How Often Are Brain Infarcts Caused by Hypotensive Episodes?

A. Torvik, M.D., and K. Skullerud, M.D.

SUMMARY Of 135 patients who were resuscitated after cardiac arrest and who died from one day to several weeks later with morphological signs of systemic cerebral anoxia, there were seven patients (5.2%) with brain infarcts probably caused by hypotensive episodes during or after the resuscitation. There was almost no increase in the frequency of recent brain infarcts with an increasing degree of cerebral atherosclerosis ($P > 0.90$). In contrast, the distribution of ten old brain infarcts in the same material showed a significant correlation to the degree of cerebral atherosclerosis ($P < 0.05$). The findings suggest that the combination of cerebral atherosclerotic stenoses and hypotensive episodes is not a major cause of brain infarcts in elderly people. It is suggested that the risk of precipitating brain infarcts by lowering BP in hypertensive patients is not much greater in atherosclerotic than in nonatherosclerotic subjects.

Introduction

It is generally accepted that the majority of brain infarcts in elderly people are caused by either thromboembolic occlusion of the feeding arteries or the combination of cerebral atherosclerotic stenoses and failure of the systemic circulation (e.g., hypotensive episodes). However, opinions differ widely concerning the roles of each of these mechanisms. Thus, Adams and vander Eecken1 and Jørgensen and Torvik2 found thrombotic or embolic occlusions of the feeding arteries in approximately 90% of all large recent infarcts. Yates and Hutchinson,4 on the other hand, stated that brain infarcts usually are caused by the combination of systemic disease and stenoses of the cerebral arteries. Most reports seem to favor the view that at least one-half of the infarcts are caused by the latter mechanism.6,7

The main reason for the difference in findings is that Adams and vander Eecken1 and Jørgensen and Torvik2 excluded small lesions and old infarcts from their studies because they felt that thromboembolic occlusions in such cases could be easily overlooked, whereas most other reports are based upon the examination of all infarcts regardless of their size or age. It is also conceivable that the high frequency of atherosclerotic stenoses in infarct-free brains has not always been fully appreciated.6,7

In order to test the effect of hypotension in this respect, we examined the brains from 135 patients who had been resuscitated after cardiac arrest and who subsequently died from one day to several weeks after the episode. If hypotension is a major cause of brain infarcts, it would be expected that patients with severe cerebral atherosclerosis would have a high incidence of brain infarcts in addition to signs of diffuse cerebral anoxia, while patients without cerebral atherosclerosis primarily would show signs of diffuse cerebral anoxia.

Methods

This study investigated 135 brains from patients who had been resuscitated after cardiac arrest or ventricular fibrillation and showed morphological signs of diffuse anoxic brain damage or recent brain infarcts. We included all patients more than 40 years of age on whom autopsy was performed at the Aker and Ullevål Hospitals in Oslo during 1970 through 1974. These cases were selected from 13,296 autopsies. All patients had survived for at least 24 hours after the cardiac arrest.

We recorded the degree of atherosclerosis in the intracranial arteries and graded it from 0 to 3. The grading system was similar to that employed in another study performed by one of the authors.4 The extracranial portions of the carotid and vertebral arteries were not systematically examined.

After fixation in 10% formaldehyde the brains were cut into coronal sections. Routine paraffin sections from the frontal cortex, hippocampus, thalamus, and cerebellum were examined. Additional sections were taken from areas with suspected lesions. The authors performed all gross and microscopic examinations.

Results

The mean age of the 135 patients examined was 65 years (table 1). Seventy-three patients were 65 years old or older. Although the majority of the cases had extensive atherosclerosis of the coronary arteries, relatively few had severe cerebral atherosclerosis (table 2). This reflects the fact that atherosclerosis develops considerably later in cerebral arteries than in the coronary arteries.6 As could be expected, the mean age of the patients increased with an increasing degree of cerebral atherosclerosis.

Cardiac arrest (or ventricular fibrillation) was caused by recent myocardial infarcts in 74 cases, by old infarcts or diffuse myocardial fibrosis in 32 cases, and by other causes (complications during or after surgery, intoxications, bronchial asthma, etc.) in 29 cases.

All of the patients remained comatose or nearly comatose during the period between the cardiac arrest and death, and all patients except two had histological evidence of systemic cerebral anoxia, which could be attributed to the cardiac arrest. The changes consisted of neuronal necrosis or nerve cell loss with gliosis in the hippocampus, thalamus, cerebellum and, to a varying extent, in the cerebral cortex. The two patients without systemic anoxic damage had recent cerebral infarcts which probably were caused by hypotension.

