The Patient With Transient Ischemic Attacks — Is This the Time for a New Therapeutic Approach?

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SUMMARY Current and future improvements in treatment to prevent cerebral infarction among patients with transient ischemic attacks may reduce neurological morbidity but may not lead to a proportional improvement in life expectancy. Because the long-term primary cause of death in these patients is myocardial infarction, it is most likely that the most important way to prolong survival may be the vigorous investigation of their cardiac status and the treatment of their coronary artery disease, even if asymptomatic.

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TRANSIENT ISCHEMIC ATTACKS (TIA) of the brain or retina are recognized precursors of cerebral infarction. Prompt evaluation and treatment are now recognized standard practice but the benefits of surgical or medical therapies in stroke prevention remain unproved. The skepticism of many physicians results in part from the unusually high mortality rate (6% per year) in patients with TIA.1-3 Because myocardial infarction is the most common cause of death among these patients, TIA should be considered not only a harbinger of cerebral infarction but also a warning signal of death from myocardial infarction. The 5% per annum long-term mortality from heart disease among patients with TIA exceeds by two and one-half fold the 1–2% annual mortality among comparably aged persons without heart disease.3-4 It even surpasses the 3–4% per annum mortality among patients with angina pectoris.5-6 The annual mortality among asymptomatic patients with one or two vessel coronary artery disease is 1.5%. The annual cardiac mortality rate among patients with TIA approximates the 6% rate among patients with asymptomatic triple vessel coronary disease.7 Based on these figures, TIA appears to surpass angina pectoris as a warning symptom of myocardial infarction.

The importance of heart disease in the prognosis of the patient with TIA is confirmed by epidemiological studies (table 1).1-3,4,6-10 Survival after TIA is influenced by a number of clinical variables including age and vascular distribution of TIA. Life expectancy is not shortened by TIA among patients who are older than 65 years but among younger patients survival is less than expected.11 Patients with vertebrobasilar events appear to survive longer than those with carotid symptoms.4 The severity of atherosclerotic lesions seen on arteriography is also a factor in prognosis for survival.12 These variables not only influence the probability of fatal cerebral infarction but also that of fatal myocardial infarction. While symptomatic heart disease, cardiomegaly, or an abnormal electrocardiogram are common in patients with TIA, all patients with TIA are at high risk of death from myocardial infarction or sudden death within five years.2-5

The high rate of fatal myocardial infarction alters the long-term results of medical or surgical therapy of TIA. Toole et al2 reported 21 cerebrovascular and 52 cardiovascular deaths during an average 5.5 year follow-up among 225 patients with TIA treated by carotid endarterectomy or medical management. The Joint Study of Extracranial Arterial Occlusion reported 11 deaths from heart disease and 3 from stroke among 169 patients treated by carotid endarterectomy, while 12 cardiovascular deaths and 9 cerebrovascular deaths occurred among 147 medically treated patients.14 In reports of medical management with oral anticoagulants, fatal myocardial infarction exceeded fatal cerebral infarction in frequency.15-17 Fatal myocardial infarction happened in four of 90 patients treated by placebo and in two of 88 patients treated by aspirin in the American trial of antiplatelet agents.18 All cardiac deaths were within five months of initiation of therapy. Similar results were reported in the Canadian Cooperative Study on antiplatelet aggregating drugs.19

In patients with TIA, coexisting heart disease increases the operative mortality of carotid endarterectomy.20 In one series of 683 operations, myocardial infarction was second to cerebral infarction as a cause of postoperative morbidity and mortality; 14 of the 16 myocardial infarctions developed in patients with pre-existing heart disease.21 In a group of patients with TIA and symptomatic coronary artery atherosclerosis, the operative mortality of carotid endarterectomy was 18.2% if no surgical treatment was directed at the heart.22 The high cardiac risk of patients with TIA is supported by the observation of Hertzer et al23 that preinfarction angina and left main coronary artery atherosclerosis are more frequent among patients who had both cerebrovascular and cardiovascular symp-
toms than among those with solely cardiac symptoms. Morris et al. found more severe coronary artery atherosclerosis among patients with TIA and cardiac symptoms who had coronary bypass than among patients who had only cardiac symptoms. These factors support the high probability of serious cardiac complications which must be weighed in the decision to recommend carotid endarterectomy.

