Predictive Value of Resting Electrocardiograms for 12-Year Incidence of Stroke in the Honolulu Heart Program

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The importance of electrocardiographic (ECG) abnormalities at baseline examination for subsequent risk of stroke was analyzed in a 12-year follow-up of 7,560 men in the Honolulu Heart Program, aged 45-68 years, who were free of coronary heart disease and stroke at baseline. Age-adjusted univariate analysis showed that men with major ST depression, left ventricular strain, left ventricular hypertrophy, major T wave inversion, and overall major ECG abnormalities had considerably higher (2.5-5.4 times) incidence rates of both thromboembolic and hemorrhagic stroke than those with normal baseline ECG. When blood pressure, age, cigarette smoking, alcohol consumption, fat intake, serum glucose concentration, serum uric acid concentration, years of education, and years lived in Japan were taken into consideration through multivariate analysis, the ECG abnormalities retained a significant relation with stroke. Our study demonstrates that resting ECG abnormalities are independent predictors of both thromboembolic and hemorrhagic stroke. (Stroke 1988;19:555–559)

Stroke is a major health problem in the developed countries, although the incidence has decreased during recent decades. Hypertension is generally regarded as the single most important risk factor for stroke, but cardiac disease, generalized atherosclerosis, impaired glucose tolerance, alcohol consumption, cigarette smoking, obesity, and hematocrit have also been reported to be associated with stroke.1-4

Our present study was conducted to analyze the association of baseline electrocardiographic (ECG) abnormalities with the 12-year incidence of stroke in a cohort of Japanese-American men living in Hawaii, after excluding those with prevalent stroke at baseline and those with coronary heart disease (CHD) before or concomitant with their stroke.

Subjects and Methods

The general design and methodology of the Honolulu Heart Program has been described in detail.7-12 Briefly, it is a prospective epidemiologic investigation of CHD in a cohort of Japanese-American men living in Hawaii, after excluding those with prevalent stroke at baseline and those with coronary heart disease (CHD) before or concomitant with their stroke.

During the second and third examinations, all men with histories or physical findings suggesting cerebrovascular disease were referred to a neurologist for type-specific diagnosis of stroke, with varying degrees of diagnostic certainty according to preset criteria.13 In addition, suspected stroke cases among hospitalized Japanese men in the appropriate birth cohort were reviewed by the same neurologist for a specific diagnosis. Definite stroke was diagnosed in cases with relatively sudden onset of a neurologic deficit lasting at least 2 weeks (or until death) with or without the presence of blood in the cerebrospinal fluid. The findings of computed tomography (CT scan) were not included in the diagnostic criteria since this diagnostic tool has become available only recently in Hawaii. The exclusion criteria comprised cases with stroke-like episodes attributable to other disease processes such as blood dyscrasias, neoplastic diseases, head injuries, surgical complications, meningitis, epilepsy, or cardiac arrest. For each death, the underlying, immediate, and contributory causes of death were determined by a panel of physicians on the...
basis of all available information including hospital records, autopsy reports, and death certificates.11

The initial examination included demographic, sociocultural, and medical history. Inquiries were made regarding dietary intake (24-hour recall), smoking, drinking, and physical activity. Anthropometric measurements, physical examination focusing on the cardiovascular system, urine analysis, lung function test, blood chemistry (including serum cholesterol, triglyceride, uric acid, and glucose concentrations), hematocrit, and a resting 13-lead (including V9) ECG were performed. The average of three determinations of blood pressure in the sitting position was used for analysis.

Copies of ECGs were sent to the University of Minnesota, where ECG findings were classified according to the Minnesota Code and divided into major and minor abnormalities according to the criteria used by the Pooling Project and the three Chicago epidemiologic studies.14,15 Major abnormalities include major ST depression (Minnesota Code 4.1, 4.2), major T wave inversion (5.1, 5.2), complete atrioventricular (A-V) block (6.1), second-degree A-V block (6.2), complete left bundle branch block (LBBB) (7.1), complete right BBB (RBBB) (7.2), unclassified intraventricular block (7.4), frequent premature beats (8.1), and atrial flutter/fibrillation (8.3). Minor abnormalities include borderline Q wave (1.3), minor ST depression (4.3), minor T wave inversion (5.3), first-degree A-V block (6.3), high left R wave (3.1), high right R wave (3.2), left axis deviation (LAD) (2.1), and right axis deviation (2.2).

ECGs were also independently read by the Honolulu Heart Program physicians, and modified criteria9 were used for left ventricular hypertrophy (LVH) and left ventricular strain (LVS), which are not specifically defined in the Minnesota Code but have been commonly used clinically. The criteria for LVH include QRS high voltage accompanied by either ST depression or T wave inversion; those for LVS include coexistence of ST depression and T wave inversion in the left precordial leads without QRS high voltage.

