Cardiac Abnormalities in Stroke Patients with Negative Arteriograms

David C. Good, M.D.,* Stuart Frank, M.D.,† Steven Verhulst, B.S.,‡ and BIMALENDRA SHARMA, M.D.†

SUMMARY Sixty-five consecutive patients with recent unequivocal TIA (33) or stroke (32), but non-diagnostic arteriograms, had two-dimensional echocardiograms (2DE) and electrocardiograms (ECG) to determine the incidence of cardiac abnormalities which could cause embolic stroke. Abnormalities were classified according to increasing probability of causing an embolic event: non-specific, possible emboligenic abnormality (PEA) or definite emboligenic abnormality (EA).

Although 2DE was abnormal in 33 patients (51%), and ECG in 38 (59%), many abnormalities were non-specific. Only four patients (6%) had EA on ECG and two (3%) on 2DE. Since one patient had EA on both tests, 2DE identified only one patient (mitral valve prolapse) not already identified by ECG. All patients with EA had a prior history of cardiac disease. PEA was present on ECG in 11 patients (17%), and on 2DE in 25 (38%). There was no correlation between age, CT results, or neurologic symptoms commonly associated with embolic stroke and the presence of EA or PEA on ECG or 2DE.

Although TIA and stroke patients with negative arteriograms have a high incidence of abnormalities on ECG and 2DE, the percentage of patients with EA is low, and cardiac history and ECG identify most patients. 2DE provides little additional information.

THE REPORTED PERCENTAGE of embolic stroke in clinical stroke registries varies between 3% and 31%.1-4 The clinical features of embolic stroke have been reviewed,1-5,6 but clinical differentiation of such patients from those with stroke due to atherosclerotic cerebrovascular disease is often difficult in individual cases.4,7

Despite diagnostic difficulties, identification of patients with embolic stroke is important clinically since anticoagulation is the treatment of choice.5,7-10 Anticoagulation has well known complications and is of no value in patients with completed stroke due to atherosclerotic disease.10 The diagnosis of embolic stroke is usually made in the presence of a specific heart disease known to result in systemic emboli, and has depended primarily on cardiac history, examination and the electrocardiogram (ECG).

Two dimensional echocardiography (2DE) is a useful non-invasive procedure for identifying endocardial thrombus,11,12 valvular heart disease,7 atrial myxoma,12,13 and other structural cardiac abnormalities which might result in embolic stroke. However, 2DE has been of little value in identifying cardiac sources of emboli in an unselected series of stroke patients.7,13 Even when cerebral or systemic emboli are suspected clinically, 2DE identifies few cardiac abnormalities commonly associated with embolization.12,14-16 A major limitation of previous studies is that cerebral arteriograms were not available for most patients. A possible reason for the low yield of 2DE in previous studies is that most stroke is due to atherosclerotic arterial disease.

In this study, a consecutive group of patients with recent cerebral ischemic events whose cerebral arteriograms were normal in the vascular distribution of clinical symptoms, and who had no other identifiable cause of stroke, were evaluated with 2DE to determine the incidence of cardiac abnormalities causative of embolic stroke. The relative value of 2DE to identify such abnormalities was compared with that of ECG.

Methods

One hundred eighty-eight consecutive patients who had conventional cerebral arteriography for ischemic stroke at two large community teaching hospitals were evaluated during a 15-month period.

Patients meeting all of the following criteria were included in the study:

1) Definite clinical diagnosis of transient ischemic attack (TIA) or stroke, defined as the sudden onset of a focal neurologic deficit in a specific vascular distribution. Patients with possible migrainous events, focal seizures, and vague or non-localized neurologic symptoms were excluded.

2) No classic "lacunar" syndrome.

3) Cerebral arteriogram performed within one month of the ischemic event.

4) Arteriogram did not demonstrate atheromatous cause for stroke meeting one of the criteria below:
CARDIAC ABNORMALITIES/Good et al

a) arteriogram normal in the vascular distribution of symptoms.
b) branch occlusion pattern classically associated with embolic stroke.

Of the 188 patients reviewed, 70 met the criteria above and 65 consented to participate in the study. The median age was 63 years (range 21–88).