Among patients who survive carotid endarterectomy, the leading long-term cause of death is myocardial infarction. Thompson et al. noted 90 of 172 long-term deaths after carotid endarterectomy were due to cardiac disease, while 23 were secondary to cerebrovascular disease. In a recent report, Norrving et al. noted 21 cardiac deaths and 1 fatal stroke among 94 patients who had carotid endarterectomy and who were followed for an average of six years. Heart disease is also the primary late cause of mortality after superficial temporal artery-middle cerebral artery anastomosis. The annual mortality from heart disease among operated patients is approximately 5%. Lye and Downs noted the 5 year survival after carotid endarterectomy was 83% while the 10 year survival was 59%. Recently, Lees and Hertzer reported the long-term survival rates among 335 patients treated by carotid endarterectomy. Twice as many patients died of myocardial infarction than from stroke. They concluded that the survival rate among patients with TIA was similar to that of patients with angiographically confirmed severe coronary artery disease. These results support Nunn’s conclusion that the basic disease process of atherosclerosis is not changed by carotid endarterectomy and thus survival is not prolonged by the operation.

It is evident from the natural history of the patient with TIA that the event is a serious warning of all the complications of generalized atherosclerosis. It is also apparent that sophisticated diagnostic studies and consequent medical or operative treatment directed only at the cerebrovascular system, are not making an impact on the high long-term mortality among patients with TIA. Heyden et al. concluded that the diagnosis of TIA carries a mortality risk by mechanisms which are not clear. If a major proportion of deaths after TIA are caused by cardiac disease, should we not investigate and treat the heart as aggressively as we try to protect the brain in the patient with TIA? The answer, it appears to us, is affirmative.

## Possible Cardiac Evaluation

The extent of cardiac evaluation required in a patient with TIA is not established. The goal is to recognize and treat the coronary artery disease before an acute myocardial infarction or sudden death occurs. While unstable angina pectoris or a recent myocardial infarction are obvious warnings of subsequent, potentially fatal cardiac events, their absence in a patient with TIA does not eliminate the risk of myocardial infarction or sudden cardiac death.

Coronary artery disease is often asymptomatic until it expresses itself as a sudden cardiac death. In the experience of the Framingham Study, one half of all persons who suffered sudden cardiac death had no prior clinical heart disease. While classic angina pectoris is very suggestive of coronary artery disease, less than 30% of patients with severe coronary atherosclerosis have classical anginal pain. Non physical abnormalities identify the patient with severe coronary artery disease. We cannot depend upon clinical symptomatology to select which patients with TIA should undergo cardiac evaluation. We must depend on diagnostic studies to detect the presence of severe heart disease in patients with TIA. The diagnostic studies used to detect coronary artery disease in patients with chest pain could be applied to patients with atherosclerotic cerebrovascular disease.

The evaluation of a patient with suspected coronary artery disease is directed toward defining the extent and severity of coronary atherosclerosis. The amount of the left ventricular myocardium in jeopardy as well as the function of the left ventricle are appraised. Non-invasive cardiac tests identify the patients most at risk but demonstration of the extent of coronary artery atherosclerosis still requires arteriography. Chest roentgenograms and resting electrocardiograms are the initial diagnostic studies in patients with suspected coronary artery disease and already are standard parts of the diagnostic evaluation of the patient with TIA. Exercise electrocardiograms, resting and exercise radionuclide studies of the heart, left ventricular angio-grams and coronary arteriography are now parts of the evaluation of selected patients with suspected coronary artery disease. Some or all of these procedures could
be used in the cardiac evaluation of the patient with TIA.

