Cerebrovascular disease and coronary artery disease (CAD) have similar risk factors and often coexist. The association is so strong that after presentation with threatened stroke, patients may be at higher risk for a myocardial infarction than for a stroke.\(^1\) The 5–6% annual mortality rate after transient ischemic attacks (TIAs) is mainly due to myocardial infarction,\(^2,3\) which is similar to the 4% annual cardiac mortality rate in patients with stable angina pectoris.\(^4\) In patients with asymptomatic carotid bruit, the risk of myocardial infarction is approximately equal to that of stroke.\(^5\) After stroke, the presence of CAD adversely affects survival.\(^6\) In spite of the recognition that CAD and cerebrovascular disease are associated, it is not currently a routine practice to evaluate patients with early cerebrovascular disease for asymptomatic or symptomatic CAD. Thallium-201–dipyridamole scintigraphy has proven to be of value in predicting cardiac risk in patients with peripheral vascular disease before peripheral vascular surgery.\(^7-10\) An abnormal \(^201\)Tl scan is an independent predictor of subsequent myocardial infarction or cardiac death and increases the risk of a future cardiac event by more than threefold.\(^11\)

To assess the prevalence of significant CAD and of coronary events among patients with asymptomatic carotid bruits or stenosis, TIAs, or small strokes, consecutive patients were prospectively evaluated according to our protocol using either \(^201\)Tl–treadmill exercise or \(^201\)Tl-dipyridamole scintigraphy (according to the degree of exercise tolerability) and coronary arteriography, when indicated.\(^12\) We followed these patients to determine whether \(^201\)Tl screening and coronary arteriography provided additional prognostic information.

**Subjects and Methods**

Patients between the ages of 18 and 80 years with asymptomatic carotid bruits with associated stenosis,
with carotid or vertebrobasilar TIAs, or with small, nondisabling strokes were eligible for study using $^{201}$Tl scintigraphy and/or coronary arteriography. The protocol was approved by the institutional review boards governing research in human subjects. Patients were excluded from the study if they had contraindications for $^{201}$Tl scintigraphy. Women of childbearing potential had serum or urine $\beta$-human chorionic gonadotropin quantification before entry. Patients with presumed or definite cardioembolic cerebral ischemia were excluded.

Risk factors for atherosclerosis and past history of stroke, TIA, angina, myocardial infarction, arrhythmias, carotid endarterectomy, coronary artery bypass grafting, coronary angioplasty, and peripheral vascular surgery were documented. Cardiac history was defined as the presence or history of angina or myocardial infarction, or as electrocardiographic (ECG) changes indicative of a prior myocardial infarction or ischemia. Carotid bruits were detected by carotid artery auscultation. Patients underwent routine blood testing; most had testing of serum cholesterol and triglyceride levels, and some had testing of high density lipoprotein and low density lipoprotein levels when the total cholesterol was elevated. Electrocardiograms were obtained on all patients. Most patients had a chest roentgenogram. Unenhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain was performed on all patients with TIAs or small strokes. Small strokes were defined as nondisabling deficits associated with a lesion by CT or MRI involving less than half a lobe of the brain.

All patients with carotid bruit underwent carotid duplex scans to determine whether stenosis was present. Patients with a carotid bruit associated with carotid stenosis of less than 50% were excluded. Noninvasive grading of carotid artery stenosis was made by the Doppler velocities and spectral broadening. Cerebral angiography was obtained at the discretion of the attending physician. Percent carotid stenosis by angiography was calculated from the minimal residual lumen (MRL) and the distal lumen (DL) by the equation $\left(1 - \frac{\text{MRL}}{\text{DL}}\right) \times 100$. Cerebral angiography, MRI, and CT of the brain were read by a single, blinded investigator.