There were 31 men and 34 women. The median time interval from TIA or stroke to arteriogram was 7 days (range 1–30 days). Conventional arteriograms using the femoral approach to study the aortic arch, carotid bifurcations and intracranial circulations by selective injection were performed in 58 patients (89%). Direct carotid punctures or combined carotid and brachial injections, including intracranial runs, were performed in 7 patients (11%). The entire extracranial and intracranial portions of both carotid arteries were evaluated in 56 patients (86%). In seven other patients, the entire intracranial circulation of one carotid and the opposite carotid bifurcation were adequately visualized. In two patients, carotid bifurcation were well seen, but the intracranial carotid circulations were not optimally visualized. Vertebral origins were evaluated in all but 3 patients and 23 (35%) had evaluation of the intracranial vertebrobasilar circulation by selective injection. Our selection criteria excluded patients with carotid siphon or intracranial stenosis in the symptomatic vascular distribution. Patients with minimal atheromatous change or other abnormality in a vascular distribution other than symptoms were included in the study, but no patient with major asymptomatic atherosclerotic disease (greater than 50% stenosis or larger ulcer) in any vascular distribution was included.

All patients were evaluated by a neurologist. Data collected included historical features of the TIA or stroke, results of cardiologic and neurologic examinations, history of prior neurologic or cardiac disease, and results of diagnostic studies including CT scan of head. Standard 12-lead ECG's were obtained at a median of 2 days after the onset of symptoms (range 1–23 days). Two-dimensional echocardiography (2DE) was obtained at a median of 7 days after the onset of symptoms (range 1–37 days) using ATL model Mark III and ATL model 300-C sector scans. Standard techniques were used including parasternal, apical and subxiphoid windows. Quality of images was judged good or excellent in 75% of the studies. At least two cardiologists experienced in echocardiography independently interpreted each ECG and 2DE study, and any differences were jointly resolved.

For the purposes of this study, ECG and 2DE abnormalities were classified according to increasing probability of causation of stroke as follows: 1) abnormal, but non-specific; 2) abnormal, possibly causative of embolic stroke—"possible embolicigenic abnormality" (PEA); or 3) abnormal, probably causative of embolic stroke—"embolicigenic abnormality" (EA) (table 1). Decisions regarding how a type of lesion should be classified were based on previous reviews of cardiac abnormalities and their association with embolism. Only lesions known to be strongly associated with embolic events were classified as EA. We elected to classify mitral valve prolapse as EA since no other cause of stroke had been found in our patients. Abnormalities which might result in endocardial thrombus were classified with PEA. Some 2DE and ECG abnormalities were non-specific and unassociated with embolic stroke. Minor ECG abnormalities included non-specific ST or T wave changes, minor rhythm and rate disturbances, axis deviations, voltage abnormalities and atrioventricular or intraventricular conduction disturbances. Non-specific 2DE abnormalities included left ventricular hypertrophy, right ventricular abnormalities, and other non-specific minor abnormalities. To permit comparison with previous studies of ECG and 2DE in stroke, we have included the number of these patients. For the purpose of data analysis, these non-specific abnormalities were grouped with normal studies.

**Results**

Of the 65 patients, 33 had TIA's and 32 had completed or progressive strokes. Symptoms were in the carotid distribution in 55 patients (85%), vertebrobasilar distributions in 6 (9%), and multiple distributions in 4 (6%). Arteriograms were entirely normal in all vascular distributions studied in 52 patients (80%). Seven patients (11%) had minimal atherosclerotic abnormalities in a vascular distribution not related to symptoms and one patient had an incidental aneurysm unrelated to symptoms. Only 5 patients (8%) had classic arteriographic evidence for embolic study (branch occlusion).
TABLE 2  Echocardiography (2DE) and Electrocardiography (ECG) Results (65 patients)

<table>
<thead>
<tr>
<th></th>
<th>ECG</th>
<th>2DE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>27 (42%)</td>
<td>32 (49%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>38 (58%)</td>
<td>33 (51%)</td>
</tr>
<tr>
<td>Non-specific</td>
<td>23 (35%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>EA</td>
<td>4 (6%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>atrial fibrillation-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute myocardial infarction-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEA</td>
<td>11 (17%)</td>
<td>25 (38%)*</td>
</tr>
<tr>
<td>previous myocardial infarction-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>left atrial enlargement-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>left atrial thrombus-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prolapsed mitral valve-1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Some patients had more than one abnormality.

