Heritability of Heart Rate Variability
The Framingham Heart Study

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Background—There is evolving evidence that heart rate (HR) is genetically determined. Heart rate variability (HRV) measured by power spectral analysis provides quantitative phenotypic markers of autonomic nervous system activity. Reported determinants of HR and HRV only partially explain their variability in the population. The purpose of this study was to assess the heritability of HR and HRV and estimate the contribution of genetic factors to their variance.

Methods and Results—Subjects who underwent ambulatory recordings at a routine examination were eligible; subjects with congestive heart failure, coronary artery disease, diabetes mellitus, and those taking cardioactive medications were excluded. We analyzed high-frequency power, low-frequency power, very low-frequency power, total power, low-frequency/high-frequency ratio, and the standard deviation of normal R-R intervals from 2-hour continuous ECG recordings. Heritability analysis was done by studying correlations between siblings (n=682, in 291 sibships, 517 pairs) and between spouse pairs (n=206 pairs) after adjusting for important covariates. Results from separate models were combined to estimate the components of variance attributable to measured covariates, additive genetic effects (heritability), and household effects. After adjusting for covariates, the correlations were consistently higher among siblings (0.21 to 0.26) compared with spouses (0.01 to 0.19). The measured covariates in general accounted for 13% to 40% of the total phenotypic variance, whereas genetic factors accounted for 13% to 23% of the variation among HR and HRV measures.

Conclusions—Heritable factors may explain a substantial proportion of the variance in HR and HRV. These results highlight the contribution of genetic versus environmental factors to autonomic nervous system activity. (Circulation. 1999;99:2251-2254.)

Key Words: heart rate • genetics • epidemiology

Recent evidence confirming the genetic determination of heart rate (HR) regulation1 suggests that genetic factors may also contribute to the beat-to-beat variability in heart rate. Heart rate variability (HRV) measured by power spectral analysis provides quantitative phenotypic markers of autonomic nervous system activity.2–4 The autonomic nervous system is of critical importance in the beat-to-beat regulation of the HR, blood pressure control, and overall stability of the cardiovascular system.5 Previous studies have shown a strong association between HR and both all-cause and cardiovascular mortality rates.6–8 Abnormalities of autonomic activity reflected by a reduced HRV are strongly associated with increased risk for cardiac events,9 sudden cardiac death10 and overall mortality.9–11 Earlier reports from Framingham and elsewhere12,13 have identified several determinants of HRV, which only partially explain the variance of HRV measures in the population.

The purpose of this study was to (1) assess the heritability of HR and HRV and (2) estimate the contribution of genetic factors to the variance in HR and measures of HRV. Recognition of the genetic determinants of HR and HRV may provide additional insight into the pathophysiology of the autonomic nervous system and offer clues toward its modulation.

Methods

Subjects
The Framingham Heart Study is a prospective epidemiological study established in 1948 to evaluate potential risk factors for coronary heart disease. The original cohort included 5209 men and women, 28 to 62 years of age. In 1971, 5124 additional subjects were entered into the Framingham Offspring Study. Study design and selection criteria have been published.14–16 Subjects for the present study were original Framingham Heart Study participants and Offspring Study subjects who had ambulatory

Received October 14, 1998; revision received January 25, 1999; accepted February 4, 1999.
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ECG recordings between 1983 and 1987 during a routine, scheduled examination at the Framingham Heart Study clinic. Subjects were excluded if they met any of the following criteria: (1) history or clinical evidence of myocardial infarction or congestive heart failure, (2) atrial fibrillation, (3) diabetes mellitus, (4) use of antihypertensive or cardioactive medication at the index examination, and (5) technically inadequate ambulatory ECG recordings. The diagnoses of myocardial infarction and congestive heart failure were established by a committee of 3 physicians who evaluated records from the Framingham Heart Study clinic examinations, interim hospitalizations, and visits to personal physicians in accordance with published criteria. Diabetes was defined as the use of insulin or an oral hypoglycemic agent or a fasting glucose level ≥140 mg/dL in the Offspring Study participants and a current or historic nonfasting oral hypoglycemic agent or fasting glucose level ≥140 mg/dL in the Cohort study participants. At the index examination, body height and weight measurements, medical history, physical examination, 12-lead resting and ambulatory ECG were routinely obtained.

Phenotypic (Heart Rate Variability) Assessments

The first 2 hours of ambulatory ECG recordings were processed for HRV. All ambulatory recordings included 2 channels of ECG information and were obtained on standard 4-track cassette tapes with the use of either a Cardiodata PR2 or PR3 pace recorder (Cardiodata Corp). The tape speed was 1 mm/s, and 1 channel was used to record a 32-Hz, crystal-controlled timing track. For analysis the tapes were played back at 120 times real time on the Cardiodata—ortara Mk5 Holter analysis system (Mortara Instrument Co), sampling each ECG channel at 180 samples/s. Beat-to-beat R-R interval data were obtained from the “beat stream file.” A linearly interpolated beat was substituted for intervals of ectopic beats or artifact less ≤2 R-R intervals. The fast Fourier transform was calculated on 100-second blocks of R-R interval data. A continuous curve was formed by linear interpolation between R-R intervals; this was subjected to a Hamming window and resampled at 1.28 times/s.

After excluding subjects with rhythm disturbances, technically inadequate recordings, antiarrhythmic drug use, congestive heart failure and coronary heart disease, diabetes, incomplete covariate data, and subjects with no eligible sibling or spouse, 1153 subjects were used for heritability analysis (Table 1). The clinical characteristics of the eligible subjects are presented separately for men and women in Table 2.

