Long-Term Anticoagulant Therapy for TIAs and Minor Strokes With Minimum Residuum

JAN E. OLSSON, M.D., RAGNAR MÜLLER, M.D., AND SUNE BERNELI, M.D.

SUMMARY One hundred seventy-eight patients with transient ischemic attacks (TIAs) or small strokes with slight symptoms persisting for more than 24 hours (incomplete recovery = IR) (TIA-IR) from both the carotid and the vertebrobasilar systems were treated with anticoagulants. Ten patients stopped the treatment because of severe side effects. Only one patient had a lethal cerebral infarction when the thrombotest values were above the therapeutic level; no other infarction happened during the treatment period. Moreover, the frequency of TIA decreased during the treatment, compared with descriptions of the natural course of TIA. One hundred four patients were observed for a mean of 21 months after the anticoagulant treatment ended. During the observation period, six patients had cerebral infarctions. This was a sixfold increase compared with the stroke incidence during treatment, and was almost identical with the incidence of strokes seen during the natural course of TIA. All the cerebral infarctions were in patients who had their initial TIA/TIA-IR from the carotid territory (within the same carotid artery which earlier had given symptoms).

The investigation shows that long-term anticoagulant treatment is useful, especially in patients with carotid TIA/TIA-IR, and that this treatment should continue as long as the patients can manage it. In patients with vertebrobasilar symptoms of malignant character, it seems feasible to terminate the treatment after about one year. The mechanism of the anticoagulant treatment is obscure, but it does not appear to influence the progress of the atherosclerotic process.

The risk of development of a stroke is highest during the first months after the first TIA; it then decreases to about 5% to 6% per year during the next five years. There also is a difference between the number of TIAs and the risk of development of a definite cerebral infarction between the territory of the carotid and vertebrobasilar arteries, with a higher incidence of TIA and a lower incidence of cerebral infarction in the vertebrobasilar arterial system than in the carotid system. Descriptions of the natural history of patients with TIA-IR are lacking.

The present investigation describes a group of patients with TIA and TIA-IR and the effect of long-term (> three months) anticoagulant (A/C) treatment.

Methods

During five and one-half years (January 1, 1969 to June 30, 1974), 112 of 209 patients with TIA from the local area of the University Hospital of Lund (about 250,000 inhabitants) were selected and treated with anticoagulants. Thirty-three patients with carotid TIA (none with vertebrobasilar TIA) were surgically treated, whereas 64 were not treated with either anticoagulants or surgery. Forty-eight of the 64 patients had only slight symptoms of vertebrobasilar TIA; therefore, anticoagulant treatment was judged to be unnecessary (see below). The other 16 were judged to be unable to manage anticoagulant treatment either due to age...
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Table 1: Sex and Age Distribution of the Patients Treated With Anticoagulants and Those Treated Surgically by Thrombendarterectomy

<table>
<thead>
<tr>
<th>A/C treatment (N = 178)</th>
<th>Men</th>
<th>Women</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>≤ 40</td>
</tr>
<tr>
<td>TIA (N = 112)</td>
<td>73</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>Carotid (N = 54)</td>
<td>36</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Vertebrobasilar (N = 58)</td>
<td>37</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>TIA-IR (N = 66)</td>
<td>47</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Carotid (N = 51)</td>
<td>35</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Vertebrobasilar (N = 15)</td>
<td>12</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Surgically treated (N = 33)</td>
<td>24</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

A/C = anticoagulant.