Screening for the presence of CAD was performed according to the protocols shown in Figures 1 and 2. Patients underwent either exercise-$^{201}$Tl scintigraphy or an intravenous dipyridamole test with $^{201}$Tl imaging. Dipyridamole-$^{201}$Tl tests were performed in patients who, by history, could not perform maximal treadmill exercise testing because of vascular claudication, severe lung disease, or orthopedic problems. Exercise testing was performed using a standard Bruce protocol. Exercise was stopped for the following reasons: fatigue, shortness of breath, attainment of 80% of the maximal predicted heart rate, or ischemic electrocardiographic changes. Dipyridamole testing was performed as previously described. A standard dose of intravenous dipyridamole (0.56 mg/kg given over 4 minutes; Boehinger Ingelheim, Ltd) was administered with an infusion pump. Heart rate, blood pressure, and a 12-lead ECG were recorded initially and every minute until the patient underwent imaging.

One minute before stopping exercise or 5 minutes after the end of the dipyridamole infusion, $^{201}$Tl was injected intravenously. For the standard protocol, patients received 111 MBq (3 mCi) i.v. $^{201}$Tl. If these patients underwent imaging at rest to look for further redistribution, they received 74–111 MBq (2–3 mCi) i.v. on a separate day. Some patients received 74 MBq (2

**Figure 1.** Diagram of screening process for coronary artery disease in patients with asymptomatic carotid stenosis, transient ischemic attacks (TIAs), or small strokes and a history or electrocardiographic (ECG) evidence of coronary artery disease (CAD).

**Figure 2.** Diagram of screening process for coronary artery disease (CAD) in patients with asymptomatic carotid stenosis, transient ischemic attacks (TIAs), or small strokes and no history or electrocardiographic (ECG) evidence of CAD.
mCi) i.v. for the immediate images and were reinjected with 37 MBq i.v. before the delayed images. If the patient weighed more than 240 pounds, either the latter doses were increased to 111 MBq and 56 MBq or planar imaging was performed.

Tomographic 201Tl imaging (180° acquisition) was performed in patients who weighed less than 240 pounds and in women without marked breast enlargement using a large field of view detector, a 0.25-inch-thick crystal, and a low-energy, all-purpose, parallel hole collimator (Siemens Orbiter). The planar images were acquired in the anterior, left anterior oblique, and lateral decubitus projections. Tomographic images were reconstructed using a standard filtered back-projection technique with a low-resolution Henning filter (Medical Data Systems, Ann Arbor, Mich.). If the immediate imaging was performed.

Data Systems, Ann Arbor, Mich.). If the immediate images were interpreted as normal, the patient did not return for delayed images. Delayed images were obtained approximately 3 hours after the immediate images. For patients imaged using the standard protocol, images were obtained after reinjection of 201Tl at rest on a separate day if only minimal redistribution of 201Tl was seen on the delayed images or if a fixed defect was identified in a patient without a history of myocardial infarction.

All ECG results were interpreted blindly according to standard criteria by a single cardiologist. The exercise ECG results were interpreted as positive if the ST segment was flat or downsloping and depressed more than 0.1 mv at 80 msec after the J point.

The 201Tl images were interpreted by two observers blinded to clinical data. The 201Tl uptake was graded on a 5-point scale with 0 indicating no defect and 4 indicating 201Tl uptake was equivalent to background. Twenty segments were scored on the tomographic images, six segments on each of three short axis images, and two apical segments on the vertical long axis. A defect was defined as fixed if no change in 201Tl uptake was noted, including that on the rest study. A reversible defect was defined as an initially abnormal 201Tl uptake (grades 3–4) that became normal (grades 0–1) on the delayed images. A partially reversible defect was defined as an initially abnormal 201Tl uptake (grades 3–4) that partially improved but did not normalize (grades 2–3). Quantitative analysis was available to confirm qualitative evaluation.

Patients were asked to undergo coronary arteriography if the 201Tl study demonstrated clearly abnormal 201Tl images or the patient developed either cardiovascular symptoms or ischemic ECG changes. Coronary angiograms were obtained in multiple projections and interpreted both visually and by quantitative analysis by a single observer. Significant CAD was defined as 50% lumen diameter stenosis or greater by quantitative analysis.

Patients were seen for follow-up by one of the investigators at intervals determined by their clinical situation, which was in general every 3–6 months. Two patients failed to report for visits and were contacted by telephone. Inquiries were made regarding cardiac or cerebral events. Cerebral events were defined as TIA or stroke during the follow-up period. Cardiac events were defined as new-onset angina, new-onset atrial fibrillation, coronary artery bypass grafting, myocardial infarction, or cardiac death.

