Cerebral Ischemia and Asymptomatic Coronary Artery Disease: A Prospective Study of 83 Patients

GIUSEPPE DI PASQUALE, M.D., ALVARO ANDREOLI, M.D.*, GIUSEPPE PINELLI, M.D.,
PAOLA GRAZI, M.D., GIANLUCA MANINI, M.D., FRANCESCO TOGNETTI, M.D.,*
AND CLAUDIO TESTA, M.D.*

SUMMARY A prospective cardiologic evaluation was performed in 83 consecutive patients with transient cerebral ischemia or mild stroke and without symptoms or electrocardiographic signs of ischemic heart disease. Patients were studied with an electrocardiographic exercise test; a positive test was followed by exercise Thallium-201 myocardial scintigraphy. Results were compared to those obtained in a group of 83 age and sex-matched healthy subjects submitted to the same study protocol. Asymptomatic coronary artery disease was detected in 28% of cerebrovascular patients with adequate electrocardiographic exercise test. A scintigraphic perfusion defect of variable extension was found in 19 of them. In the control group the electrocardiographic exercise test was positive in only 6% (p < 0.01). Our results support the concept that: 1) asymptomatic ischemic heart disease is often associated with cerebrovascular disease; therefore cerebral ischemic attacks may be a marker of coronary artery disease, 2) an active investigation of the heart should be considered in cerebrovascular patients in order to plan optimal, comprehensive management.

THERE IS INCREASING EVIDENCE that the prognosis of patients with cerebrovascular disease is critically influenced by coronary artery disease (CAD). A 5% cardiac yearly death rate has been described. Moreover, in the long-term follow-up of large series of patients, cardiac disease has been responsible for the 18-59% of deaths. It has been reported that the risk of fatal CAD during the five years following a transient cerebral ischemic attack exceeds the risk of recurrent stroke. This impressive cardiovascular mortality may jeopardize the effectiveness of medical and surgical treatment of cerebral ischemia alone. Nevertheless, a careful cardiologic evaluation is not usually part of the routine evaluation of these patients, and is usually limited to the detection of possible cardiac sources of embolism and to those cases with clinically overt CAD. CAD is asymptomatic in a large proportion of subjects in the general population. The association of atherosclerosis of coronary and cerebral arteries is a well-recognized entity and a vigorous cardiologic investigation may be indicated in all patients with cerebral ischemia.

Prospective studies aimed at detecting a coexistent asymptomatic CAD in patients with cerebral ischemia are rather sparse in the literature. In the present study, the incidence of asymptomatic CAD in patients with cerebrovascular insufficiency using noninvasive cardiologic screening was prospectively studied and compared to results from age and sex-matched healthy controls.

Materials and Methods

We prospectively studied 83 consecutive patients admitted to the 1st Neurosurgical Division of the Bellaria Hospital of Bologna (Italy) during the period July 1984-September 1985. Patients were selected according to the following criteria:

1) Transient ischemia or mild stroke of the carotid system;
2) Absence of angina and of historical and electrocardiographic (ECG) evidence of previous myocardial infarction.

There were 65 males and 18 females, aged between 22 and 73 years (mean: 53.7 years) (fig. 1). On the basis of symptoms and neurological examination 45 cases were classified as Transient Ischemic Attack (TIA), 10 as Reversible Ischemic Neurological Deficit (RIND), and 28 as mild stroke. All patients were carefully scrutinized for the identification of risk factors such as cigarette smoking, diabetes mellitus, arterial hypertension, hypercholesterolemia, hematocrit > 45%, or oral contraceptive use. Results are summarized in table 1.

All patients underwent computerized tomography (CT) scanning of the brain (table 2). An angiographic study of the carotid and vertebral arteries by brachial or femoral route was performed in 78 cases (table 3). Each patient received an echotomographic study of the carotid bifurcations.

In all cases, a standardized, non-invasive cardiological protocol was adopted. This consisted of clinical evaluation, standard ECG, chest X-ray, and exercise testing. When indicated, exercise Thallium-201 myocardial perfusion scintigraphy was performed. Coronary angiography was carried out in selected cases. The exercise test was performed on a motorized treadmill according to the Bruce protocol. Complete ECG and blood pressure were recorded at one-minute intervals during exercise and recovery. All treadmill tests were maximal or limited by exhaustion, systolic blood pressure > 240 mm Hg, or ST-segment depression > 3 mm.