Statistical Analysis

In the univariate analysis, age-adjusted 12-year incidence rates of total stroke, as well as of thromboembolic and hemorrhagic stroke separately, were calculated for the following categories of baseline ECG abnormalities: major abnormalities, minor abnormalities, high left R wave, major ST depression, major T wave inversion, sinus tachycardia, LAD, LVH, LVS, minor ST depression, minor T wave inversion, complete RBBB, and premature beats. In addition, incidence rates were calculated for those with all other codable ECG abnormalities, as well as for those with completely normal ECGs. Other specific ECG abnormality categories did not contain sufficient numbers of men to calculate incidence rates.

Using the Mantel-Haenszel χ2 test,17 the age-adjusted incidence rates of total stroke, as well as of types of stroke, for men with individual ECG abnormalities were compared with those for men without that specific ECG abnormality, men with normal ECG, and men with all other codable abnormalities.

In the multivariate analysis, independent contributions of ECG abnormalities to the development of stroke were examined taking into account possible confounding effects of other risk factors for stroke. Such risk factors were selected on the basis of significant correlations (p < 0.05) with incident cases of stroke. Nine variables were significantly correlated with total stroke: systolic and diastolic blood pressure, age at baseline exam, serum glucose concentration, serum uric acid concentration, cigarette smoking, alcohol consumption, fat intake, years of education, and years lived in Japan. All except uric acid concentration were also correlated with thromboembolic stroke, while five (blood pressure, age, cigarette smoking, alcohol consumption, and uric acid concentration) were correlated with hemorrhagic stroke. These risk factors were used as covariates in the multivariate analysis using a logistic model with an iterative likelihood method,18 in which each ECG abnormality that was significantly related to stroke in the univariate analysis was examined for its independent role in the prediction of stroke. In the multivariate analysis, only the ECG abnormalities that contained at least 15 cases of stroke were analyzed. Thus, for total stroke, major abnormalities, high R wave, major ST depression, major T wave inversion, sinus tachycardia, and pooled LVH and LVS (LVH-LVS) were entered into the model, one at a time, with the nine covariates. LVH and LVS were pooled to obtain a sufficient number of stroke cases. For thromboembolic stroke, all these abnormalities except high R wave were analyzed. For hemorrhagic stroke, only major ECG abnormalities contained a sufficient number of stroke cases (n = 10) to permit multivariate analysis.

Results

Table 1 presents the number and percentage of men with each ECG abnormality or group of abnormalities by the Minnesota Code and other criteria. Based on the Minnesota Code, only one third of the men (n = 2,722) had completely normal baseline ECGs. Almost one half (n = 3,683) of the abnormalities were classified as neither major nor minor by the Pooling Project criteria and are termed other codable items. Table 1 also shows the 12-year, age-adjusted total stroke incidence according to selected baseline ECG abnormalities. During the follow-up period, 4.2% (n = 320) of the men at risk developed stroke. These included 69 cases of hemorrhagic stroke and 224 cases of thromboembolic stroke, while 27 cases were classified as unspecified stroke. A significant association was found between baseline major ST depression, major T wave inversion, LVH, LVS, high R wave, sinus tachycardia, and major ECG abnormalities and subsequent development of total stroke, with relative risk ranging from 1.6 to 5.4 (Table 2). Similar patterns were noted for thromboembolic and hemorrhagic strokes (Table 2). However, minor ST depression,
TABLE 1. Age-Adjusted 12-Year Stroke Incidence by ECG Abnormalities Classified According to Minnesota Code, Honolulu Heart Program

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency of abnormality</th>
<th>Total stroke incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Major abnormalities</td>
<td>7,145</td>
<td>275</td>
</tr>
<tr>
<td>Minor abnormalities</td>
<td>6,800</td>
<td>284</td>
</tr>
<tr>
<td>High left R wave (3.1)</td>
<td>7,162</td>
<td>292</td>
</tr>
<tr>
<td>SV depression</td>
<td>7,400</td>
<td>217.7</td>
</tr>
<tr>
<td>Minor T wave inversion</td>
<td>7,512</td>
<td>317</td>
</tr>
<tr>
<td>Right bundle branch block (7.2)</td>
<td>7,439</td>
<td>313</td>
</tr>
<tr>
<td>Premature beats (8.1)</td>
<td>7,502</td>
<td>315</td>
</tr>
<tr>
<td>Sinus tachycardia (8.7)</td>
<td>7,248</td>
<td>296</td>
</tr>
<tr>
<td>LVH-LVS</td>
<td>7,513</td>
<td>311</td>
</tr>
<tr>
<td>LVH-LVS</td>
<td>7,497</td>
<td>307</td>
</tr>
<tr>
<td>Left axis deviation (2.1)</td>
<td>7,273</td>
<td>306</td>
</tr>
<tr>
<td>Other codable items</td>
<td>3,877</td>
<td>168</td>
</tr>
<tr>
<td>Normal</td>
<td>4,838</td>
<td>233</td>
</tr>
<tr>
<td>Abnormal</td>
<td>2,722</td>
<td>360</td>
</tr>
<tr>
<td>Total</td>
<td>7,560</td>
<td>320</td>
</tr>
</tbody>
</table>