Table 2: Occurrence of Hypertension and Angiographical Findings in Anticoagulant-Treated Patients With TIA and TIA-IR

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>TIA (N = 112)</th>
<th>Carotid (N = 94)</th>
<th>Vertebrobasilar (N = 38)</th>
<th>TIA-IR (N = 66)</th>
<th>Carotid (N = 51)</th>
<th>Vertebrobasilar (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>16</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Angiography performed</td>
<td>77</td>
<td>44</td>
<td>33</td>
<td>54</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>Carotid angiography</td>
<td>44</td>
<td>34</td>
<td>10</td>
<td>40</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Arch angiography</td>
<td>48</td>
<td>18</td>
<td>30</td>
<td>28</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Normal finding</td>
<td>21</td>
<td>12</td>
<td>9</td>
<td>14</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Atherosclerosis in symptom-giving artery</td>
<td>52</td>
<td>29</td>
<td>23</td>
<td>35</td>
<td>28</td>
<td>7</td>
</tr>
<tr>
<td>Atherosclerosis in several arteries</td>
<td>26</td>
<td>14</td>
<td>12</td>
<td>19</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Pathologically slow circulation without visible atherosclerosis</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

Angiography of one carotid artery or arch aortography or both was performed. Table 2 lists a detailed description of the angiographical findings.

Table 3 lists the number of ischemic attacks before anticoagulant treatment. Two patients had had strokes previously involving other vascular territories. Both patients had been surgically treated by thrombendarterectomy one and ten years before the actual symptoms, respectively. About half of the TIA patients had only one attack before anticoagulant treatment began and 80% of the TIA patients had fewer than five attacks before treatment. Of the patients with TIA-IR, 65% had a single attack before anticoagulant treatment, and only 6% of the TIA-IR patients had more than five attacks before the treatment.

Anticoagulant treatment was instituted as soon as possible after the first ischemic attack and arrival at the hospital.

If no common contraindications against anticoagulant therapy were present, if the CSF was clear, and if hypertension was regulated, then treatment was given orally with Dicumarol®. If treatment was instituted in direct connection with a TIA or after a TIA-IR, the patients also had repeated intravenous injections of heparin (10,000 and 12,000 I.U. alternately) every six hours until the TT values fell below 20%. The effect of the therapy was controlled by measuring the reduction of the prothrombin time with the test (TT) described by Owren. The initial Dicumarol® doses were about 200 to 250 mg per day, and the usual maintenance

vanced) or mental reduction. The surgically treated patients were those who had an ulcerated plaque and were suitable for operation. This was performed by thrombendarterectomy of the internal carotid artery in order to eliminate the need for long-term anticoagulant therapy. During this period another 66 patients with TIA-IR from the same local area of Lund were treated with anticoagulants. They were selected according to the same considerations as the patients with TIA. Table 1 gives the sex and age distribution of the surgically treated patients and the distribution of those treated with anticoagulants.

Our aim was to give long-term (> three months) anticoagulant therapy to all patients with symptoms of carotid ischemia, except those surgically treated, and all patients with "malignant" symptoms of vertebrobasilar ischemia, i.e., those with symptoms of long tracts and those with repeated attacks of cortical visual disturbances. Usually patients with attacks of diplopia and vertigo, for example, were not treated.

None of the patients had had strokes previously within the actual arterial territory or had cardiac arrhythmia. Hypertension, defined as a blood pressure equal to or greater than 160/90 found at more than two readings in the hospital, or a history of elevated blood pressure treated with hypotensive drugs, was found in 27% of the anticoagulant-treated patients and the distribution of those treated with anticoagulants.

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Angiography was performed in 70% of those with TIA and in 82% with TIA-IR. This was usually done to demonstrate surgically removable extracranial stenotic plaques, but in some instances it was performed to establish the diagnosis against intracerebral hematomas. The angiography usually was performed after anticoagulant therapy was begun and when the thrombotest (TT) values were on a constant level within the therapeutic range.
TIA (N = 112) 53 (47.3) 37 (33) 22 (19.6)
Carotid (N = 54) 28 (51.9) 16 (29.6) 10 (18.5)
Vertebralbasilar (N = 58) 25 (43.1) 21 (36.2) 12 (20.7)
TIA-IR (N = 66) 43 (65.2) 19 (28.8) 4 (6.1)
Carotid (N = 51) 33 (64.7) 15 (29.4) 3 (5.9)
Vertebralbasilar (N = 15) 10 (66.7) 4 (26.7) 1 (6.7)

*Numbers in parentheses are percent.

dosage was 25 to 75 mg per day, according to the TT values. During the first weeks of treatment, the patients often had repeat lumbar puncture to exclude any reaction in the CSF, indicating a hemorrhagic intracranial state.

