Temporal electrical heterogeneity for detecting coronary artery disease: results in a heterogeneous cardiac population

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■ **BACKGROUND** A new 22-lead electrocardiographic test has been advocated as a screening tool for coronary artery disease and has been shown to have accuracy similar to stress elctrocardiography in specific patient populations.

■ **OBJECTIVE** To determine the accuracy of this test for detecting coronary artery disease in patients undergoing coronary angiography for a variety of cardiac conditions.

■ **METHODS** We prospectively determined the temporal electrical heterogeneity (TEH) index at rest in 70 patients who had no angina or Q waves on the resting 12-lead electrocardiogram before they underwent coronary angiography.

■ **RESULTS** Twenty-six of the 70 patients had significant coronary artery disease, defined as 70% stenosis or greater in at least one major epicardial coronary artery. A TEH index of 80 or more had a sensitivity of 58%, a specificity of 75%, and a positive predictive value of 58%. The group with significant coronary disease had a mean TEH index of 77.2, and the group without coronary disease had a mean index of 65.5 ($P = .02$), despite similar clinical characteristics and indications for angiography.

■ **CONCLUSION** The TEH index shows promise as a screening tool for coronary artery disease in a heterogeneous cardiac population. However, larger studies are needed before it can be endorsed for widespread clinical use.

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SILENT CORONARY artery disease is a frequent cause of premature death in the United States. Sudden death is the first and only manifestation of disease in 18% of patients with this problem.[1] Because coronary artery disease is unpredictable, physicians use a variety of invasive and noninvasive tests and clinical profiles to screen for it. Both cross-sectional[2] and longitudinal[3] studies have shown that electrocardiographic (ECG) testing during exercise to detect asymptomatic coronary artery disease has a high rate of false-positive and false-negative results. Angiographic studies typically reveal that only approximately 20% of asymptomatic patients with positive stress ECG results have clinically significant coronary disease.[2–4] This low positive predictive value limits the usefulness of the stress test to screen asymptomatic patients. Because of these limitations, current guidelines for periodic screening do not recommend exercise testing to screen healthy adults.[5–8]

A 22-lead ECG system has been developed that measures electrophysiologic changes in myocardium that may be associated with clinically significant coronary dis-

ease. Focal delay in the rate of action potential propagation is thought to result in areas with deviations in myocardial conduction velocity, which this system can detect. The degree of these deviations is reported as a nondimensional index between 0 and 150 (temporal electrical heterogeneity [TEH] index), representing altered microdepolarization velocity derived from beat-to-beat changes in Fourier amplitude. The technique is called variance electrocardiography or variance analysis.

TABLE 1
INDICATIONS FOR ANGIOGRAPHY IN PATIENTS WITH OR WITHOUT CORONARY ARTERY DISEASE

	Patients with coronary artery disease, n = 26	Patients without coronary artery disease, n = 44
Nondiagnostic exercise tolerance test	10 (38%)	15 (34%)
Cardiomyopathy	1 (4%)	4 (9%)
Valve disease	6 (23%)	16 (36%)
Peripheral vascular disease	11 (42%)	6 (14%)

Several studies in selected patients undergoing arteriography have found that the sensitivity of the TEH index for detecting significant coronary disease ranges from 70% to 79%, its specificity ranges from 76% to 88%, and its positive predictive value ranges from 55% to 91%.[9,10] Variance electrocardiography has advantages over the standard stress test in that it is performed with the patient at rest. This obviates the need for a physician to be in attendance and removes the minuscule but real risk[11,12] of myocardial instability in the face of physical exercise. Both these advantages might make the test useful in patients with potential coronary disease and especially applicable to patients who cannot adequately exercise.

We undertook this prospective study to assess the accuracy of the TEH index in a group of patients without angina who were undergoing coronary arteriography for a variety of indications.