Patients with positive exercise test underwent bicycle exercise Thallium-201 myocardial scintigraphy within two weeks. At the appearance of at least 1.5 mm ST-segment depression 2 mCi of Thallium-201...
were injected intravenously and the patient was requested to continue the exercise 60 to 90 seconds. Each patient underwent imaging in the supine position under a PHO Gamma V scintillation camera both immediately after the isotope administration (exercise) and four hours later (delayed rest) for the redistribution scan.\textsuperscript{19} Using a medium-sensitivity, parallel-hole collimator we obtained images in the standard views. Each image was subdivided into 3 segments corresponding to the territories of distribution of the left anterior descending, circumflex and right coronary arteries. Images were stored in a computer for processing, semiquantitative analysis and elaboration of circumferential profiles.

All studies were interpreted independently by two experienced observers, without knowledge of clinical, electrocardiographic data. Processed images and semiquantitative data were used for the final interpretation.

The control group was made up of 83 consecutive, healthy individuals without symptoms of cerebral and coronary artery disease who were evaluated for a normal check-up or for an insurance policy motive. They were 60 males and 23 females aged 34-74 years, with an average of 52.3 years. They were submitted to the same cardiologic protocol as the former "cerebrovascular" group. The two groups were comparable as regards male/female ratio and age. Risk factors were determined also in the control group.

Statistical analysis was performed using the Student t test and the Chi-square test with Yates' correction.

### Results

The analysis of risk factors revealed a significant prevalence of cigarette smoking and diabetes ($p < 0.01$) in the cerebrovascular group (table 1).

The exercise test was considered adequate in 75 out of 83 cerebrovascular patients. The remaining 8 cases were discarded due to an insufficient exercise performance: two patients experienced leg claudication, five complained of early fatigue during the test, and one showed severe arterial hypertension demanding interruption of the examination. Twenty-one (28\%) of 75 patients with an adequate ergometric study exhibited a positive test in the absence of angina (fig. 2). The endpoints of the test were exhaustion in 17 cases, ST-segment depression $> 3$ mm in two, and severe hypertension in the remaining two. The incidence of abnormal exercise test was not significantly different among TIA, RIND and stroke patients; nor a correlation was found between the severity of angiographic lesions and the occurrence of positive exercise test. Conversely, a close correlation was found between the presence of angiographic lesions and abnormal exercise test. In fact, as many as 16 of 21 cases with abnormal exercise test exhibited stenotic or occlusive lesions on angiography. On the other hand only 2 of 19 patients with normal cerebral arteriograms had a positive exercise test (table 4).

Exercise Thallium-201 myocardial scintigraphy of those 21 cases with positive exercise test was consistent with a perfusion defect in 19 and was normal in two. Of these 19 cases the perfusion defect was reversible in 13 and stable in 6. It involved 5 segments in one patient, 4 segments in two, 3 segments in four, 2 segments in seven, and one segment in five. Two pa-

### Table 1: Incidence of Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients with Cerebral Ischemia</th>
<th>Healthy Subjects (Control group)</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (\textgreater 10 cigarettes)</td>
<td>38</td>
<td>28</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36</td>
<td>31</td>
<td>ns</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>15</td>
<td>9</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15</td>
<td>--</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit \textgreater 45%</td>
<td>8</td>
<td>Not considered</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8</td>
<td>30</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\textsuperscript{31} and 13 patients with two and three associated risk factors, respectively.\textsuperscript{13 and 1 subjects with two and three associated risk factors, respectively.}

### Table 2: CT Findings in 83 Patients with Cerebral Ischemia

<table>
<thead>
<tr>
<th></th>
<th>No of cases</th>
<th>Normal</th>
<th>Focal ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>45</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>RIND</td>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Mild stroke</td>
<td>28</td>
<td>7</td>
<td>21</td>
</tr>
</tbody>
</table>

### Table 3: Angiographic Findings in 83 Patients with Cerebral Ischemia

<table>
<thead>
<tr>
<th></th>
<th>No of cases</th>
<th>ICA Atheroma or stenosis</th>
<th>ICA occlusion</th>
<th>MCA occlusion</th>
<th>Not performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>45</td>
<td>11</td>
<td>23</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>RIND</td>
<td>10</td>
<td>3</td>
<td>5</td>
<td>--</td>
<td>2</td>
</tr>
<tr>
<td>Mild stroke</td>
<td>28</td>
<td>5</td>
<td>14</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

ICA = Internal Carotid Artery; MCA = Middle Cerebral Artery.
patients with a positive exercise test at a low workload and with extensive scintigraphic perfusion defects underwent coronary angiography. These studies showed three-vessel CAD in one instance and collateralized obstruction of the left anterior descending artery associated with critical proximal stenosis of the circumflex in the second case.

