normal cerebral blood flow.1-3 In a previous study,7 the author, using the method described below, did not find significantly reduced cerebral blood flow in 13 neurologically intact patients subject to TIA. Thus, the abnormality underlying TIA, at least, must be either precarious and unstable cerebral blood flow (hemodynamic instability) or some other factor which does not cause constantly lowered cerebral blood flow, such as intermittent platelet microemboli.5

Normally, there is autoregulation of the cerebral blood flow despite wide variations in the systemic perfusion pressure. This is accomplished by changes in the caliber of the small cerebral arteries, which appropriately alters their resistance so that relatively constant cerebral blood flow is maintained.8 However, increased blood carbon dioxide (CO₂) tension...
does lessen cerebral vascular resistance resulting in increased flow. With low perfusion pressure, the effect of increased CO$_2$ tension diminishes, and in severe hypotension it disappears as though maximal decrease in vascular resistance had already been attained. Thus, it can be considered that there is a functional cerebrovascular reserve or ability of the vessels to lower their resistance in response to decreased blood pressure, and that a measure of this reserve is the responsiveness of the cerebral blood flow to increased CO$_2$ tension.

Atherosclerotic narrowing of cerebral arteries might conceivably predispose to focal ischemia of the brain without preexisting lowered blood flow in any of several possible ways. The brain's ample collateral circulation suggests that for a critical degree of ischemia to occur in one region beyond a given point of narrowing, compromise of the collaterals by widespread lesions elsewhere would be necessary. If so, the resulting decreased pressure in all arteries distal to the multiple points of narrowing would induce a generalized compensatory autoregulatory dilatation. Blood flow would be maintained, but there would be a lessened responsiveness to increased CO$_2$ tension. Thus, cerebral blood flow would be more dependent than normally upon systemic perfusion pressure, and insufficiency of flow, particularly in those regions supplied by the most severely affected arteries, would be imminent.

On the other hand, focal cerebral ischemia might be the result of obstruction to flow only to the one region affected. In this case, compensatory autoregulatory dilatation would occur only in this one region, and here circulatory sufficiency would be precarious. Responsiveness to CO$_2$ would be decreased in this region but preserved elsewhere.

Presumably, if either of the above theories is correct, both cerebral infarction and TIA could result from systemic hypotension. Any factor leading to decreased perfusion pressure to the brain could compromise the precarious circulation beyond the most severely affected arteries. Whether permanent tissue damage or TIA occurred would depend upon the duration of the focal ischemia, or perhaps upon whether or not thrombosis resulted from the process.

An entirely different possibility is that TIA, at least, does not result from the above-postulated mechanism but from platelet microemboli thrown from thrombi on more proximally located atheromata. If so, cerebral blood flow in these patients would be normally responsive to CO$_2$.

This paper reports studies attempting to define a hemodynamic instability in six patients with TIA. The findings are discussed in terms of the possible cause of TIA, and how it may relate to that of cerebral infarction.

**Methods**

Cerebral blood flow was measured with a method which uses externally placed gamma ray detectors attached through rate meters to direct-writing recording galvanometers. One detector is put on the chest wall over the heart, and another is placed against the side of the head. Intravenous injection of a bolus of radioactive indicator produces a time concentration curve on the recorder from the region monitored by each of the detectors. Theoretically, the difference in length between the left ventricular and head curves is inversely proportional to the blood flow through the region producing the latter curve, and this flow can be expressed quantitatively in arbitrary units as a flow index.

The technique and derivation of the theoretical background for the method have been reported together with measurements in 51 normal adult subjects indicating that the normal flow index is in the range of 16.0 plus or minus 3.5. The basic hypothesis has been tested using curves made from a flow model.

For the present report, six patients with TIA within the internal carotid distribution and ten normal control subjects were studied. All of the TIA patients and four of the normal subjects were studied using two head detectors, one placed against each side of the head in order to obtain bilateral flow indices. In the remaining six normals, a single left-sided head detector was used. The head detectors were placed in a uniform location laterally so that for each a significant portion of the monitored region would be in the ipsilateral internal carotid artery distribution.

In each instance, the cerebral blood flow index was measured with the subject resting supine. A second reading was then made ten minutes after the subject had begun to breathe 6% CO$_2$ in air from a non-rebreathing mask with a flow of 10 liters per minute.