Exercise electrocardiography is the most common non-invasive diagnostic study used in the evaluation of patients with possible coronary artery disease. Testing is performed in the presence of a physician and assesses both symptoms and electrocardiographic and blood pressure responses during exercise. It has a remarkable safety record. Complications are 3.6 myocardial infarctions, 4.8 serious cardiac arrhythmias and 0.5 deaths per 10,000 tests. The study is terminated if the patient develops severe anginal pain, if the patient's blood pressure drops despite an increased workload, if neurological signs or pallor develop, if serious arrhythmias occur or if there is a 0.2 mV depression or elevation of the ST segment on the electrocardiogram. It is not diagnostic if the patient is taking digitalis or antianginal drugs. An abnormal resting electrocardiogram, in particular if changes are consistent with hypertensive heart disease are present, will invalidate an exercise study.

The sensitivity of exercise electrocardiography in the detection of coronary artery disease may approach 70%. Its specificity is approximately 90%. The patient's clinical presentation influences the sensitivity and specificity of exercise electrocardiography. A positive exercise test is highly predictive of coronary artery disease in a patient with classic angina, but a negative study has a low correlation with the absence of significant disease. Stress testing has been recommended to detect latent coronary artery disease in patients who do not have cardiac symptoms but who may be at high risk. However, the value of exercise electrocardiography in asymptomatic patients has been questioned because false positive results do occur.

Radionuclide angiography enhances the accuracy of diagnosis when done in association with standard treadmill exercise testing. Thallium-201 perfusion scintigrams using either exercise or dipyridamole to induce coronary artery vasodilation may detect areas of myocardial ischemia at risk. Thallium-201 accumulates in myocardial cells at a rate proportional to coronary flow. Perfusion images of the left ventricular myocardium are obtained. Areas of borderline perfusion will be detected by impaired uptake of the radioisotope during exercise. Defects in the septal region correlate with disease of the left anterior descending coronary artery. Posterolateral wall defects accompany stenosis of the left circumflex artery. Inferior wall perfusion defects are associated with stenosis of the posterior descending coronary artery. Thallium-201 scintigrams have a sensitivity in detecting coronary artery disease of approximately 80% and a specificity that approaches 90%.

Exercise radionuclide ventriculography can detect regional or generalized impaired cardiac performance. Technetium-99 labeled red blood cells are injected immediately before scanning. Exercise will demonstrate abnormalities in ventricular function not apparent at rest. The study is abnormal if the left ventricular ejection fraction fails to increase by more than 5–10% or if regional wall abnormalities develop. The study has a sensitivity and specificity that exceeds 90% for detection of coronary artery disease. False negative studies are more likely to occur in patients with single vessel disease than among patients with diffuse disease. The presence of antianginal drugs such as calcium-channel blockers, propranolol or nitrates invalidate the radionuclide studies. Complications of Thallium-201 perfusion scans and exercise radionuclide ventriculography are very low. The precautions for exercise electrocardiography can be applied to exercise radioisotope studies. If the patient cannot exercise because of neurological or other deficits, Thallium-201 scans using dipyridamole induced vasodilation can be obtained. The amount of radiation exposure in these two studies is much less than arteriography.

Coronary arteriography is the most definite diagnostic procedure for detection of coronary artery disease. It will demonstrate the site and severity of coronary artery stenosis in all coronary vessels. In a review of the more than 14,000 coronary arteriograms performed in the state of Washington, there were 26 deaths (0.19%), 18 myocardial infarctions (0.13%) and nine strokes (0.06%). A similarly low rate of neurological complications of coronary arteriography was reported by Dawson and Fischer.

The cardiac evaluation of the patient with TIA should be determined on a case-by-case basis. In an attempt to reduce unnecessary studies and expenses, it may be reasonable to dispense with the non-invasive procedures and proceed directly to coronary arteriography to determine the extent of coronary artery disease in those patients with TIA who have a history of classic angina pectoris or who have had a well-documented myocardial infarction. In those patients without cardiac symptoms, an exercise electrocardiogram could be a screening procedure. If the patient with TIA has an abnormal exercise electrocardiogram, coronary arteriography could then be recommended. While its sensitivity in the detection of coronary artery disease is less than the radionuclide techniques, the widespread availability and lower costs of the exercise electrocardiogram makes it the most reasonable initial non-invasive cardiac study in patients with TIA.