Seven patients (5.2%) had recent brain infarcts which had originated at the time of the cardiac arrest, as judged by the macroscopic and microscopic examinations of the lesions (table 3). Five of these patients had histological evidence of brain anoxia in addition to the infarcts (Cases 1, 2, 4, 5, and 6). None of them had thrombi or emboli in the intracranial...
arteries and none had mural thrombi in the heart. The extra-
cranial portions of the carotid arteries were examined and
found to be patent in only two cases. Although it cannot be
definitely proved, it seems likely that most or all of these in-
farcts were caused by a hypotensive episode during or after
the resuscitation. It is remarkable that there was almost no
increase in the incidence of recent brain infarcts with an in-
creasing degree of atherosclerosis (P > 0.90, table 2).

Hemiplegia was recorded in three patients (Cases 2, 4,
and 5) and one patient was diagnosed as having a "brain
stem lesion" (Case 7). In two cases the infarcts probably
were too small to be diagnosed clinically as focal lesions
(Cases 3 and 6). The clinical diagnosis was definitely missed
in one case (Case 1).

Ten patients (7.4%) had old brain infarcts which had
developed a long time before the episode of cardiac arrest,
and the distribution of these cases showed a clear correla-
tion to the degree of cerebral atherosclerosis (table 2). Thus cases
with moderate or severe cerebral atherosclerosis had a
significantly higher frequency of old infarcts than those with
slight or no atherosclerosis (P < 0.05).

**Discussion**

The present investigation confirms the observation made
by other researchers that circumscribed brain infarcts may
develop in some cases after hypotensive episodes. It should
be pointed out that the infarcts which occurred following
cardiac arrest did not develop while there was circulatory
arrest, but rather during the period of hypotension and in-
complete perfusion after the onset of the resuscitation. This
hypotensive period may be of varying duration and depth
and, in some of the cases, the circulation may have been
fully restored almost immediately after onset of the resusci-
tation. The cerebral anoxic damage does not give any infor-
mation about the hypotensive episode, and detailed clinical
information about the resuscitation period was lacking in
most of the cases. The severity of the hypotension in our
study, therefore, is uncertain and the number of recent brain
infarcts (5.2%) does not necessarily represent the true in-
icidence after severe hypotensive episodes.

Thus, the total number of infarcts gives little information
about the general role of hypotension in brain infarction.
However, assuming that all recent infarcts were caused by
hypotension, it was remarkable that there was almost no in-
crease in incidence with an increasing degree of athero-
sclerosis (table 2). Such correlations would be expected
should the combination of atherosclerotic stenoses and
hypotension be a major cause of brain infarcts.

The objection could be raised that the grading of ather-
sclerosis was unreliable and that the number of cases with
severe cerebral atherosclerosis was too small to allow firm
conclusions. It should be noted, however, that the number of
old brain infarcts did increase significantly with the degree
of cerebral atherosclerosis (table 2). This shows that the
methodology was sufficient to demonstrate the general im-
portance of atherosclerosis in the development of cerebral
infarcts, and the lack of correlation for the infarcts caused
by hypotension, therefore, is probably real and not caused
by incidental factors.

The present study, therefore, does not support the concept
that hypotension is a major factor for the precipitation of
brain infarcts in elderly atherosclerotic patients. There is no
doubt that such cases do occur, but other mechanisms
probably are more important. Furthermore, our findings
suggest that the risk of precipitating brain infarcts by lower-
ing the blood pressure in hypertensive patients may not be
much greater in atherosclerotic than in nonatherosclerotic
subjects.

| TABLE 1 Age, Sex and Cause of Cardiac Arrest in 135 Cases |
|-----------------|-----------------|-----------------|
| Total number of cases | Men | Women | Total |
| Mean age | 64 | 67 | 65 |
| Number of cases ≥ 65 years | 53 | 20 | 73 |
| Recent MI | 60 | 14 | 74 |
| Myocardial fibrosis and old MI | 24 | 8 | 32 |
| Other causes of cardiac arrest | 20 | 9 | 29 |
| MI = myocardial infarction. |