The results of ECG and 2DE are shown on table 2. When all abnormalities of any type were totaled, there were 33 of 65 (51%) patients with abnormal 2DE. However, in six patients, abnormalities were non-specific. While 38 of 65 (58%) ECG's were abnormal, 23 were non-specific. Five of 65 patients (8%) had EA on at least one diagnostic study and four of these were identified by ECG (3 atrial fibrillation, one acute myocardial infarction). Additional information was provided by 2DE in only one case, a patient with mitral valve prolapse and no other cause of stroke. When 2DE was evaluated independently, only two patients had EA (table 2). In addition to the patient with mitral valve prolapse, one patient had a left atrial thrombus. However, this patient was identified on ECG as having atrial fibrillation. No patient had a left ventricular thrombus, left ventricular aneurysm, valvular vegetations, mitral stenosis or other valve abnormality, or cardiac tumor. Eleven patients (17%) had PEA on ECG and 25 (38%) on 2DE (table 2).

CT scans were performed in 55 patients (85%), usually within one day of hospitalization. In 45 patients, CT scan was normal and in 10 revealed ischemic stroke. No patient had a "hemorrhagic" stroke. There was no correlation between CT scan results and abnormality on ECG or 2DE. All patients with EA had normal CT scans.

Twelve of 65 patients (18%) had symptoms traditionally associated with embolic stroke (seizure at onset-1, "lightning-like onset"-4, loss of consciousness at onset-3, multifocal stroke or systemic emboli-4). There was no correlation between any of these symptoms, or the aggregate group of symptoms, and EA or PEA either singly or combined. In fact, no patient with EA on ECG or 2DE had any neurologic symptom of embolic stroke.

Results of ECG or 2DE could not be correlated with age, sex, findings on arteriogram (branch occlusions), or history of previous stroke.

The relationship between test results and type and distribution of ischemic event is shown on table 3. All patients with EA presented with carotid distribution TIA's and none had completed stroke. When compared to all other patients, this was statistically significa-
The diagnosis of embolic stroke is usually considered in the presence of cardiac condition associated with systemic embolization, but the presence of such an abnormality does not necessarily imply causation of stroke. The strength of association between emboli and cardiac lesions varies considerably; acute myocardial infarction, rheumatic valvular disease, atrial fibrillation, and atrial myxoma are highly correlated with systemic embolization.7,12 We have labeled these “embolicigenic abnormalities” (EA). Mitral valve prolapse as a risk factor for stroke is more controversial,13 but we have elected to include this in the EA category. The association of embolization with other cardiac abnormalities including mitral annulus calcification, regional or generalized left ventricular wall hypokinesis and left atrial enlargement is more tenuous,14 and we have elected to call these “possible embolicigenic abnormalities” (PEA).

Previous studies have reported ECG abnormalities15-21 and 2DE abnormalities12-16,22,23 in populations of stroke patients. However, the relative values of ECG and 2DE in assisting in the diagnosis of embolic stroke have seldom been discussed in previous reports. In most studies evaluating embolic stroke or cardiac function in stroke, the frequency and result of cerebral arteriography is unreported. Such information is critical since the most common cause of ischemic stroke is atherosclerotic arterial disease.

We felt that TIA or stroke patients with no atherosclerotic abnormalities on arteriogram might have a higher incidence of EA on 2DE or ECG than unselected stroke patients. This hypothesis is of major clinical relevance for individual patients with negative arteriograms in whom discovery of a cardiac abnormality might alter therapy. Previous studies of patients with normal arteriograms have consisted of small numbers of patients and detailed cardiologic data is lacking.24,25

This study demonstrates that the frequency of EA is very low, even in patients with nondiagnostic arteriograms and no other cause for stroke, and that ECG is more helpful than 2DE in providing supportive evidence for embolic stroke for these patients. The ECG alone provided strong objective evidence that a vascular event was embolic in four of the five patients who had EA. The total percentage of abnormal ECG’s in our study (58%) is lower than the 68% of abnormal ECG’s reported by Dimant and Grob.19 However, 6% of our patients, as compared to 5% of Dimant and Grob’s had ECG evidence for embolic source of stroke. While many patients had ST segment changes, T wave abnormalities, premature beats, QT interval changes and other abnormalities, these abnormalities were classified as non-specific since they could have been incidental or due to autonomic hyperactivity associated

### Table 4 Cardiac History (65 patients)

<table>
<thead>
<tr>
<th>Any cardiac history</th>
<th>26 (40%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old MI</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>Recent MI</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Congestive failure</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Valvular disease, unspecified</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Murmur, unspecified</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (14%)</td>
</tr>
</tbody>
</table>

*Some patients had more than one abnormality.

