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, general 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.5–12 Briefly, it is a prospective epidemiologic investigation of CHD and stroke among men of Japanese ancestry who were born in the years 1900–1919 and lived on the Hawaiian island of Oahu in 1965.

In the initial examination, carried out during 1965–1968, 8,006 eligible men aged 45–68 years participated. In our present analysis, those with prevalent CHD and/or stroke at baseline were excluded, as well as those who, during follow-up, developed CHD before their stroke. Our present study was based on 320 new cases of stroke identified during the 12-year follow-up of 7,560 men at risk. Of these, 224 strokes were thromboembolic, 69 strokes were hemorrhagic, and 27 were unspecified stroke.

New cases of stroke were ascertained by repeat examinations carried out 2 and 6 years after the initial examination, as well as by a continuous community surveillance of morbidity and mortality through periodic review of hospital discharge rosters, death certificates, and obituary columns of local newspapers.12 Nearly complete follow-up for mortality was achieved by this surveillance system. The data on nonfatal stroke also are very reliable because medical practice in Honolulu is such that virtually all patients with suspected stroke are hospitalized.

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, meningocerebralitis, fat embolism, 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 Code14 and divided into major and minor abnormalities according to the criteria used by the Pooling Project and the three Chicago epidemiologic studies.15,16 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 criteria17 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 \( \chi^2 \) 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 either 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>6,820</td>
<td>284</td>
</tr>
<tr>
<td>High left R wave (3.1)</td>
<td>7,162</td>
<td>292</td>
</tr>
<tr>
<td>ST depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major (4.1, 4.2)</td>
<td>7,465</td>
<td>296</td>
</tr>
<tr>
<td>Minor (4.3)</td>
<td>7,512</td>
<td>317</td>
</tr>
<tr>
<td>T wave inversion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major (5.1, 5.2)</td>
<td>7,394</td>
<td>295</td>
</tr>
<tr>
<td>Minor (5.3)</td>
<td>7,472</td>
<td>313</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>Left ventricular hypertrophy</td>
<td>7,513</td>
<td>311</td>
</tr>
<tr>
<td>Left ventricular strain</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>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.

TABLE 2. Relative Risks of Stroke for Men With Selected Baseline ECG Abnormalities Compared With Those Without Specific Abnormality, Honolulu Heart Program

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Total stroke</th>
<th>Thromboembolic</th>
<th>Hemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major ST depression</td>
<td>5.4 (3.3-9.1)</td>
<td>5.4 (3.0-9.8)</td>
<td>5.6 (2.2-14.5)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>4.5 (2.4-8.7)</td>
<td>4.9 (2.4-10.3)</td>
<td>2.1 (0.3-16.3)</td>
</tr>
<tr>
<td>Left ventricular strain</td>
<td>4.2 (1.9-9.2)</td>
<td>4.1 (1.7-9.9)</td>
<td>5.0 (1.1-21.7)</td>
</tr>
<tr>
<td>Major T wave inversion</td>
<td>3.6 (2.3-5.7)</td>
<td>3.6 (2.1-6.1)</td>
<td>3.5 (1.4-8.9)</td>
</tr>
<tr>
<td>Major abnormality</td>
<td>2.5 (1.8-3.6)</td>
<td>2.3 (1.5-3.6)</td>
<td>2.8 (1.4-5.7)</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>1.9 (1.2-2.9)</td>
<td>1.8 (1.0-3.0)</td>
<td>1.4 (0.5-4.0)</td>
</tr>
<tr>
<td>High left R wave</td>
<td>1.6 (1.0-2.4)</td>
<td>1.2 (0.7-2.1)</td>
<td>2.7 (1.3-5.5)</td>
</tr>
</tbody>
</table>

95% confidence intervals are in parentheses.

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-
orrhagic stroke, in addition to major ECG abnormalities, high R wave remained as a significant predictor only when systolic blood pressure was not included as a covariate.

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 in the Framingham Study that when all five major CHD risk factors (systolic blood pressure, cholesterol, cigarette smoking, glucose intolerance, and ECG evidence of LVH) were considered jointly, they were as predictive of brain infarction as of myocardial infarction. Of these, blood pressure and ECG evidence of LVH were the strongest independent predictors, with a fivefold increased risk for stroke in men and a sixfold increase in women. In Japan, ECG evidence of LVH also increased the risk of stroke threefold to fivefold. In our present study, baseline LVH-LVS increased the risk of stroke more than fourfold, making it as predictive of stroke as of total CHD in this population.

This association was present even after adjusting for other risk factors such as blood pressure, serum glucose concentration, and cigarette smoking. Our finding that LVH-LVS was strongly associated with stroke, even after controlling for blood pressure, may indicate that LVH-LVS represents a more advanced or prolonged stage of hypertension.

The close relation between LVH-LVS and hypertension is further demonstrated through clinical studies among hypertensive subjects, which show that these ECG changes diminish or disappear when blood pressure is normalized using antihypertensive treatment.

High R wave, the other hypertensive ECG abnormality we investigated, has been found as a risk factor for stroke in Japan. In our study, the independent relation between high R wave and hemorrhagic stroke disappeared when we adjusted for hypertension but not when we adjusted for other risk factors, indicating that this ECG abnormality most likely is a marker of hypertension.

Our finding of a significant relation between ischemic ECG abnormalities and stroke agree well with the results of other studies. In Evans County, Georgia, in Japan, and in Sweden, depressed ST segments are associated with increased risk of stroke. In our study, major ST depression carried the highest relative risk among all ECG abnormalities for later development of total stroke (relative risk 5.4). This was, in fact, even greater than the relative risk of this abnormality for total CHD in this population.

Our findings of an increased risk of stroke for ischemic ECG abnormalities can be interpreted two ways. First, the ischemic ECG changes could be due to hypertension, which in turn causes LVH, and thereby causes increased myocardial tension and consequently increased myocardial oxygen demand. The imbalance between oxygen demand and blood supply results in myocardial ischemia. Alternatively, ischemic ECG abnormalities can be considered signs of coronary atherosclerosis and resultant myocardial ischemia. ECG abnormalities may also indicate a more generalized atherosclerosis that affects the cerebral arteries as well. Supporting the first view are findings that ST-T abnormalities in hypertensive subjects diminish when hypertension is controlled. This is explained as reversal of left ventricular wall thickening and thus decreased myocardial oxygen demand.

Supporting the second view are several clinical studies that have identified cardiac disorders as important risk factors for stroke. 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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