Cardiac Workup of Ischemic Stroke
Can We Improve Our Diagnostic Yield?

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Background and Purpose—Discovering potential cardiac sources of stroke is an important part of the urgent evaluation of the ischemic stroke patient as it often impacts treatment decisions that are essential for determining secondary stroke prevention strategies, yet the optimal approach to the cardiac workup of an ischemic stroke patient is not known.

Methods—A review of the literature concerning the utility of cardiac rhythm monitoring (ECG, telemetry, Holter monitors, and event recorders) and structural imaging (transthoracic and transesophageal echocardiography) was performed.

Results—Data supporting a definitive, optimal, and cost-effective approach are lacking, though some data suggest that appropriate patient selection can improve the diagnostic and therapeutic yield of rhythm monitoring and echocardiography in the evaluation of stroke etiology.

Conclusions—Based on available data, an algorithmic approach for the evaluation of patients with acute ischemic cerebrovascular events that takes into account therapeutic and diagnostic yield as well as cost-efficiency is proposed. (Stroke. 2009;40:2893-2898.)

Key Words: diagnostic method ■ stroke ■ echocardiography ■ electrocardiography

Cardiac sources are the pathogenesis for 15 to 30% of strokes in the United States. Assessing for potential cardiac sources of stroke is an important part of the urgent ischemic stroke evaluation, as it often impacts treatment decisions. Appropriate early risk factor management is essential for reducing recurrent cerebrovascular events. Considerable disagreement exists among experts in regards to the extent of cardiac testing in stroke patients. Data supporting a definitive, optimal, and cost-effective approach is lacking. After a review of the literature, a systematic approach for the cardiac evaluation of patients with acute cerebrovascular events that takes into account therapeutic and diagnostic yield as well as cost-efficiency will be proposed.

Methods
We performed separate PubMed and Medline (1950 to the present) searches with the subject headings “electrocardiography,” “electrocardiography, ambulatory,” “arrhythmias, cardiac,” “telemetry,” and the keywords “Holter monitor,” “event loop recorder,” “implantable atrial fibrillation,” “echocardiography” all combined separately with “stroke,” including all subheadings. We then limited the search to English language, humans, and adults. Articles were reviewed then selected based on relevant data and publication in a reputable clinical journal. The references of chosen articles were further explored and provided additional data. For echocardiography, only studies with >100 subjects were included. Few of the trials were blinded or had control groups, but each sought to evaluate the utility of rhythm monitoring or echocardiography in the work-up of cerebral ischemia or was a review of this topic. The definitions of cardiac source of embolism (SOE) and indications for oral anticoagulation (OAC) use vary with each article and reader must take this into account when interpreting the data presented.

Abnormalities of Cardiac Rhythm

The ECG
There is relative consensus that patients presenting with acute stroke or transient ischemic attack (TIA) should be evaluated with a standard 12-lead ECG. ECG in this setting serves 2 purposes: to identify potential mechanisms of stroke, and to look for evidence of coexisting acute or chronic cardiac disease.

ECG abnormalities occur in as many as 60% to 90% of all stroke patients. The most common changes reported are QT prolongation and nonspecific ST changes. Most often these findings suggest the presence of underlying cardiac disease; however, even after excluding patients with known preexisting heart disease, up to one third of patients may demonstrate abnormalities on ECG. Atrial fibrillation (AF) can be detected on ECG in up to 25% of patients with first-ever ischemic stroke. New-onset AF is detected less often; however, this may be increased almost 3-fold by performing serial ECGs. ST segment changes suggesting acute myocardial infarction (MI) may also imply a potential etiology of an ischemic stroke. In one of the largest series reported, left ventricular (LV) thrombus was found in 5.1% of patients with acute MI: 11.5% with anterior MI and in 2.5% with MI in other sites. The subsequent risk of embolism in the following 6 to 12 months after an anterior Q-wave MI is 2.2% to 6%.

Special Report
Previously unrecognized MI, p-wave abnormalities, and LV hypertrophy have all been associated with an increased risk of stroke.\textsuperscript{8,9,10} ECG findings may also have prognostic significance in stroke patients. Ventricular arrhythmias, concurrent MI, and a prolonged QT interval have all been associated with increased mortality in stroke patients.\textsuperscript{11–13}

Telemetry Monitoring
The major limitation of a standard ECG is that it may not detect transient arrhythmias. It is therefore recommended that hospitalized patients with acute stroke undergo continuous cardiac rhythm monitoring for a minimum of 24 hours.\textsuperscript{1} In spite of this common practice, there is insufficient data on the utility of inpatient telemetry for stroke patients. One early study found that 67\% of patients admitted to an intensive care stroke unit developed conduction or rhythm abnormalities on 24-hour monitoring, however this was a small study and included both ischemic and hemorrhagic strokes.\textsuperscript{14} In a more recent larger study, ECG abnormalities were observed in 60\% of patients with cerebral infarction.\textsuperscript{15} In multivariate analyses of these patients, 3-month mortality was predicted by AF, atrioventricular block, ST-changes, and inverted T-waves independent of stroke severity, prestroke disability, and age.