Results

Initial Treatment Period (< Three Months)

Long-term anticoagulant treatment was intended to be given to 178 patients (table 1). However, 19 patients could not fulfill the treatment during the first three months. Therefore, they are described separately.

One of these patients, a 69-year-old man, had a fatal cerebral infarction during the first month of treatment. He noted the first symptoms of cerebral ischemia in December, 1969. For 15 minutes he had a sensory disturbance in his right leg. He did not see a doctor until three months later, when a similar numbness of his right leg occurred, followed by impaired sensitivity on his right side including his face, weakness of his right leg, and speech difficulties. This attack lasted one hour. The next day he was free from symptoms, but was admitted to the hospital and anticoagulant treatment was instituted. After the treatment began, he had two further TIAS with weakness and numbness of his right leg. The TT values were 40% and 16%, respectively.

Angiography of the left carotid artery showed slight atherosclerotic irregularity in the proximal part of the internal carotid artery. He had no hypertension, the ECG and EEG were normal, and there was no cardiac enlargement. The routine analyses of blood and urine were normal, and there were no hemorrhagic findings in CSF at two investigations. The TT values were within therapeutic ranges one week after the treatment began and thereafter no TIA appeared. He went home free from symptoms.

Three days later, he suddenly became ill with nausea, vomiting, vertigo, weakness of his left arm and leg, and dysarthria. Analysis of the CSF was normal, but the TT value was 38%. His condition deteriorated and he became tetraplegic and comatose and then died two days later.

Autopsy showed widespread atherosclerosis in the cranial arteries with occlusion of the left vertebral artery, and fresh infarctions of the brain stem and the cerebellum. Marked atherosclerotic changes also were found in the aorta. There was left cardiac ventricular enlargement.

Four patients died from myocardial infarctions during the first three months, one in connection with angiography.

In ten patients the treatment was stopped for various reasons: three patients could not manage the controls, two had large subcutaneous hematomas and became anemic, one had a bleeding ulcer, one with TIA-IR (after his symptoms worsened) had a definite cerebral infarction with total hemiparesis before the therapeutic TT level was reached, one had pancreatic cancer, one had rheumatic arthritis and could not relinquish the use of aspirin, and one had liver damage. Another four patients had symptoms (hematuria, hemorrhagic CSF reaction, confusion, social inability to manage the treatment) so severe that the anticoagulant treatment had to be stopped. However, as new cerebral ischemic symptoms appeared, the indications for anticoagulant treatment were judged to be so strong that the treatment was reinstituted three to six months later. Meanwhile the patient with hematuria had had nephrectomy for unilateral pyelonephritis.

The Period of Long-Term Anticoagulant Treatment

Thus, 163 patients (including the four who temporarily stopped the treatment) remained and had long-term anticoagulant treatment (> three months). Table 5 shows the length of treatment. The mean anticoagulant duration of the TIA patients was 25 months and of the TIA-IR patients, 17 months.

There were no strokes during this time, whereas 24 patients on one or more occasions had neurological symptoms judged to be those of cerebral ischemia. The symptoms were usually in the same arterial territory as before. Table 6 cites the number and localization of the symptoms. Most of the patients had symptoms from the vertebrobasilar territory. The pathogenesis of these attacks was not quite obvious in all patients, and it seems probable that in some the attacks were caused by factors other than microembolism. Some attacks occurred when the TT values were within therapeutic ranges. Two of these patients are described below.