METHODS

Patient selection

Patients scheduled for coronary angiography at The Cleveland Clinic Foundation from November 1, 1990 to January 5, 1991 were screened for inclusion in the study. Patients with known coronary artery disease, typical angina pectoris, a Q-wave infarction on the 12-lead electrocardiogram, or a rhythm other than normal sinus were excluded. A total of 76 patients qualified, and 74 agreed to participate.

We obtained data for all 74 patients regarding (1) coronary risk factors such as age, sex, hypertension, smoking, hypercholesterolemia, and family history; (2) ECG evidence of ventricular hypertrophy using Estes-Romhilt criteria; and (3) indications for angiography.

Electrocardiographic data

We used a prototype variance cardiograph (Vital Heart Systems, Inc, Beverly, Mass) to analyze temporal electrical heterogeneity. The system uses 22 discrete skin electrodes, each having a solid-state current-limiting circuit for patient protection. An active noise-cancellation technique minimizes line noise and other interference. Ten of the leads are the same as in standard 12-lead electrocardiography, and additional unipolar leads are distributed at specific locations on the anterior and posterior thorax.

Preprocessing consists of low-pass filtering (0.05 Hz to 1500 Hz), voltage amplification (1000×), and digitization (4 kHz). A total of 220 preprocessed QRS complexes per lead are acquired and stored in random-access memory. All cardiac cycles are acquired in two equal sampling periods while the patient is at rest. All cycles are digitized using a 16-bit analog-to-digital converter.

A computer system collects all ECG data using both analog and digital filters to remove baseline wander and noise artifact. The computer program establishes a template of a normal sinus-rhythm cardiac cycle to screen ectopic activity and extraneous noise. Each ectopic beat and subsequent cardiac cycle is removed from the analysis to construct the template; uncharacteristic beats are rejected during acquisition using criteria based on baseline noise, RR interval and QRS duration. The resultant signals are then stored on a hard disk or on magnetic tape.

The program analyzes data from normal cardiac cycles only. Each accepted beat is compared with the template, and the square of the difference between the two (representing temporal heterogeneity) is calculated over the entire PT cycle. The aver-

TABLE 2
RISK FACTOR PROFILE IN PATIENTS WITH AND WITHOUT CORONARY ARTERY DISEASE

	Patients with coronary artery disease, n = 26*	Patients without coronary artery disease, n = 44†
Tobacco use	5 (19%)	8 (18%)
Hypertension	9 (35%)	18 (41%)
Diabetes mellitus	2 (8%)	5 (11%)
Hypercholesterolemia	10 (38%)	17 (39%)

*Mean age, 67.3 years
†Mean age, 65.2 years

age difference is calculated for all accepted beats recorded by each lead. The difference curve is normalized with respect to QRS amplitude, and the integrated area under the curve is calculated. The area associated with each of the 22 leads is termed a "difference score." The ensemble of 22 individual difference scores is then converted into an "ischemic" or TEH index (ranging arbitrarily from 0 to 150) using a multivariate regression equation derived from previous empirical data. Healthy subjects tend to have indices below 70, and patients with coronary artery disease tend to have indices over 90.[13] We considered an index of 80 or greater as abnormal or "positive" based on earlier data.

Coronary angiography

All patients subsequently underwent coronary angiography by either the brachial or femoral route. Views were obtained in standard left and right oblique projections using 5-inch amplification. Two angiographers reviewed the angiograms qualitatively. Stenoses of 70% or larger in at least one major coronary artery were considered significant or positive for coronary artery disease.

RESULTS

Seventy-six potential patients were identified. Two refused to participate, and four had inadequate studies due to ventricular ectopy in three and intermittent pacing in one. Therefore, the study population comprised 70 patients. Twenty-six patients were found to have significant coronary artery disease at catheterization. The catheterizations were done for a variety of reasons, making this a nonhomogeneous population (*Table 1*). There were no significant differences between patients with and without coronary artery disease except for a higher prevalence of peripheral artery disease in patients with coronary atherosclerosis (*Table 2*).