In addition to potentially life-threatening arrhythmias, identifying patients with paroxysmal AF (pAF) and atrial flutter (AFL) is essential as these arrhythmias carry a similar risk of recurrent stroke as chronic AF and should be managed similarly. Reported rates for the detection of newly-diagnosed pAF during inpatient cardiac monitoring are 4\% to 8.4\%.\textsuperscript{16,17}

Holter Monitors
Holter monitors are small lightweight devices which can be strapped around the shoulder or waist and are capable of continuously recording ECG data from 2 or 3 ECG leads onto magnetic tape or a digital recorder.\textsuperscript{18} Patients may mark clinical events for review and correlation with abnormalities on ECG. Holter monitors are typically limited to 24 to 48 hours of monitoring. In a recent review of cardiac monitoring in stroke patients, Holter monitoring detected new-onset AF/AFL in 4.6\% of patients.\textsuperscript{19} This is similar to a detection rate of 1\% to 5\% reported in an earlier review.\textsuperscript{20} Patients in these studies were unselected, which may have contributed to the low rate of detection. One study concluded that given the overall cost of $9,400 for the diagnosis of 1 case of pAF, routine Holter monitoring in stroke patients should not be recommended.\textsuperscript{21} However, although an initial Holter monitor may not reveal a clinically significant arrhythmia, it still could be useful in identifying patients in whom extended cardiac monitoring may be warranted. Wallmann et al found that patients with >70 premature atrial beats per 24 hours on initial Holter monitoring had a 26\% occurrence of occult AF when monitoring was extended to 7 days.\textsuperscript{22}

Event Recorders
Event recorders allow for up to 30 days of cardiac rhythm monitoring. Older monitors were limited in detecting asymptomatic pAF as they required patient activation to record events. Newer generation monitors have been proven superior in arrhythmia detection by automatically recording tachy- or bradyarrhythmias.\textsuperscript{23}

Two recent prospective studies have evaluated the utility of event recorders in diagnosing pAF after stroke or TIA. In 149 consecutive patients studied by Jabaudon et al, event recorders detected pAF in 5.7\% with a mean duration of monitoring of 159 hours.\textsuperscript{24} Barthelemy et al reported a similar overall rate of 6.7\% in 60 consecutive patients with a mean duration of monitoring of 70.1 ± 30.9 hours.\textsuperscript{25} In this later study, one third of the cases of pAF went undetected by conventional ECG and Holter monitoring. In a recent retrospective study, Tayal et al found a substantial 23\% rate of detection of pAF in 56 consecutive patients with cryptogenic stroke or TIA using mobile cardiac outpatient telemetry for a median time of 21 days.\textsuperscript{26}

Patient Selection for Cardiac Monitoring
Given the relatively low yield of pAF detection in unselected patients, it is unlikely to be cost-effective to perform outpatient cardiac monitoring in all stroke patients. Limiting the use of continuous monitoring to patients with suspected cardioembolic or cryptogenic stroke may increase their yield. As examples, Jabaudon et al did not report any cases of pAF in patients with lacunar infarct, Barthelemy et al detected pAF in approximately 15\% of patients with cryptogenic stroke, and the 23\% pAF detection rate reported by Tayal et al included only patients with cryptogenic stroke. In addition, findings on echocardiography known to increase the risk of pAF, such as a dilated left atrium (LA) or mitral valve disease, might also be helpful in selecting patients for prolonged rhythm monitoring. Age is another important factor in selection, given the increased incidence of AF with age.

Future Research
The ongoing EMBRACE pilot study is evaluating the utility of prolonged 30-day external cardiac rhythm monitoring in detection of atrial fibrillation.\textsuperscript{27} Implantable loop recorders capable of monitoring patients for 14 months may also prove to be valuable; however, the use of these devices in the detection of occult arrhythmias in stroke patients has not been investigated to our knowledge.