The fact that radionuclide cardiac studies are available in only a small number of hospitals is a drawback. In addition, the cost of these studies (approximately $500.00 per procedure) is a formidable obstacle to their widespread utilization in a patient with TIA. Coronary arteriography would be reserved for those patients with at least suggestive evidence of coronary artery disease as detected by the non-invasive methods. The risks of the non-invasive cardiac studies are sufficiently low in patients with known severe coronary artery diseases, that they can safely be applied in patients who are without cardiac symptoms.

The high yield of the cardiological evaluation in patients with cerebrovascular disease has been recently demonstrated by Rolak et al. They performed Thallium-201 scans and exercise radionuclide ventriculo-
grams in 47 patients with TIA or mild stroke. Thirteen of 15 patients who had clinical evidence of heart disease and 14 of 32 patients without symptoms of coronary artery disease had abnormal studies. Coronary arteriography confirmed high-grade stenotic lesions in 17 of 20 patients studied. In all, 57% of their patients with TIA or small stroke had significant coronary artery disease. It seems appropriate that further prospective studies on the usefulness of these cardiac diagnostic procedures in patients with TIA be undertaken.

Possible Cardiac Treatment in the Patient with TIA

The ideal management of associated heart disease in a patient with TIA has not been established. Patients without cardiac symptoms and negative non-invasive cardiac studies could receive only treatment directed at coronary disease risk factors, such as hypertension and hypercholesterolemia. Follow-up visits could include a review of cardiac symptoms and sporadically repeated non-invasive cardiac studies.

Cardiac revascularization in patients with cerebrovascular disease has been advocated. Coronary artery bypass grafting should be considered for those patients who have severe or unstable angina refractory to medical therapy. Those patients with three vessel coronary artery disease or stenosis of the left main coronary artery who do not have symptoms may warrant surgery. The timing of coronary and cerebrovascular operations in patients with symptoms in both the cerebral and coronary circulations has not been resolved. In patients with symptomatic coronary and carotid artery stenoses, a simultaneous coronary bypass operation and carotid endarterectomy may be the most prudent, although unproved, course. The risk of the cardiac operation needs to be considered. The operative mortality of coronary artery bypass is approximately 1% and the incidence of complicating stroke is 1–3%. Although one report did not find a higher incidence of cerebrovascular risk factors among patients with stroke after bypass, it is possible that the stroke complication rate might be higher among patients with TIA.

Before recommending cardiac surgery to patients who are asymptomatic, the influence of coronary artery bypass on survival must be positive. Two long-term studies show a favorable trend of increased survival among surgically treated patients when compared to medically-managed patients. Surgery prolongs survival among patients with stenosis of the left main coronary artery, those with severe three-vessel disease or those persons with angina and ST depression on resting electrocardiogram. The four-year survival after surgery among operated patients aged 45–65 is 93% and among older patients is 84%. The quality of life is improved, myocardial ischemia is decreased and survival is prolonged after coronary artery bypass surgery in selected subsets of patients. Whether coronary artery bypass surgery on asymptomatic, severe coronary atherosclerosis could improve survival among patients with TIA is not known. The available evidence suggests that the risks of surgery are sufficiently low and the risks of subsequent cardiac death sufficiently high, that coronary artery bypass surgery would be reasonable in carefully selected patients with TIA.

Percutaneous transluminal coronary angioplasty is an alternative to surgery in many patients with coronary artery disease. Patients with single-vessel disease appear to be the most suitable for this procedure. As many as 15% of patients who might otherwise have surgery may be successfully treated by transluminal angioplasty.

Medical alternatives include beta-adrenergic blocking drugs, long-acting nitrates, calcium channel blockers, anti-platelet aggregating drugs and control of risk factors. While the medical therapies offer relief of symptoms with coronary artery disease, data showing improved survival are not presently available. The value of medical treatment of the heart in patients with TIA has not been studied.

The challenge for the physician who cares for the stroke-prone patient is not only to avoid the complications of cerebrovascular atherosclerosis but also to recognize and treat if possible the co-developing coronary artery disease. We need to know the degree of coronary atherosclerosis and its prognosis. We need to know the influence of surgical or medical cardiologic therapy on survival of patients with TIA. Now is the time for a careful study of heart disease in patients with TIA.

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