### Discussion

The diagnosis of embolic stroke is usually considered in the presence of cardiac condition associated with systemic embolization, but the presence of such an abnormality does not necessarily imply causation of stroke. The strength of association between emboli and cardiac lesions varies considerably; acute myocardial infarction, rheumatic valvular disease, atrial fibrillation, and atrial myxoma are highly correlated with systemic embolization.7,12 We have labeled these “embolicigenic abnormalities” (EA). Mitral valve prolapse as a risk factor for stroke is more controversial,13 but we have elected to include this in the EA category. The association of embolization with other cardiac abnormalities including mitral annulus calcification, regional or generalized left ventricular wall hypokinesis and left atrial enlargement is more tenuous,14 and we have elected to call these “possible embolicigenic abnormalities” (PEA).

Previous studies have reported ECG abnormalities15-21 and 2DE abnormalities12-16,22,23 in populations of stroke patients. However, the relative values of ECG and 2DE in assisting in the diagnosis of embolic stroke have seldom been discussed in previous reports. In most studies evaluating embolic stroke or cardiac function in stroke, the frequency and result of cerebral arteriography is unreported. Such information is critical since the most common cause of ischemic stroke is atherosclerotic arterial disease.

We felt that TIA or stroke patients with no atherosclerotic abnormalities on arteriogram might have a higher incidence of EA on 2DE or ECG than unselected stroke patients. This hypothesis is of major clinical relevance for individual patients with negative arteriograms in whom discovery of a cardiac abnormality might alter therapy. Previous studies of patients with normal arteriograms have consisted of small numbers of patients and detailed cardiologic data is lacking.24,25

This study demonstrates that the frequency of EA is very low, even in patients with nondiagnostic arteriograms and no other cause for stroke, and that ECG is more helpful than 2DE in providing supportive evidence for embolic stroke for these patients. The ECG alone provided strong objective evidence that a vascular event was embolic in four of the five patients who had EA. The total percentage of abnormal ECG’s in our study (58%) is lower than the 68% of abnormal ECG’s reported by Lavy19 and the 89% reported by Dimant and Grob.20 However, 6% of our patients, as compared to 5% of Dimant and Grob’s had ECG evidence for embolic source of stroke. While many patients had ST segment changes, T wave abnormalities, premature beats, QT interval changes and other abnormalities, these abnormalities were classified as non-specific since they could have been incidental or due to autonomic hyperactivity associated
with stroke. Although intermittent atrial arrhythmias are another cause of embolic stroke, we were primarily interested in 2DE and ECG results and long-term ECG monitoring was not routinely done. Only two patients (3%) had EA on 2DE, and both had a known history of cardiac disease. Abnormal 2DE studies were found in 33 of 65 (51%) of patients but most abnormalities were PEA or non-specific.

Previous studies using 2DE in stroke patients have been reported. Greenland, et al evaluated consecutive unselected stroke patients with 2DE and found cardiac lesions responsible for embolic stroke in 3 of 95 (3.2%) and 29 of 350 (8.3%) patients. Several large studies retrospectively evaluated patients referred to echocardiogram laboratories for evaluation of cardiac source for suspected cerebral or systemic embolus. Come et al found lesions responsible for embolus in only 11 of 280 patients (3.9%), and Robbins et al reported that 2DE identified the heart as a likely source of embolus in 13 of 116 (11.2%) of patients studied. In both studies, all patients had prior cardiovascular disease. Donaldson and colleagues studied 62 patients with TIA or stroke referred to cardiologists after no underlying cause for the neurological event could be determined. In those patients with known heart disease at the time of referral, 22% had EA on 2DE. As in other series, the yield of EA was low in patients with no heart disease. Lovett et al identified an intracardiac thrombus in 6.5% of 138 patients in whom there was no obvious cause for cerebral ischemia or in whom a cardiac source of emboli was suspected. The percentage of intracardiac thrombus was higher in patients with atrial fibrillation (13.3%) and patients with other cardiac problems (9.4%).

The conclusion of all previous studies has been that 2DE was unlikely to identify EA in patients with no history of cardiac disease, but the frequency and result of cerebral arteriography has seldom been reported. In the report of Knoppers et al only 27 of 95 patients had arteriography, which was normal in eight cases. Only 51 of 280 patients studied by Come et al had vascular studies of any type and 49% of these suggested "an extracardiac source for thromboemboli."