### Results

The study group consisted of 39 men and 21 women, aged 34 to 78 (mean, 62) years. No patient had complications from the tests. Fifteen patients had asymptomatic carotid stenosis. Forty-five patients had symptomatic cerebrovascular disease (24 carotid distribution TIA; 11 vertebralbasilar distribution TIA; 15 small, nondisabling strokes). The results of the 201Tl tests according to the type of cerebrovascular disease present are listed in Table 1. No significant difference existed in the prevalence of abnormal 201Tl test results between those who had asymptomatic and those who had symptomatic cerebrovascular disease (p=0.71, Fisher’s exact test, one-sided).

Fifty-three of sixty patients (88%) had carotid duplex and/or cerebral angiography (34 patients underwent cerebral angiography and 49 had carotid duplex studies). The degree of carotid stenosis was not related to the severity of CAD. Analysis of patients according to cardiac history is detailed in Table 2. The prevalence of abnormal 201Tl test results was 33% in patients with no cardiac history and 58% in patients with a cardiac history (p=0.054). Also, 11 of 26 (42%) patients with an abnormal 201Tl test had no history of CAD. The only risk factor that was significantly associated with an abnormal 201Tl test was a history of peripheral vascular disease (p=0.032). While the prevalence of abnormal 201Tl test results was the same among men and women in

### Table 1. Results of Thallium-201 Scintigraphy According to Cerebrovascular Disease Type

<table>
<thead>
<tr>
<th>Cerebrovascular disease type</th>
<th>Test results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>201Tl dipyridamole</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal</td>
<td>3</td>
</tr>
<tr>
<td>201Tl graded exercise treadmill</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal</td>
<td>4</td>
</tr>
</tbody>
</table>

### Table 2. Results of Thallium-201 Scintigraphy According to Cardiac History

<table>
<thead>
<tr>
<th>Cardiac history*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cardiac history</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Abnormal</td>
</tr>
<tr>
<td>Type defect</td>
</tr>
<tr>
<td>Fixed</td>
</tr>
</tbody>
</table>

Fifty-nine patients underwent 201Tl testing; one had coronary arteriography only (see text).

*By history and electrocardiographic criteria.

†Defined as history of angina or myocardial infarction, or electrocardiogram with myocardial infarction or ST changes.

*p<0.054 compared with patients with no cardiac history (Fisher’s exact test, one-sided).
Three of seven patients with normal 201 Tl studies had probably normal (201 Tl abnormality most likely due to medical illness that precluded testing, and one received patient declined the test, three had serious, concomitant of the two patients with 201 Tl studies interpreted as abnormal 201 Tl test results had significant CAD. Neither normal studies (mean age, 57.2 years; p<0.001).

CVD, cerebrovascular disease; CAD, coronary artery disease; ACB, asymptomatic bruit; ACS, asymptomatic carotid stenosis; TIA, transient ischemic attack; NL, normal.

Our study, patients with abnormal results were significantly older (mean age, 67.2 years) than those with normal studies (mean age, 57.2 years; p<0.001).

Coronary arteriography was performed in 25 patients (Table 3). Fourteen of fifteen patients with definitely abnormal 201 Tl test results had significant CAD. Neither of the two patients with 201 Tl studies interpreted as probably normal (201 Tl abnormality most likely due to attenuation) had significant coronary artery stenosis. Three of seven patients with normal 201 Tl studies had significant CAD by angiography, with two demonstrating "balanced disease" (i.e., comparable, severe stenosis in all three coronary arteries). The other patient had angiina with an occluded bypass graft to a second-order artery by angiography. Not all patients with reversible defects on 201 Tl tests had coronary arteriography: one patient declined the test, three had serious, concomitant medical illness that precluded testing, and one received medical therapy without undergoing coronary arteriography at the recommendation of his physician.

The following treatments were administered during the follow-up study period: aspirin, 58 patients; warfarin (Coumadin, Du Pont Pharmaceuticals), two patients; carotid endarterectomy, 13 patients; and nitrates, calcium channel blockers, or β-blockers, 17 patients. Percutaneous transluminal coronary angioplasty was performed in one patient and coronary artery bypass grafting in two patients as a result of abnormal 201 Tl tests and significant CAD.