**Case Reports**

Six patients between 43 and 77 years old, each with a history of previous TIA, and ten control...
CBF REACTIVITY TO CO$_2$ IN TIA PATIENTS

Subjects between 26 and 61 years old were studied. All of the former had experienced brief neurological deficits attributable to dysfunction in a region of the brain supplied by one of the internal carotid arteries. Brief case histories follow.

CASE 1
A 49-year-old white man with diabetes since childhood began having episodes of left-sided weakness six months previously, characterized by onset with "numbness" in the left hand, progressing rapidly to the left face, arm and leg. Usually the left hand and arm became weak, occasionally so severely that the arm hung lifelessly. After 30 to 60 minutes the symptoms cleared completely. On the average these attacks occurred once weekly, without relation to meals, posture, medication or any other known factor.

Examination revealed bilateral diabetic retinopathy. A barely audible systolic bruit was heard over the right carotid artery at the level of the angle of the mandible. Detailed neurological examination was normal.

CASE 2
A 57-year-old white man began experiencing infrequent and brief episodes of blindness in his left eye at 44 years of age. These attacks were rapid in onset, occurred spontaneously without relation to any known factor, and lasted several minutes before clearing completely. Shortly after their onset he had a myocardial infarct from which he recovered. Afterward, he had angina pectoris. In addition, rare attacks of right hemiparesis with dysphasia developed, also rapid in onset, lasting one to several hours, and occurring separately from the amblyopia. The last such episode occurred six months previously.

At the age of 54 he was found to have diabetes mellitus.

Physical examination revealed no neurological deficit. Carotid pulsations were equal and no bruits were heard, but the retinal artery pressures measured 80/55 on the right and 60/40 on the left. 

CASE 3
A 70-year-old white man was hospitalized because of random episodes of right hemiparesis with aphasia starting two years previously and usually lasting less than one hour. They were of rapid onset, and the arm and hand were more severely involved than the leg. Probably less than ten such attacks had occurred.

On examination there were no neurological deficits. Systolic bruits were audible easily in both carotids, and a palpable thrill was present over the left.

CASE 4
A 43-year-old white man had been well until three weeks previously, after which he had three episodes of left-sided weakness of rapid onset, without precipitating factors and lasting several hours before clearing completely. The arm and hand were more profoundly involved than the leg, but on every occasion he was unable to walk during the attack. Neurological examination revealed no abnormalities. Both carotid pulsations were present and there were no bruits.

CASE 5
A 55-year-old white man was hospitalized because of acute myocardial infarction. Past medical history revealed intermittent attacks of rapidly developing left-sided "numbness" with left hand weakness of six years' duration. These occurred three to four times per year without apparent precipitating cause, and lasted 15 to 30 minutes.

Neurological examination 16 days following his myocardial infarction revealed no abnormalities. A faint systolic bruit was heard at the tip of the right mastoid process.

CASE 6
A 77-year-old white woman had experienced two episodes of right-sided weakness, most marked in the arm, associated with impaired speech. These were separated by seven months. The first lasted approximately 24 hours before clearing and was more severe than the second, which was of one hour's duration.

Six months prior to the first attack, she had suffered a "stroke" with the rapid onset of left hemiparesis, greater in the arm than in the leg. Her deficit progressively improved during the ensuing weeks, but slight hand weakness persisted together with a disagreeable sensation in both limbs. She also had difficulty in orienting her clothing when dressing and some impairment in her sense of direction.

Neurological examination revealed mild left hemiparesis, more marked in the arm, with hyperreflexia and a Babinski sign on that side. Cutaneous sensibility, position sense and ability to perceive vibration were slightly impaired on the left side, and constructional dyspraxia was also demonstrated. Carotid pulsations were bilaterally equal and no bruits were heard. Two months following the last episode of right-sided weakness, she became ill and died of small bowel infarction. Autopsy revealed widespread systemic and cerebral atherosclerosis, but the carotid arteries in the neck were not examined. The brain had a small right parietal infarct. The left cerebral hemisphere was unremarkable.