During the last days of July, 1972, a 74-year-old woman had an attack of weakness of her right hand and had difficulty in finding words which lasted for two hours. Two weeks later, she had similar symptoms with speech disturbances from four to five hours, and rightsided weakness lasting up to three days. She was hospitalized and anti-
TABLE 5 Length of Long-Term Anticoagulant Treatment

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>TIA (N = 101)</th>
<th>TIA-IR (N = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-12</td>
<td>27 (26.7)*</td>
<td>22 (35.5)</td>
</tr>
<tr>
<td>12-24</td>
<td>43 (42.6)</td>
<td>27 (43.5)</td>
</tr>
<tr>
<td>≥24</td>
<td>31 (30.7)</td>
<td>13 (21)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are percent.

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coagulant treatment with heparin and Dicumarol® was immediately instituted. Therapeutic TT values were reached within one week. Angiography of the left carotid artery showed a slight atherosclerotic plaque in the dorsal part of the proximal internal carotid artery and a slight decrease in the circulation within the left temporoparietal cerebral area. She had slight cardiac hypertrophy, but normal blood pressure at repeated intervals (120/80 mm Hg). Routine laboratory analyses of blood, CSF, and urine were normal.

The anticoagulant treatment has continued. She has had several TIAIs and TIAIs-IR. Figure 1 shows the temporal profile of these attacks and the corresponding TT values. All attacks were from the territory of the left carotid artery, with speech disturbances and rightsided weakness. However, at the last neurological investigation in October, 1975, she was normal without any remaining neurological symptoms.

A woman (74 years old) had a rightsided hemiparesis with speech disturbances and central rightsided facial paresis in March, 1972. These symptoms disappeared after about ten days, but in November, 1972, she had an attack with speech disturbances that lasted 24 hours. Arch aortography showed marked stenosis of the left vertebral and subclavian arteries, whereas the carotid arteries were free from atherosclerosis. Anticoagulant treatment was instituted. In December, 1972, she had numbness of her left hand for a few hours (TT value 70%). In January, 1973, she had weakness of her left hand followed by severe headache (TT value 7%). Between these attacks, she had several attacks of headache, often unilaterally, which had earlier been judged as migraine and sometimes had been preceded by rightsided weakness as an aura. Because of this, the anticoagulant treatment was withdrawn in November, 1973. Six months later (April, 1974), she had an attack with weakness of her right arm and speech disturbances lasting for one hour; in July, 1974, she had a new attack with speech difficulties and severe unilateral headache lasting 17 hours. Since then, she has not had any neurological symptoms except headaches.

In some patients, inability to manage anticoagulant therapy caused new attacks. This is best exemplified in the following patient.

TABLE 6 Number of Patients Who Had TIA/TIA-IR During Anticoagulant Treatment and Number of TIA/TIA-IR in Each Arterial Territory

<table>
<thead>
<tr>
<th>No. of TIA/TIA-IR</th>
<th>Total no. of patients with TIA/TIA-IR in each arterial territory</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA (N = 101)</td>
<td>5 9 7 21 (20.8)*</td>
</tr>
<tr>
<td>Carotid (N = 46)</td>
<td>— 4 2 6 (13)</td>
</tr>
<tr>
<td>Vertebrobasilar (N = 55)</td>
<td>5 5 5 15 (27.3)</td>
</tr>
<tr>
<td>TIA-IR (N = 62)</td>
<td>— — 3 3 (4.8)</td>
</tr>
<tr>
<td>Carotid (N = 48)</td>
<td>— — 1 1 (2.1)</td>
</tr>
<tr>
<td>Vertebrobasilar (N = 14)</td>
<td>— — 2 2 (14.3)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are percent.

During the latter half of 1969, a 54-year-old man had repeated attacks of speech disturbances which did not exceed 24 hours in duration. Left carotid angiography showed local atherosclerosis in the proximal part of the left arteria cerebri media. Anticoagulant treatment was instituted in January, 1970. He was free from symptoms until March, 1971, when he had an attack with aphasia (TT value 50%). In August, 1972, he had a new attack with speech disturbances (TT value 100%) and admitted that he had not followed the prescribed doses of Dicumarol®. He showed a progressing mental change and was unable to manage the treatment. He moved away in 1974 and it has been impossible to contact him since.