*p<0.05, †p<0.01, ‡p<0.001; significantly different from those without specific abnormality. NS, no significant difference.

minor T wave inversion, RBBB, LAD, premature beats, and overall minor abnormalities had no significant association with any type of stroke.

One or more major abnormalities were found in 5.5% (n = 415) of the participants, and among these, 29.2% (n = 121) had complete RBBB with no other major abnormalities. RBBB did not show any significantly increased risk for later development of stroke in this population, and after excluding RBBB from the major abnormalities the 12-year incidence rate increased from 97.4 per 1,000 to 129.3 per 1,000.

In our study, 32 men were excluded because they developed CHD before they suffered a first stroke. Exclusion of these cases from the analysis made no difference in the relative risk of stroke for any of the various ECG abnormalities studied.

When comparing stroke incidence rates among men with individual ECG abnormalities with those among men with normal ECG at baseline, the significance levels tended to increase, in some instances considerably. For example, minor abnormalities and sinus tachycardia became highly significant (p<0.001), while high R wave reached the p<0.01 level. The significance levels remained unchanged when comparing with men who had other codable ECG abnormalities at baseline.

Table 3 presents logistic coefficients (β) for ECG abnormalities that were significantly associated with total stroke in the multivariate analysis taking into account the nine covariates. The significance of each β was tested by dividing it by its standard error and relating this statistic (Z value) to a table of standard normal deviates using the two-tailed significance level.

Among the ECG abnormalities examined in the multivariate analysis, major ST depression, major T wave inversion, LVH-LVS, and major ECG abnormalities remained as independent and significant predictors of total and thromboembolic stroke. For hem-
Discussion

In our present study we found that ECG abnormalities commonly associated with hypertension, such as high R wave and LVH-LVS, were significant predictors of stroke, even after taking into account other risk factors. Furthermore, ECG abnormalities commonly associated with myocardial ischemia, such as ST depression and T wave inversion, were also found to be independent predictors of stroke. Relative risks of these ECG abnormalities were about the same for thromboembolic and hemorrhagic stroke, except for high R wave, which was associated only with hemorrhagic stroke. ECG abnormalities that were not significantly related to stroke in our study included minor ST-T changes, premature beats, LAD, and RBBB.

Among the hypertensive ECG abnormalities, LVH and LVS consistently have been found to increase the risk of stroke as well as of CHD. Kannel et al found that CHD almost tripled the risk of stroke and that cardiac failure was associated with a more than fivefold increased risk among both men and women in Framingham. Mettinger et al reported that a significantly higher proportion of stroke cases had overt ischemic heart disease before their stroke than controls. In a case-control study, Herman et al found that acute myocardial infarction was an independent risk factor for stroke. According to Kagan, 40% of all stroke decedents had a myocardial scar. Toole et al reported that myocardial infarction predisposed to stroke and was at the same time the most frequent cause of death in stroke victims. In a postmortem study based on the Honolulu Heart Program cohort, Stemerman et al also found that men with cerebral infarcts showed higher grades of atherosclerosis of the coronary arteries and aorta than men without cerebral infarcts.

Atrial fibrillation, Q waves, and A-V block have also been reported to be associated with increased risk for subsequent stroke. We were not able to investigate this due to the small number of men with these abnormalities.

In conclusion, we have found a strong relation between baseline ECG abnormalities and risk of stroke. This association is most likely due to hypertension in combination with atherosclerosis and to a lesser extent with other common risk factors for CHD and stroke. The clinical implications of our findings are several. They confirm that hypertension and hypertensive ECG findings are important risk factors for stroke. Further, for patients with ischemic ECG findings, physicians should pay attention not only to the control of risk factors for CHD, but also to preventive measures for stroke. Such measures include close monitoring and treatment of hypertension and control.
of other stroke risk factors such as cigarette smoking, alcohol consumption, and glucose intolerance.

References


Key Words: Asian Americans • cerebrovascular disorders • electrocardiography • epidemiology • risk factors
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