Results
Table 1 gives the results of all the measurements. Resting flow indices and those during CO$_2$ breathing are shown for right and left
TABLE 1
Cerebral Blood Flow Indices in Normal Subjects and TIA Patients Before and During CO₂ Breathing

<table>
<thead>
<tr>
<th>Normal subjects</th>
<th>Age</th>
<th>Resting</th>
<th>Flow Index left CO₂</th>
<th>% Increase</th>
<th>Resting</th>
<th>Flow Index right CO₂</th>
<th>% Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>10.06</td>
<td>14.45</td>
<td>43.64</td>
<td>9.24</td>
<td>15.68</td>
<td>69.7</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>12.55</td>
<td>33.56</td>
<td>167.41</td>
<td>12.47</td>
<td>25.54</td>
<td>104.81</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>13.97</td>
<td>17.81</td>
<td>27.49</td>
<td>16.10</td>
<td>18.47</td>
<td>14.72</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>19.23</td>
<td>23.07</td>
<td>19.97</td>
<td>20.61</td>
<td>27.22</td>
<td>32.07</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>11.28</td>
<td>17.04</td>
<td>51.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>11.51</td>
<td>19.23</td>
<td>67.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>12.22</td>
<td>18.85</td>
<td>54.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>15.53</td>
<td>15.75</td>
<td>1.42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>16.49</td>
<td>29.21</td>
<td>77.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>16.81</td>
<td>24.85</td>
<td>47.83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>42.5</td>
<td>13.97</td>
<td>21.38</td>
<td>55.73</td>
<td>14.61</td>
<td>21.72</td>
<td>55.33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transient ischemia patients</th>
<th>Age</th>
<th>Resting</th>
<th>Flow Index Affected side CO₂</th>
<th>% Increase</th>
<th>Resting</th>
<th>Flow Index Nonaffected side CO₂</th>
<th>% Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>16.80</td>
<td>19.81</td>
<td>17.91</td>
<td>16.65</td>
<td>20.67</td>
<td>24.14</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>14.50</td>
<td>16.70</td>
<td>12.84</td>
<td>16.51</td>
<td>18.37</td>
<td>10.90</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>14.71</td>
<td>32.55</td>
<td>121.28</td>
<td>15.77</td>
<td>34.77</td>
<td>120.48</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>19.04</td>
<td>24.51</td>
<td>28.73</td>
<td>19.10</td>
<td>21.24</td>
<td>11.20</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>10.56</td>
<td>12.61</td>
<td>19.41</td>
<td>11.15</td>
<td>12.79</td>
<td>14.71</td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>13.76</td>
<td>21.13</td>
<td>53.56</td>
<td>11.02</td>
<td>15.31</td>
<td>38.93</td>
</tr>
<tr>
<td>Mean</td>
<td>58.5</td>
<td>14.95</td>
<td>21.22</td>
<td>42.29</td>
<td>15.03</td>
<td>20.52</td>
<td>36.73</td>
</tr>
</tbody>
</table>

sides in the normal controls and for affected and nonaffected sides in the TIA patients. In addition, the increase in flow index during CO₂ breathing in each case is expressed as the percent of the respective resting flow index.

The means of the resting flow indices from right and left sides in the normal controls and from affected and nonaffected sides in the TIA patients closely approximate each other, and using the t test there are no significant differences among these means. None of them differs significantly from the above-mentioned normal flow index from a previous study.7

Inhalation of CO₂ increased the flow index over the resting value in every case except for one normal control. The mean percentage increase in the potentially ischemic regions does not differ significantly from that for the nonaffected sides in the TIA patients, and neither of these differ significantly from the mean increase for either side in the normal controls. This holds true even if the data from the control subject whose flow index did not change with CO₂ are excluded.

These data show normal cerebral blood flow indices, as measured by this method, in six patients with TIA in the internal carotid artery distribution. In addition, the increase in flow index in response to CO₂ in these patients was normal, both on the previously affected sides and on the nonaffected sides, as compared with that of normal controls.