During the long-term anticoagulant treatment, five patients died, four from myocardial infarctions (table 7). Seven months after the anticoagulant treatment began, one patient died of hemothorax due to rupture of the left subclavian artery, which ten years before had been operated on by thrombendarterectomy because of atherosclerosis.

Complications During Anticoagulant Treatment

During anticoagulant treatment, 31 patients (17.4% of the entire study) had side effects from the anticoagulants (table 8). Usually, the side effects were slight, such as subcutaneous hematomas and nose and gingival bleedings, and did not necessitate stopping the treatment. They normally occurred when the TT values decreased below 5% and disappeared when the anticoagulant dose was corrected. No patient died from complications of the anticoagulant treatment, but in nine patients (5.1%), treatment had to be stopped because of severe side effects: one patient had bilateral subdural hematomas and was operated upon, four had gastrointestinal bleeding, and one had to be operated on for bleeding ulcers (during surgery, he had a brain stem in-
### Table 8: Number of Patients With Side Effects During Anticoagulant Treatment

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 3 months (N = 5)</td>
</tr>
<tr>
<td>Subdural hematomas</td>
<td>—</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1 (1)*</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hemorrhagic CSF reaction</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>—</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>—</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>—</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>—</td>
</tr>
<tr>
<td>Subcutaneous hematomas</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses denote patients whose treatment had to be permanently or temporarily withdrawn.
†Some patients had both epistaxis and subcutaneous hematomas together with other side effects.

Fraction caused by a decrease in blood pressure; slight symptoms remain), two patients had hematuria, and two others (during the first days of therapy) had large subcutaneous hematomas. The possibility that this was an effect of the heparin injections cannot be excluded, but treatment with Dicumarol® alone was not tested. In two patients, anticoagulant treatment was temporarily stopped because of hematuria and hemorrhagic CSF reaction. The first patient was found to have pyelonephritis and had nephrectomy. Five months later, he had new cerebral ischemic symptoms and was given anticoagulant treatment for one year with slight hematuria occurring on one occasion, but without major side effects. The other patient, who had hemorrhagic findings in CSF, had a slight stroke 23 months later and was thereafter given simple treatment with anticoagulants for ten months. The hematuria was so slight in three cases that treatment could be continued after correction of the anticoagulant dosage.

### Observation Time After Anticoagulant Treatment

During the actual observation time (January 1, 1969 to June 30, 1975), the long-term (> three months) anticoagulant treatment was terminated in 104 patients. These patients were observed from 1 to 70 months (mean 21 months) after the anticoagulants were withdrawn. Figure 2 gives the temporal profile of the individual observation times.

During the observation period 16 patients (15.4%) had new cerebral ischemic symptoms (fig. 3). Three patients died of cerebral infarctions that occurred within one month and after 13 and 18 months, respectively, after withdrawal of the treatment. Anticoagulants were not reinstituted and after 18 and 20 months' observation time, no malignant symptoms have appeared.

Twelve patients died during the observation period (table 7), most of them from cardiac disorders.

The history of the ten patients who should have been treated with anticoagulants but could not manage it or had severe immediate side effects has also been followed. The observation period of these patients was between 4 and 51 months (mean of 25 months). The patient who definitely had a cerebral infarction before the treatment was adjusted had, had repeated attacks of dizziness and blurred vision, respectively, after withdrawal of the treatment. Anticoagulants were not reinstituted and after 18 and 20 months' observation time, no malignant symptoms have appeared.
24 months later, epileptic seizures and a more pronounced hemiparesis than earlier and died from this and broncho-pneumonia. Two patients with carotid TIA had definite cerebral infarctions 14 and 48 months after the treatment was discontinued, whereas three patients with vertebrobasilar symptoms continued with repeated TIsAs without having definite cerebral infarctions. However, of these five patients one is somewhat disabled by frequent attacks of rotational vertigo, two are free from symptoms after 14 and 17 months' observation, and two died from cancer but were free from neurological symptoms 4 and 22 months after the treatment ended.