Patients received follow-up for 61-591 (mean, 311) days. Complications that occurred during follow-up included new onset of angina in four patients (7%); atrial fibrillation in two (3%); TlAs in three (5%); recurrent strokes in two (3%); and death in two (3%), resulting from suicide in one patient and mesenteric thrombosis in a patient with atrial fibrillation.

During follow-up, cardiac events were more common than cerebral events (Table 4). There was no difference in the follow-up event rate between those patients with symptomatic or those with asymptomatic cerebrovascular disease. The cerebral event rate was numerically greater in patients with carotid stenosis ≥50% (p=NS). Those patients with reversible 201 Tl defects had a numerically greater cardiac event rate (p=NS). In patients with any abnormality on 201 Tl testing or with normal 201 Tl results but with development of cardiac symptoms, coronary angiography showing one or more vessels with ≥50% stenosis was associated with a higher numeric cardiac event rate than the group with <50% coronary arterial stenosis. Analysis of patients with reversible 201 Tl defects and coronary arterial stenosis of ≥50% showed a 29% cardiac event rate during the
TABLE 4. Characteristics of Patients With Follow-up Events

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cerebral Event*</th>
<th>Cardiac Event†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./n</td>
<td>%</td>
</tr>
<tr>
<td>History of cerebrovascular symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4/15</td>
<td>9</td>
</tr>
<tr>
<td>No</td>
<td>1/15</td>
<td>7</td>
</tr>
<tr>
<td>Carotid stenosis ≥80%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2/14</td>
<td>14</td>
</tr>
<tr>
<td>No</td>
<td>2/39</td>
<td>5</td>
</tr>
<tr>
<td>Carotid stenosis ≥50%†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4/30</td>
<td>13</td>
</tr>
<tr>
<td>No</td>
<td>0/23</td>
<td>0</td>
</tr>
<tr>
<td>Reversible thallium defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0/20</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>5/39</td>
<td>13</td>
</tr>
<tr>
<td>Coronary stenosis ≥50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0/18</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>1/7</td>
<td>14</td>
</tr>
</tbody>
</table>

*Defined as TIA or stroke.
†Defined as new-onset angina, new-onset atrial fibrillation, coronary artery bypass grafting, myocardial infarction, or cardiac death.
‡By either carotid duplex or cerebral angiography; not all patients had the tests.

follow-up period compared with a 9% cardiac event rate among those without a reversible 201Tl defect (p=0.055; Figure 3). These patients had a similar cerebral event rate (0% versus 11%, p=NS; Figure 3).

Discussion

This study showed that abnormal 201Tl test results had similar prevalence in patients with asymptomatic and those with symptomatic carotid stenosis. CAD was common, even among patients with no cardiac history. In our patients, an abnormal 201Tl test result was more common with advanced age and symptomatic peripheral vascular disease. Most important, our follow-up data indicated that the combination of a reversible 201Tl test and significant stenosis on coronary arteriography was significantly associated with cardiac events during the follow-up period.

Several prior studies have reported the prevalence of CAD in patients with symptomatic cerebrovascular disease, each with significant limitations. Hertzer et al19 studied 506 patients with asymptomatic carotid bruits or TlAs using coronary arteriography with subjective visual interpretations and detected severe “operable” CAD in 37% of patients clinically suspected of having CAD and in 16% of patients without suspected CAD. Because coronary arteriography is limited by subjective interpretation, potential complications, and expense, it is not routinely used for screening in patients with cerebrovascular disease symptoms. Rokey et al20 prospectively evaluated 50 patients with TIAs or small strokes and no history of CAD. Using both exercise-radiouclide ventriculograms and stress-201Tl scintigraphy, significant CAD confirmed by coronary arteriography was found in 58% of the patients, but this study lacked follow-up data regarding the clinical significance of abnormal tests. Expense usually limits the routine use of combined 201Tl scintigraphy and radionuclide ventriculography screening. Di Pasquale et al21 studied 190 patients with carotid distribution TIAs or small strokes using exercise electrocardiography and, if results were abnormal, exercise-201Tl scintigraphy. Their rate of detection of asymptomatic coronary artery disease was 23%, which was increased 10-fold compared with healthy controls. Di Pasquale et al22 subsequently investigated 38 patients with stroke and no prior angina or myocardial infarction who were unable to exercise with 201Tl-dipyridamole tests and found that 23 of these patients (60%) had abnormal 201Tl tests. In comparison, the prevalence of abnormal exercise-201Tl tests in asymptomatic volunteers aged 40-96 (mean 60) years was 14%.23 These studies lacked confirmation of the 201Tl data by cardiac catheterization.21-23