**Discussion**

The method used for measuring cerebral blood flow for these experiments permits estimation of flow through the region monitored by an uncollimated gamma ray detector placed against the side of the head. The detectors were placed laterally and in a uniform location in each case so that a significant portion of the monitored region would be in the ipsilateral carotid artery distribution. Of course, the detector of necessity monitors extracerebral tissue in addition to a large and indeterminate portion of the ipsilateral cerebral hemisphere, and it might also monitor the opposite hemisphere to some extent as well. However, the contribution to the flow index of vascular structures within the range of a detector theoretically is directly proportional to the volume of blood each contains and inversely proportional to the

---

Thompson, Stroke, Vol. 2, May-Jun 1971
square of the distance of each from the detector,\textsuperscript{7,12} and together these factors tend to emphasize the contribution from the vessels of the cerebral tissue nearest the detector. Theoretically, therefore, the flow index from a detector placed laterally against the side of the head would be most significantly influenced by flow through the distribution of the ipsilateral internal carotid artery. Furthermore, a previous study\textsuperscript{7} showed that 19 patients with cerebral infarction within the internal carotid distribution had significantly low flow indices on the infarcted sides as measured by this method. All had normal flow indices on the opposite sides. These patients had neurological deficits similar in degree to those experienced by the present group so that it is reasonable to conclude that the potentially ischemic regions in these TIA patients would be large enough to permit blood flow changes within them to be detectable by this method.

The data from the patient with an old infarct are of interest. The infarct was on the side not affected by TIA, and including the resting flow index from the infarcted side among those from “nonaffected” sides does not significantly reduce the mean. Evidently this is because the infarcted side flow index, though somewhat low, is not markedly so. However, the above-mentioned measurements in 19 patients with cerebral infarction showed the side-to-side difference in flow indices to be the most consistently reliable indication of reduced flow on the infarcted side.\textsuperscript{7} This was true even though the majority of infarcted side flow indices were markedly reduced. The side-to-side difference of 2.74 in the present patient is larger than any other among the subjects of this report, and, based on the above-cited 19 patients, it indicates a moderately lowered flow on the infarcted side.

The preserved responsiveness of the cerebral blood flow to CO\textsubscript{2} in these six TIA patients militates against the theory that hemodynamic instability due to fixed obstruction to flow as discussed above is the basis of TIA. On the other hand, the concept that TIAs are due to platelet microemboli does not require that hemodynamic instability be postulated, and the results of these experiments are interpreted as favoring the theory that platelet microemboli are a cause of TIA.

Skinhøj et al.\textsuperscript{4} recently reported investigations similar to the present ones showing normal CO\textsubscript{2} reactivity in a group of TIA patients. They also concluded that this contradicts the hemodynamic instability theory of the pathogenesis of TIA. It does not necessarily follow, however, that all TIAs are based on the same mechanism. Denny-Brown\textsuperscript{18} reported patients in whom transient focal neurological deficits occurred in association with drops in blood pressure or cardiac output, suggesting hemodynamic instability as the cause in these patients. The attacks in such cases often were more prolonged than were those in the present series, and with some the deficit did not clear completely. Also, these patients were particularly prone to cerebral infarction which usually occurred within a few weeks after the onset of initial symptoms.\textsuperscript{10} From this it is probable that hemodynamic instability is the basis of some episodes of transient focal neurological deficit, although the clinical picture may differ from that of more typical TIAs of shorter duration with complete recovery. In addition, the frequent occurrence of cerebral infarction within a relatively short time after the onset of symptoms in such cases is evidence that hemodynamic instability may be the basis of infarction. Certainly it would seem that this mechanism would present a greater potential for permanent tissue damage than would platelet microemboli.

If the above conclusions are correct, the mechanism underlying cerebral infarction may differ from that underlying typical TIAs of brief duration with complete recovery, particularly if these occur over a prolonged period of time. However, this is speculative, and the results of the present experiments do not shed light on the basic mechanism of cerebral infarction as could have been inferred if evidence of hemodynamic instability in TIA patients had been found. They are compatible with the theory that platelet emboli are an important cause of TIA and are presented in support of this theory.

References

2. McHenry LC: Cerebral blood flow studies in middle cerebral and internal carotid artery
occlusion. Neurology (Minneap) 16: 1145-1151, 1966
Reactivity of Cerebral Blood Flow to CO2 in Patients With Transient Cerebral Ischemic Attacks

STEPHEN W. THOMPSON

_Stroke_. 1971;2:273-278
doi: 10.1161/01.STR.2.3.273

_Stroke_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1971 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/2/3/273

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Stroke_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Stroke_ is online at:
http://stroke.ahajournals.org/subscriptions/