Discussion

The natural history of TIA is studied in several investigations (Table 9). The material in the table is arranged according to increasing observation period. About 5% to 6% of the patients who had completed strokes yearly during the first five years; thereafter the frequency decreased. However, most of the strokes occurred during the first year after the development of TIA, especially during the first months.

Patients with TIA within the vertebrobasilar system have a good prognosis, whereas patients with carotid symptoms have a poor prognosis. However, the prognosis of patients with hemiparesis manifested from the vertebrobasilar territory is as bad as that of those with carotid symptoms, while on the contrary, patients with vertebrobasilar symptoms have more TIsAs without having completed strokes.

Patients with TIA can be treated medically with anticoagulants, clofibrate, dipyridamole (Persantin®), aspirin, or sulfinpyrazone (which has recently been suggested). Moreover, patients with carotid TIA and atherosclerotic plaques in the neck part of the carotid arteries can be surgically treated with thrombendarterectomy. Comparative studies have shown that the prognosis for those patients surgically treated and for those medically treated is about equal, especially if the immediate operative and postoperative morbidity and mortality are considered in the surgically treated patients.

Most earlier studies have compared anticoagulant-treated patients with nontreated and surgically treated patients. According to our experience and that of other authors, we think that anticoagulant treatment is useful in TIA patients, and therefore, for ethical reasons, we have given all patients who fulfilled our criteria (see Methods) anticoagulant therapy. Thus, we have not omitted any patients who were able to manage the controls of the treatment and, therefore, we have no control material, but have compared our results with those given in the literature and observed the results of the treatment with the patients as their own controls after withdrawal of the anticoagulants.

Our results can be summarized thus: Of the original 178 patients, one patient died from a cerebral infarction during the first month after institution of anticoagulant treatment (this happened when the TT values were above the therapeutic level [35%]), four patients died from cardiac disorders, and ten were excluded for various reasons during the first three months of treatment. One hundred sixty-three patients fulfilled the long-term (> three months) anticoagulant treatment and, of these, none had cerebral infarction, but 24 patients (14.7%) had new TIA/TIA-IR. Of the entire 178 patients, 31 (17.4%) had side effects of the treatment, and nine patients (5.1%) had such severe complications that the treatment had to be withdrawn.

If the results are compared with those of the literature (Table 9), a fatal cerebral infarction occurred in only one of 178 patients (0.6%) during the treatment and TIA/TIA-IR in 14.6% of 163 long-term treated patients. As the patients were treated for 3,632 days (mean 20 months), i.e., 1.7 patient years (treatment time/number of patients X 12), the incidence of completed strokes and TIA/TIA-IR was 0.6 and 1.1 patients per year, respectively. These results are considerably better than those of the natural history of TIA (Table 9) and the reduction of completed strokes and TIA during long-term anticoagulant treatment is better than or comparable to other results of anticoagulant therapy.

Also, when the patients are compared with themselves after treatment, the results of the anticoagulant therapy can be regarded as good. When the study was terminated, the 104 patients who had finished the anticoagulant treatment had been treated for 2,046 days (mean 20 months), i.e., 1.6 patient years. During this period, no patients had strokes but eight patients (7.7%) had TIA/TIA-IR, i.e., an incidence of TIA/TIA-IR in five patients per year. After withdrawal of the treatment, the 104 patients were observed for 2,150 days (mean 21 months), i.e., 1.7 patient years. During this period, six patients had cerebral infarctions (5.8%), three being fatal, and 16 patients had TIA/TIA-IR (15.4%), which corresponds to an incidence of completed strokes in 3.5 patients per year and of TIA/TIA-IR in 9.4 patients per year.

When the results are regarded, one must also take into consideration that the most critical period of new strokes and TIA is during the first months and the first year after the development of TIA. The patients aged about two years during the observation time, but this cannot explain the differences in the results, even if the incidence of strokes increases with age.