<p>| TABLE 2 Degree of Cerebral Atherosclerosis and Number of Brain Infarcts in 115 Cases With Cardiac Arrest* |
|----------------------|-----------|-----------|-----------|-----------|</p>
<table>
<thead>
<tr>
<th>Grade</th>
<th>No. of cases</th>
<th>Mean age (P &gt; 0.90)</th>
<th>Recent brain infarction (P &gt; 0.90)</th>
<th>Old brain infarction (P &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>25</td>
<td>55</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>67</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>70</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>71</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
<td>65</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>*Degree of atherosclerosis not recorded in 20 cases.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<p>| TABLE 3 Characteristics of Seven Cases With Recent Brain Infaracts Among 135 Cases of Cardiac Arrest |
|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age, sex</th>
<th>Cause of cardiac arrest</th>
<th>Survival (days)</th>
<th>Cerebral atherosclerosis (grade)</th>
<th>Location and size of brain infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49 M</td>
<td>Recent MI</td>
<td>42</td>
<td>0</td>
<td>Total MCA territory</td>
</tr>
<tr>
<td>2</td>
<td>79 F</td>
<td>Cardiac arrhythmia</td>
<td>6</td>
<td>2</td>
<td>Total MCA territory</td>
</tr>
<tr>
<td>3</td>
<td>70 M</td>
<td>Myocardial fibrosis</td>
<td>16</td>
<td>2</td>
<td>Putamen, 4 mm; cerebellum, 2 cm</td>
</tr>
<tr>
<td>4</td>
<td>60 M</td>
<td>Recent MI</td>
<td>21</td>
<td>0</td>
<td>Watershed infarction, MCA/ACA territory</td>
</tr>
<tr>
<td>5</td>
<td>72 F</td>
<td>Bronchial asthma</td>
<td>5</td>
<td>2</td>
<td>Watershed infarction, MCA/ACA territory</td>
</tr>
<tr>
<td>6</td>
<td>58 M</td>
<td>Recent MI</td>
<td>5</td>
<td>0</td>
<td>MCA territory, 2 cm</td>
</tr>
<tr>
<td>7</td>
<td>52 F</td>
<td>Postoperative complications</td>
<td>21</td>
<td>0</td>
<td>Bilateral, total MCA territory</td>
</tr>
<tr>
<td>MI = myocardial infarction.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CARDIAC OUTPUT IN DOGS DURING INFUSION OF BETAHISTINE. /Smith et al. 257

By exclusion then, it seems that the main cause of brain infarcts may be sudden vascular occlusion and not stenosis. Most of the occlusions may be caused by thromboemboli, as suggested previously. However, it should be noted that some of the occlusions may be caused primarily by rupture of atherosclerotic plaques, which are easily overlooked when secondary thrombosis has occurred. Furthermore, many of the vascular occlusions in the deep-seated small infarcts of hypertensive subjects apparently are caused by degenerative changes in the vascular walls and not by primary thrombi.19

References

Distribution of Cardiac Output in Dogs During Intravenous Infusion of Betahistine

KATHLEEN A. SMITH, B.S., M.S., AND MAURICE W. MEYER, PH.D., D.D.S.

SUMMARY Cardiac output (CO), arterial blood pressure (ABP), heart rate (HR), blood gases and blood flow (BF) to the brain, heart, kidney and skeletal muscles and other cephalic tissues in five dogs were studied before and at 30 minutes of betahistine infusion (0.12 to 0.2 mg per minute per kilogram). The particle distribution method using radioactive labeled 153Ce (15 μ) and 85Sr (15 μ) microspheres was utilized to quantify and assess BF and CO. In the five dogs, the increase in CO averaged 20.8%; ABP remained constant, and HR increased in all but one exception where it decreased slightly concomitantly with a decrease in Paco2. Brain BF increased (+ 29.6%) in the dogs whose Paco2 remained constant. The BF increased to the heart (25.4%) and skeletal muscle (80%), while BF to the kidney and other tissues did not change. The change in HR appears to account for the change in CO. The dilating effect of betahistine on blood vessels, in the skeletal muscle, brain and heart could reduce peripheral resistance and decrease ABP. Thus, the increase in HR may be mediated through baroreceptor mechanisms rather than by a direct effect of betahistine. In addition, a decrease in Paco2 is more effective for decreasing cerebral BF than betahistine is for increasing blood flow.

WE HAVE STUDIED the effect of betahistine hydrochloride on the distribution of cardiac output (CO) in five dogs using the particle distribution method. This microsphere or particle distribution method has been previously used3 to quantitate and assess organ and/or regional blood flow (BF) in different experimental animals.

An earlier study1 suggested that the vascular properties of betahistine may be similar to the properties of histamine. Various investigators, therefore, have examined hemodynamic changes during and after betahistine administration. After a single intravenous injection of betahistine (0.055 to 0.44 mg per kilogram) in dogs, Anderson and Kubicek5 observed a decrease in arterial blood pressure (ABP) concomitant with a 54% increase in basilar artery blood flow using an electromagnetic blood flow transducer.

Phillips, also using a bolus injection and flowmeter techniques in dogs, found a significant elevation in coronary blood flow (58.6% to 200%) with minor changes in heart rate (HR) and arterial blood pressure. The blood flow response tended to be dose dependent, increasing with larger dosages. When betahistine (0.1 to 0.48 mg per kilogram per minute) was administered over a longer period of time, coronary blood flow increased five to six seconds after the beginning of the infusion. In a preliminary study in dogs, Dueland suggested that CO increased following a four-hour infusion of betahistine during hemorrhagic shock. Kubicek and Anderson found that 11 of 12 dogs recovered from induced hypovolemic shock after betahistine treatment, whereas 66% of the controls died. Studies in experimental animals to examine BF and hemodynamic changes in numerous organs and tissues simultaneously during betahistine administration have not been made. In this study we have determined the blood flows to major organs and tissues such as the brain, heart, kidney and skeletal muscle. The CO for each animal and the BF to other cephalic tissues were also calculated.
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