Our study also demonstrated a high prevalence (33%) of patients with CAD (as detected by 201Tl testing) in the group without a history of CAD. Prior studies have shown a 16-60% rate of detection of asymptomatic CAD in patients with cerebrovascular disease. A strength of our protocol was the confirmation of 201Tl abnormalities by quantitative coronary arteriography and follow-up to assess the clinical importance of these abnormalities.

Coronary arteriography has traditionally provided the “gold standard” for detection of significant CAD. However, studies have demonstrated that angiographic characterization of coronary artery obstruction may not
provide information about future coronary events.24-25 In addition, studies have demonstrated the ability of 201Tl variables to predict the presence or absence of coronary events.10,11,12,26-34 Therefore, with coronary angiography alone, one can determine the presence of coronary artery stenosis but cannot reliably predict coronary events. Other studies have documented the prognostic significance of silent ischemia documented by 201Tl scintigraphy.10,23,35,36

To optimize the sensitivity and predictive value of 201Tl, we had the same two observers interpret the 201Tl studies, quantitative analysis was available to confirm qualitative evaluation, and quantitative coronary angiography was performed. Therefore, in our study, the sensitivity (true positives/positive tests) was 14/15 (93%). The predictive value (true positives/true positives + false positives) was also 14/15, although the one patient labeled as false positive had a 43% stenosis by quantitative angiography. In patients with a history of angina, we might consider altering our original protocol and have these patients go directly to coronary angiography; with normal 201Tl test results, they could still be referred for coronary angiography to exclude severe three-vessel (“balanced”) disease. However, the combination of reversible 201Tl defects and abnormal coronary angiography had prognostic significance in our patients.

The cardiac event rate (7% new angina, 3% atrial fibrillation, no cases of myocardial infarction or cardiac death) was low in our study. The typical annual rate of cardiac death among patients with cerebrovascular disease is 5-6%.23 The low incidence of cardiac events may be related to the routine use of aspirin and the close follow-up in our patients. The use of aspirin has been shown to reduce mortality and myocardial infarction rates in patients with unstable angina and is probably useful in primary prevention of myocardial infarction in patients who are at high risk for developing significant CAD.37 After our initial work-up, 17 patients were started on medical therapy for CAD, two who developed angina underwent successful percutaneous transluminal coronary angioplasty, and two underwent coronary artery bypass grafting. The finding of a significantly higher cardiac event rate (29%) among patients with reversible 201Tl defects and coronary arterial stenosis of ≥50% compared with the rate among those without abnormal 201Tl test results (9%) emphasizes the prognostic importance of performing routine screening with 201Tl scintigraphy in patients with both asymptomatic and symptomatic cerebrovascular disease. In this era of intense investigation of new therapeutic interventions for stroke prevention, it is still important to pay attention to the management of coexistent coronary artery disease. Performing 201Tl scintigraphy (and then coronary arteriography when the 201Tl test is abnormal) in all patients with cerebrovascular disease, whether or not they are asymptomatic and whether or not there is a history of CAD, can identify patients at higher risk for subsequent cardiac events. It is of interest that patients with abnormal 201Tl test results had a higher prevalence of coronary events especially given that treatment was altered based on the abnormal results. Therefore, it is possible that even more patients with abnormal 201Tl test results might have had coronary events if treatment had not been altered.

Acknowledgment

The authors express appreciation to Ms. Karen Flack for her excellent technical assistance.

References


Coronary artery disease and cardiac events with asymptomatic and symptomatic cerebrovascular disease.
B B Love, M Grover-McKay, J Biller, K Rezai and C R McKay

Stroke. 1992;23:939-945
doi: 10.1161/01.STR.23.7.939

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/23/7/939