Abnormalities of Cardiac Structure
While the American Stroke Association Guidelines recommend a clinical cardiovascular examination, cardiac enzyme tests, and a 12-lead ECG in all stroke patients, there are no formal recommendations for the performance of echocardiography.\textsuperscript{1}

The Diagnostic Yield of Echocardiography
The relative ease of the performance of transthoracic echocardiogram (TTE) and the higher sensitivity of transesophageal echocardiogram (TEE) are well established. TTE is widely available, noninvasive, cheaper, and easier to perform than TEE, but it is clearly less sensitive for the detection of
Cardiac SOE. TEE is not as widely available, is invasive, more expensive, and takes longer to perform than TTE, but has a much higher diagnostic yield. Although the sensitivity of TTE and TEE for LV thrombi is similar, LA thrombi are detected on TTE in only 39% to 73% of patients, versus 93% to 100% on TEE.\(^{28,29}\) In addition, a patent foramen ovale (PFO) is detected as low as 50% of the time on TTE and 89% to 100% on TEE and only 58% to 62% of vegetations are seen with TTE compared to 82% to 100% with TEE.\(^{28,29}\) Although TEE is considered very safe in the general population with a major complication rate of 0.02%,\(^{20}\) paradoxical air emboli during the evaluation for PFO has been reported,\(^{30}\) and the potential for periprocedural hypotension may be of greater consequence in the patient with an acute ischemic stroke.\(^{31}\)

The optimal timing of performing echocardiography is not known. The importance of the early detection of cardiac SOE to initiate secondary stroke preventative measures must be balanced with safety in the setting of an acute stroke. Until further information on the risk of TEE after acute stroke, delaying TEE until patients are hemodynamically stable and ordering bubble studies only in patients in whom the detection of PFO is likely to change management is a prudent approach.

### The Therapeutic Yield of Echocardiography

What abnormality is detected on echocardiography is an important question, but even more relevant is how what is detected will effect clinical decisions. Although some findings will clearly alter management, such as infectious endocarditis, intracardiac tumors, or the detection of a thrombus, many findings may not change management because they are already known from a patient’s past medical history, such as mechanical heart valves or a recent MI, are detected by other modalities, such as AF on telemetry, or do not usually change treatment, such as mitral valve prolapse or mitral annular calcifications. Even more challenging are findings with uncertain optimal management strategies, such as PFO, atrial septal aneurysm (ASA), lone spontaneous echo contrast (SEC), a low ejection fraction, and aortic arch atheroma.

Reported therapeutic yield for echocardiography in stroke patients ranges widely, from 2% to 37.2% for TTE\(^{28,32,33}\) and 8% to 32% for TEE.\(^{34,35,36}\) These inconsistencies are attributable to differences in study design, such as retrospective versus prospective data, consecutive versus referred patients, patient selection by characteristics such as age, history of cardiac disease or stroke subtype, how a cardiac SOE is defined, and what is considered an indication for OAC.

### Patient Selection for Cardiac Structural Imaging

A few authors have addressed the issue of patient selection to improve the diagnostic and therapeutic yield of echocardiography. Clinical signs or symptoms of heart disease are important factors to consider when evaluating the stroke patient. Whereas the yield of TTE in stroke patients with clinically apparent heart disease is approximately 25%, in patients without clinical heart disease the yield is <10%.\(^{7}\) The yield of TEE is >50% in patients even without clinically overt heart disease, primarily because of the detection of LA thrombi (LAT), LA SEC, complex aortic atheroma, PFO, and ASA.\(^{7}\) Arguably, the detection of these findings on TEE still may not change management. LAT and SEC are usually seen in patients with AF or significant mitral valve disease, which are often detected by other means and already have an indication for OAC.\(^{37,38}\) Statins have been shown to be beneficial in complex aortic atheroma, but there is no clear consensus on antiplatelet versus OAC therapy for secondary stroke prevention.\(^{39}\) The clinical relevance and management of patients related to the detection of a PFO and ASA must be individualized and in most cases do not warrant treatment with OAC.