<table>
<thead>
<tr>
<th>Table 9</th>
<th>Natural History of TIsAs, Incidence of New TIsAs, Completed Strokes and Deaths from Strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of pts</td>
</tr>
<tr>
<td>Ostfeld et al. (1973)</td>
<td>176</td>
</tr>
<tr>
<td>Ziegler and Hassanine (1973)</td>
<td>144</td>
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<tr>
<td>Baker et al. (1968)</td>
<td>79</td>
</tr>
<tr>
<td>Toole et al. (1975)</td>
<td>198</td>
</tr>
<tr>
<td>Siekert et al. (1963)</td>
<td>160</td>
</tr>
<tr>
<td>Whisnant et al. (1973)</td>
<td>56*</td>
</tr>
<tr>
<td>Goldner et al. (1971)</td>
<td>73</td>
</tr>
</tbody>
</table>

*Almost all with positive angiograms.
e.g., antihypertensive, diuretic, or cardiac, was changed when anticoagulant treatment was withdrawn.

The incidence of completed strokes after withdrawal of the anticoagulant treatment was almost as high as that reported during the natural history of TIA (table 9). All strokes were localized in the territory of the carotid arteries, and within the same carotid artery in which the initial TIA/TIA-IR had developed.

The principal finding of this investigation was that patients with TIA/TIA-IR seemed to be protected from strokes during anticoagulant treatment, but after withdrawal of the therapy the risk of strokes seemed to be as high as if the patients had not had any treatment, i.e., they seemed to follow the natural course after TIA. This was found especially in patients with carotid symptoms, as all strokes appeared in this territory. It is questionable whether the length of anticoagulant treatment in these patients should be life-long or as long as the patients can manage the treatment; the patients with vertebrobasilar symptoms, even those with long-tract symptoms, can have a shorter period of treatment, probably about one year.

The mechanism of anticoagulant treatment in cerebral ischemia is obscure, but perhaps it acts by reducing the "hypercoagulable state" seen in patients with thromboembolic cerebrovascular disease and in elderly persons, and not by stopping the atherosclerotic process.

There is no evidence that atherosclerotic changes in the vessels decrease during the treatment. One of our patients, a 65-year-old man, had arch angiography before and after a four-year period of anticoagulant treatment. He had attacks of leftsided carotid TIA in October, 1971. Arch arteriography showed occlusion of the left carotid artery, proximal stenosis of the right internal carotid artery, and stenosis of the right subclavian artery. He had long-term anticoagulant treatment until January, 1974, and was free from symptoms during this period, but had repeated attacks of speech disturbance, loss of vision bilaterally, rotational vertigo, and weakness of his left arm after withdrawal of the treatment. He was examined again in June, 1975, with arch arteriography, which showed a marked progress of the atherosclerotic plaques. Anticoagulant treatment was reinstituted and he again became free from symptoms.

Several patients had normal angiograms; in our study 77 patients (69%) with carotid symptoms were angiographically investigated, and of these, 25 (33%) had normal findings in the symptom-giving artery, whereas of 54 (82%) angiographically investigated patients with vertebrobasilar symptoms, 20 (37%) had normal symptom-giving vessels. These findings are comparable with those described earlier in patients with TIA, within both the carotid and the vertebrobasilar territories. Moreover, according to Marshall and Wilkinson, TIA patients with normal angiographical findings seem to have the same prognosis as those with atherosclerotic plaques in the symptom-giving arteries. However, this was not confirmed by Bradshaw and Brennan.