The obtained data were compared to those of controls. In 78 of these 83 healthy subjects the exercise test was adequate, reaching at least 85% of the maximal heart rate. This examination yielded an abnormal result in 5 cases (6.4%). Myocardial perfusion scintigraphy in these cases revealed reversible perfusion defects in 3 subjects and was normal in 2.

In none of the cerebrovascular cases did the detection of CAD contraindicate a cerebral angiographic study. Twenty-seven patients were selected for surgical treatment: sixteen underwent carotid thrombendarterectomy, 10 extra-intracranial arterial bypass, and one both procedures. Exercise test was abnormal in 8 cases (30%) of this surgical group, paralleling the results in the nonsurgical group (27%). No cardiac complications occurred in the postoperative course.

All 83 patients received antiplatelet medications. Those 21 cases with a positive exercise test were additionally treated for CAD.

### Discussion

A fatal CAD is the major cause of death in patients with cerebral ischemia treated either medically or surgically. Hence the cardiac status of these patients should not be ignored.

Our study supports the need of actively seeking a CAD in patients presenting with a cerebral ischemic attack. Ancillary investigations are an important supplement to symptoms and ECG evidence in these patients, because an associated CAD is often subclinical. The critical importance of this cardiologic work-up has prospectively been demonstrated by Rokey et al. In a group of 34 patients admitted for cerebral ischemia with neither history nor ECG signs of CAD who were studied with myocardial scintigraphy and in some cases coronary angiography these authors found 14 cases (41%) of CAD. Another prospective investigation by Herzter yielded a 27% angiographic prevalence of critical coronary artery stenoses in patients undergoing carotid endarterectomy.

In our series of patients with transient cerebral ischemia or mild stroke and without cardiologic signs and symptoms, the prospective evaluation with an exercise ECG test and exercise myocardial scintigraphy resulted in a 28% rate of asymptomatic CAD. This prevalence is four times greater than that in our control group of healthy individuals with absent cerebral and cardiac symptoms.

A positive treadmill test was found in only 5 of these cases (6%), thus according to the data in the literature: 1 to 5% of middle-aged, healthy-looking individuals studied with exercise test will show an asymptomatic CAD. A significant prevalence of risk factors in patients with cerebral ischemia was the unique discriminating finding. The comparison of our groups reinforces the opinion that:

1) Cerebral ischemic events may be considered as useful predictive factors of asymptomatic CAD, and
2) even the most aggressive treatment, if limited to only cerebrovascular disease, may fail to improve overall mortality.

It is known that cerebral ischemia itself may induce resting ECG changes possibly conditioning the result of exercise test. However, neurogenic ST-T abnormalities were never observed in our cases.

We can conclude that, in a remarkable proportion of patients with cerebral ischemia, a coexistent asymptomatic CAD is present...
tomatic CAD can be expected. The exercise treadmill test followed by exercise Thallium-201 myocardial scintigraphy can be proposed as safe as well as reliable examinations in the non-invasive screening of these patients. 

Acknowledgments

We express our gratitude to David G. Sherman, M.D.; Robert G. Hurt, M.D. (Division of Neurology, The University of Texas, San Antonio, USA) and Harold P. Adams, Jr., M.D. (Department of Neurology, The University of Iowa, Iowa City, USA) for stylistic suggestions; and to Giuseppe Stefanelli for typing the manuscript.

References

Cerebral ischemia and asymptomatic coronary artery disease: a prospective study of 83 patients.
G Di Pasquale, A Andreoli, G Pinelli, P Grazi, G Manini, F Tognetti and C Testa

*Stroke*. 1986;17:1098-1101
doi: 10.1161/01.STR.17.6.1098

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 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/17/6/1098

**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/