Whereas many authors site the enhanced diagnostic yield of TEE as evidence of its universal need in all stroke patients,\(^{34–36}\) others emphasize the importance of evaluating the yield of TEE in different subsets of patients and focus on how results will impact clinical decision making.\(^{40–43}\) Stranding et al reported an 8% change in therapy based on TEE findings in 441 patients in sinus rhythm with no history of heart disease, however details of which findings led to the change in therapy are not given.\(^{44}\) The authors later reexamined the same cohort of patients and found that 8% of patients in sinus rhythm (SR) with vascular risk factors had major cardiac SOE on TEE versus only 1% of patient in SR without vascular risk factors \((P=0.024).\)\(^{45}\) Leung et al found a very low yield for TEE in 824 consecutive patients after stroke or other suspected embolic event who were in SR and had a normal TTE.\(^{43}\) Although the authors did not directly comment on patient’s history of cardiac disease, SR and a normal TTE could be considered markers of a negative cardiac history. Harloff et al prospectively collected data on 503 consecutive ischemic stroke patients and then retrospectively divided them by TOAST criteria into cardioembolic, large-artery atherosclerotic, small-vessel disease, stroke of other determined etiology, and stroke of undetermined etiology.\(^{34}\) They found TEE was unlikely to change management in the cardioembolic group as most patients already had an indication for OAC. In patients with large and small vessel disease, as well as those with other known SOE, the therapeutic yield of TEE was only 3%. They concluded that TEE can safely be omitted in a patient whose etiology of stroke can be classified on the basis of routine diagnostic testing. Of the 212 patients with stroke of undetermined etiology, a remarkable 100% had abnormalities detected on TEE, 30.6% of whom had a change in treatment based on TEE findings alone. Their data suggest that TEE may not be necessary in patients with cardioembolic, large artery, lacunar, or stroke of other determined etiology, but support the use of TEE after a nondiagnostic TTE in patients with cryptogenic stroke. De Bruijn et al evaluated 231 consecutive patients with a recent cryptogenic TIA or stroke with TTE followed by TEE.\(^{35}\) The authors state that patients with preexisting indications or contraindications for OAC were excluded, so presumably patients were not in AF. TEE detected a major risk factor with an indication for OAC in 16% of patients who had negative TTEs; however, this was almost entirely attributable to the detection of LAT in 16% of patients. These results should be questioned given that the rate of LAT in patients in SR is typically 1% to 2%.\(^{37,38}\) However, the finding of slow LA flow (≤55 cm/s) or...
low EF (≥35%) on TTE have been reported to predict the presence of SEC or LAT on TEE in patients in SR, and these finding could be used for patient selection for the performance of TEE.46 Lastly, several studies subdivided patients by age and concluded that age should not be a criterion for selecting patients for TEE.35,43,45

The Cost-Effectiveness of Echocardiography
The cost-effectiveness of echocardiography in the work-up of stroke has been addressed by few authors. The Canadian Task Force on Preventative Health Care performed a review of the literature to help develop guidelines for the use of echocardiography in stroke patients.47 They concluded there was insufficient evidence to recommend for or against routine echocardiography in patients (including young patients) without clinical cardiac disease, but echocardiography should be performed in all patients with clinical evidence of heart disease and recommended TEE as the initial test based on sensitivity and cost-effectiveness data. However, their cost analysis was based solely on computer modeling using a hypothetical cohort of patients in SR with first stroke and not actual patient data.47,48 A subsequent cost analysis that also used computer modeling but used different statistical parameters concluded that evidence did not support the widespread use of echocardiography in stroke patients.49 A more systematic analysis of the cost-efficiency based on data obtained from real patients is needed.

Future Research
Defining the optimal treatment strategies for each potential cardiac SOE will help delineate the role of echocardiography in the workup of stroke. The results of ongoing trials to evaluate the optimal treatment of PFO (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment – RESPECT, Evaluation of the STARflex Septal Closure System in Patients with a Stroke or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a PFO - CLOSURE 1, and the Patent Foramen Ovale and Cryptogenic Stroke – PC-Trial), congestive heart failure with ejection fraction <35% (Warfarin-Aspirin Reduced Cardiac Ejection Fraction Study – WARCEF) and aortic arch disease (Aortic Arch Related Cerebral Hazard – ARCH) will enhance our understanding of the best therapeutic approaches to these disorders and the impact of TTE and TEE on patient management.

Conclusion
We propose the following systematic approach to the performance of cardiac testing in stroke patients that balances diagnostic and therapeutic yield as well as cost-efficiency (see Figure). A cardiovascular history and examination, ECG, CXR, and 24-hour telemetry should be performed in all patients to identify those with clinical evidence of heart disease, and imaging of the brain and intracranial and extracranial cerebrovasculature should be analyzed to determine a putative mechanism of stroke. Patients who are found to already have indications or contraindications for OAC and no other reason to perform an echocardiography or extended rhythm monitoring should forgo these studies. Patients with no clinical evidence of heart disease or imaging that suggests cardiac SOE should have a TTE followed by TEE if nondiagnostic. In these patients, if TEE was unrevealing and no arrhythmias were detected during hospitalization, extended outpatient rhythm monitoring should be considered. In patients in whom a SOE has a low detection rate on TTE, such as young patients in whom a cardiac tumor or PFO may be relevant or a patient with no cardiac history and a cryptogenic stroke, it may be more cost-effective to proceed directly to TEE, as TTE has a very low yield in these patients. Given the limitations of the data presented, this suggested approach is based on expert opinion and prospective data are needed to test its validity.
Disclosures

None.

References


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