Even if the effect of anticoagulant treatment — reducing the frequency of TIA/TIA-IR and preventing completed strokes — is accepted, some hesitate to use the treatment because of the risk of complications, especially the risk of intracranial hemorrhage, which sometimes occurs in treated patients. In our material, no patient died of bleeding complication, but nine (5.1%) had such severe complications that the treatment had to be withdrawn. Remaining symptoms due to these complications were present in two patients: one had a brain stem infarction during an operation for a bleeding ulcer, and the other had to be operated on for bilateral subdural hematomas (this patient later had a cerebral infarction). As the complications of anticoagulant treatment usually are not lethal or give remaining symptoms, and the incidence of strokes is rather high, the indication for anticoagulant treatment in TIA/TIA-IR patients seems to be rather strong. However, it is necessary to carefully control and inform the patients. The TT controls must be done between one and four times a month, and it is advisable for the controls to be performed at the hospital where the treatment was instituted. If these conditions are present, it seems advisable to give all patients with carotid TIA/TIA-IR life-long anticoagulant treatment, and patients with vertebrobasilar long-tract symptoms, treatment for at least one year.

References

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An Evaluation of Hypocarbia and Hypercarbia During Carotid Endarterectomy

W. H. BAKER, M.D.,* J. A. RODMAN, M.D.,† R. W. BARNES, M.D.,* AND J. L. HOYT, M.D.†

SUMMARY One hundred consecutive patients were randomly given hypocarbic (PacO2 < 25 torr) or hypercarbic (PacO2 > 60 torr) general anesthesia during carotid endarterectomy to test the effect of the two regimens upon the incidence of postoperative neurological deficit. An indwelling shunt was not used. One patient died, two have permanent neurological deficits and two have temporary neurological deficits. Although hypocarbic patients had fewer neurological complications than hypercarbic patients, the difference was not statistically significant (p < 0.13). Hypercarbia significantly increased the incidence of intraoperative arrhythmia. Also, no relationship was found between the incidence of postoperative stroke and the internal carotid back pressure or the time of carotid occlusion.

CAROTID ENDARTERECTOMY is a safe, time-tested, and effective method of treatment for selected patients with cerebrovascular insufficiency. However, the details of the operative management of these patients are still a subject of debate. One of these controversies is the use of hypercarbia or hypocarbia during carotid thromboendarterectomy to protect the brain and thus decrease the incidence of postoperative neurological deficits.

PacO2 is a major factor in determining cerebrovascular resistance. With an increasing PacO2 cerebrovascular resistance decreases and total cerebral blood flow (CBF) increases, while a decrease in PacO2 increases resistance and lowers total CBF.1, 2

However, in an ischemic area of the brain, the vessels may show a lack of responsiveness to changes in PacO2 or a “cerebral vasomotor paralysis.” In this case, administration of CO2 to a patient might lower the vascular resistance in the nonischemic areas, thus stealing blood from a local area of vasomotor paralysis. Conversely, hypocarbia will increase the vascular resistance of the brain in all areas except the area of vasomotor paralysis. The collateral pressure will be elevated and the blood flow in the ischemic area will be increased.3

Hypercarbia, therefore, has been used as an adjunct to general anesthesia for carotid endarterectomy because it enhances total CBF.4 Hypocarbic has been used by its proponents because it enhances regional blood flow in areas of vasomotor paralysis.5

The following randomized study was designed to compare the effects of hypocarbia and hypercarbia given during general anesthesia upon the incidence of postoperative stroke for carotid endarterectomy.

Methods

One hundred consecutive patients scheduled for carotid endarterectomy were randomized into hypercarbic (PacO2 > 60 torr) and hypocarbic (PacO2 < 25 torr) groups. The following standardized anesthetic technique was used to eliminate many variables that affect CBF.

Anesthetic Technique

Following the administration of 0.6 mg atropine, Fentanyl was injected slowly intravenously until the patient had slurring of speech. Nitrous oxide (70%) and oxygen (30%) were then started. D-tubocurarine was used to avoid trunchal rigidity, to facilitate tracheal intubation, and to control respiration at 1½ Radford in each group. The lungs were ventilated mechanically with a Bennet volume ventilator and...
Long-term anticoagulant therapy for TIAs and minor strokes with minimum residuum.
J E Olsson, R Müller and S Berneli

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