An interesting feature of previous studies of 2DE in stroke is the high incidence of abnormalities, which we have designated "possible embolicigenic abnormalities" (PEA). Lovett and colleagues reported that 23.2% of their total series had such abnormalities, including enlarged or hypokinetic left heart chambers, possible thrombus, cardiomyopathy, and displaced pacemaker wire. Greenland et al noted a high proportion of regional or diffuse wall motion abnormalities and mitral annulus calcifications in their unselected stroke series. Come et al found PEA in 97 of 280 (35%) of patients screened for cardiac source of embolus. Bergeron and Shah found a variety of cardiac disorders possibly related to the cerebral event in 74 of 170 (43%) of patients. In our study, 25 of 65 (38%) patients had PEA. While one must be cautious about overinterpretation of this data, the possibility that some of these 2DE abnormalities might be related to embolic events cannot be dismissed lightly.

Technical difficulties regarding interpretations of 2DE have been discussed elsewhere. The sensitivity and specificity of 2DE varies according to the type of lesion under study. Experience in interpretation of 2DE is critical, and inter-observer difference in interpretation is a potential problem. In this study, any differences in interpretation between two cardiologists were jointly resolved.

Patients in our study were selected on the basis of having negative arteriograms. Findings on arteriography do not always correlate with the pathologic characteristics of the artery and a negative arteriogram does not exclude the possibility of atherosclerotic disease as a cause of stroke. However, atherosclerotic arterial disease as the cause of most strokes is widely accepted, and a normal cerebral arteriogram of the extra and intracranial vasculature is still the best way to exclude local atherosclerosis as a cause of stroke. Intravenous digital subtraction angiography (DSA) has a lower degree of image resolution than conventional arteriography. This study was completed before the availability of DSA and, therefore, is a unique opportunity to use ECG and 2DE to evaluate stroke patients in whom atherothrombotic disease has been excluded as definitively as possible.

Although a few patients had minimal atherosclerotic changes in vascular distributions which did not correlate with clinical symptoms, 80% had normal arteriograms. Five patients had "branch occlusions," a finding associated with embolic stroke. Sequential arteriographic studies of patients with embolic stroke have shown that the percentage of normal or nondiagnostic arteriograms increases rapidly after the onset of the ischemic event, and that some arteriograms are normal even shortly after the stroke occurs. In our study, the median time from event to arteriography was 7 days (range 1–30 days), and for those with branch occlusions 5 days (range 2–11 days). It is possible that earlier arteriography may have yielded a higher incidence of branch occlusions.

Several features of patient selection should be noted in interpreting our study results. While care was taken to exclude patients with classic lacunar syndromes, migrainous events, and non-descript neurologic symptoms, it is conceivable that patients with atypical lacunar strokes could have been included. Since all patients were selected on the basis of having had an arteriogram, some stroke patients with previously recognized EA, such as atrial fibrillation, were probably excluded because arteriograms were never performed. The study design may also have selected for patients with TIA, and for younger patients. There was a high correlation between cardiac abnormality and TIA in this study. While this is at variance with the impression that embolic events are usually strokes, we found in many patients with TIA in at least one study. We can not be certain that any of our patients actually had embolic events. However, since none had any other identifiable cause for TIA or stroke, an embolic...
event seemed possible in all patients. As previous reports have indicated, clinical neurologic symptoms are not usually helpful, and none of the patients with EA had any such symptoms. We believe that it is very difficult to identify embolic TIA or stroke solely on the basis of neurologic symptoms or findings. CT scan results were not correlated with EA or PEA.

This study shows that the diagnostic yield of 2DE in discovering cardiac abnormalities causative of ischemic stroke is low, even in patients with no demonstrable atherosclerotic changes on cerebral arteriography, and when 2DE is performed soon after the onset of symptoms. A history of cardiac disease and abnormalities on ECG, especially atrial fibrillation, are most likely to result in clinical suspicion of embolic stroke. Even among all patients with a cardiac history or an abnormal ECG, only 8% had EA on 2DE. As in previous studies, those patients with EA on 2DE had a history of cardiac disease. While 2DE may confirm suspected cardiac lesions in some patients, it should be used selectively.

References

24. Toole JF, Yuson CP: Transient ischemic attacks with normal angiograms: Serious or benign prognosis? Ann Neurol 1: 100-102, 1977
Cardiac abnormalities in stroke patients with negative arteriograms.
D C Good, S Frank, S Verhulst and B Sharma

Stroke. 1986;17:6-11
doi: 10.1161/01.STR.17.1.6

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/17/1/6

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/