A TEH index of 80 or higher had a sensitivity of 58% (15 of 26), a specificity of 75% (33 of 44), and a positive predictive value of 58% for detecting coronary artery disease. The overall diagnostic accuracy was 69%. The group of patients with coronary disease had a significantly higher mean TEH index than the patients without coronary disease, 77.2 vs 64.5 ($P = .02$).

Forty patients also underwent stress ECG testing. Eight tests were not diagnostic, for a variety of reasons. Of the 32 patients with diagnostic tests, 15 had coronary artery disease. The sensitivity of the stress ECG test in these 32 patients was 87%, the specificity was 47% and the positive predictive value was 59%. Combining the results of the stress ECG test and TEH index in these 32 patients gave an overall sensitivity of 100%, a specificity of 35% and a positive predictive value of 58%. In the 32 patients in whom both tests were done, results were concordantly positive in seven with one false-positive error, concordantly negative in six with no errors, and discordant in 19, stress ECG being in error in 10 and the TEH index being in error in nine.

DISCUSSION

Several studies in selected patient populations have shown reasonable accuracy for variance electrocardiography. Deedwania and Gnawed[10] prospectively tested 65 patients with documented coronary artery disease and 21 normal volunteers. They found that the sensitivity of the TEH index was 79%, its specificity was 76%, its positive predictive value was 91%, and its overall clinical accuracy was 78% in predicting coronary artery disease. Tschida and Gobel[9] retrospectively tested the technique in 181 patients with angiographically documented coronary artery disease and 237 age- and gender-matched low-risk controls. The group with coronary artery disease had a mean TEH index of 90.7, compared with 57.4 in the control group ($P < .001$). The overall sensitivity was 77.3%, the specificity was 88.2%, and the overall clinical accuracy was 83.5%.

Kroll and Anderson[14] screened 404 asymptomatic police officers and compared temporal heterogeneity with standard stress ECG testing that used the Bruce protocol. Subjects who had abnormal results on either test underwent single-photon computed tomography thallium imaging, which was used for "definitive" diagnosis. Of the 404 tested, 23 had abnormal TEH indices and 42 had abnormal stress ECG results. Two subjects had abnormal results on both tests. Of 23 thallium tests performed because of positive 22-lead ECG results, eight were positive and 15 were negative, giving the TEH index a positive predictive value of 34.8%. Of 42 thallium tests performed because of abnormal stress ECG results, 10 were positive and 32 were negative, giving stress ECG testing a positive predictive value of 23.8%. The rate of false-positive tests was significantly lower for the 22-lead ECG test (3.7%) than for the stress ECG test (7.9%) ($P < .005$).

Justis and Hession[15] compared the sensitivity of the TEH index with that of standard 12-lead electrocardiography for diagnosing coronary artery disease in 188 patients presenting to the emergency room with acute chest pain. Forty-one of these patients were subsequently found to have an infarct based on creatine phosphokinase isoenzyme values. The sensitivity of the TEH index was 78%, and the sensitivity of the 12-lead ECG test was 51.2% ($P < .005$). The investigators concluded that the TEH index provided emergency-room physicians with a more sensitive tool for diagnosing coronary artery disease than 12-lead ECG and clinical factors and could potentially increase the number of patients appropriately admitted or referred for early diagnostic studies and intervention. Variance electrocardiography has not been previously evaluated in cardiac patients referred to a tertiary referral center. This group frequently has concomitant noncoronary heart disease such as valvular disease, cardiomyopathy, and hypertensive heart disease and typically has a high rate of false-positive or nondiagnostic exercise stress tests. Although the number of patients in our study is relatively small, the test results do predict coronary disease with an accuracy at least as good as the standard stress ECG test.

SUMMARY

This study demonstrates that this high-fidelity 22-lead ECG system may help detect coronary artery disease in a heterogeneous cardiac population. Variance electrocardiography appears to have predictive value similar to standard exercise stress testing and has the advantage of being a resting test. As refinements in this technique evolve, its clinical value may continue to increase. Larger studies and cost-effectiveness analyses of this new technique are needed before it can be endorsed for widespread use in detecting coronary artery disease.

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