Results

Ambulatory ECG recordings were available on 3420 subjects. After excluding subjects with rhythm disturbances, technically inadequate recordings, antiarrhythmic drug use, congestive heart failure and coronary heart disease, diabetes, incomplete covariate data, and subjects with no eligible sibling or spouse, 1153 subjects were used for heritability analysis (Table 1). The clinical characteristics of the eligible subjects are presented separately for men and women in Table 2.

Correlations

The mean unadjusted, age-adjusted, and fully adjusted correlations are presented for sibling pairs and spouse pairs in Table 3 and Table 4, respectively. The correlation is a measure of the degree of similarity between subjects. Similarity in age and clinical variables among siblings and spouses inflated the similarity with respect to HRV; when these variables were accounted for, the correlations declined. After adjusting for covariates, the correlations were consistently higher among siblings (0.21 to 0.26) compared with spouses (0.01 to 0.19).

Statistical Analysis

The overall aim of the analysis was to determine the extent to which genes, measured environmental factors, and household factors contribute to variation in HR and 6 preselected measures of HRV (HF, LF, VLF, TP, LF/HF ratio, and 2-hour SDNN). Clinical covariates in the multivariate model included age, sex, body mass index, systolic and diastolic blood pressure, coffee and alcohol consumption, and cigarette smoking.

Three linear regression models were fitted for HR and each HRV variable, separately for men and women: (1) unadjusted, (2) age-adjusted, and (3) age- and covariate-adjusted. HRV variables were also adjusted for HR in the fully adjusted model. Residuals from each fitted model were used in subsequent analyses. To analyze genetic contributions to HRV, separate analyses on first-degree relatives (sibship members) and on unrelated subjects (spouse pairs) were undertaken. The SAS procedure MIXED was used to estimate and test significance of within sibships and within spouse-pair correlations. Results from separate models were combined to produce synthetic estimates of variance components.

<table>
<thead>
<tr>
<th>TABLE 1. Derivation of Study Sample</th>
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<tbody>
<tr>
<td>Subjects with ambulatory ECG data</td>
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<tr>
<td>Exclusions</td>
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<tr>
<td>Rhythm, artifact, antiarrhythmic use</td>
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<tr>
<td>Coronary heart disease or</td>
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<tr>
<td>congenestive heart failure</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Cardiac medications</td>
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<tr>
<td>Incomplete covariates</td>
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<tr>
<td>No spouse or sibling in study</td>
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<tr>
<td>Eligible study sample</td>
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<table>
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<tr>
<th>TABLE 2. Descriptive Data</th>
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<tr>
<td>Sibling</td>
</tr>
<tr>
<td>(n=682; 517 pairs)</td>
</tr>
<tr>
<td>Covariates</td>
</tr>
<tr>
<td>Men (n=331)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
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<tr>
<td>Coffee, cups/d</td>
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<tr>
<td>Smoker, %</td>
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<td>Alcohol, oz/wk</td>
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BMI indicates body mass index; SBP, systolic blood pressure; and DBP, diastolic blood pressure. Results are expressed as mean±SD or as percentages.
Components of Variance

Table 5 shows the components of variance for HR and the panel of HRV variables. The columns in the table represent the proportion of the overall phenotypic variance attributable to genetic factors, measured environmental factors (including sex and age), and household effects. For the HRV variables, genetic factors contributed to 13% to 23% of the overall phenotypic variance, whereas measured covariates contributed to 13% to 40%. The proportion of the total phenotypic variability of HRV measures due to household effects was smaller (1% to 13%). When the model included heart rate as a predictor of HRV, the variance in HRV attributable to genetic factors was diminished (9% to 22%).

Discussion

Our findings suggest that genetic factors contribute substantially to the variance in HR and HRV. We have simultaneously estimated the contribution of genes and a variety of epidemiological covariates to the phenotypic variability in the mean HR and HRV. To our knowledge, no previous study has sought to distinguish the effects of environmental and genetic factors on HR and HRV measures.

Power spectral analysis of HRV provides a measure of the state of sympathovagal balance modulating sinus node activity. It has been shown that power in the HF range is a quantitative marker of parasympathetic cardiac function; that the power in the LF range can be influenced by both sympathetic and parasympathetic activity; and the ratio of these 2 spectral power components is considered by some as the balance of sympathetic and parasympathetic activity. SDNN reflects all the cyclic components responsible for variability in the period of recording, whereas the physiological interpretation of VLF warrants further elucidation.

Contrary to earlier belief, the autonomic nervous system is not simply a noncognitive and automatic part of brain function, but the autonomic and central nervous system are intimately related. Recent observations of high heritability of brain function (75% to 90%) as assessed by rhythmic brain-electrical activity on electroencephalogram suggest that autonomic nervous system activity may also have a heritable component. Also, respiratory sinus arrhythmia, which is thought to be vagally mediated, has been observed to have a large heritable component. Recent animal data suggesting that the regulation of heart rate is genetically determined imply that genetic factors may contribute to the beat-to-beat variability in HR.

Components of Phenotypic Variance

The covariates, genetic effects (heritability), and household effects accounted for 37% to 61% of the total phenotype variability in most of the HRV measurements. The variance in heart rate due to the genetic effect accounted for a relatively larger proportion of the phenotypic variability (2- to 3-fold) than that of measured covariates. The reduction in the genetic variance of the HRV measures after inclusion of HR in the model could be explained by the possibility of HR and HRV sharing common genes. The further contribution of household effects toward accounting for variation in heart rate was marginal (8%). With the exception of LF/HF ratio, the contribution of genetic factors to the variance in HRV was lower than that caused by measured environmental covariates.

With the use of correlations as a measure of the degree of similarity between subjects, the correlations between spouse pairs enabled us to estimate the household effects from the data independent of additive genetic effects. Household effects are attributable to unmeasured nongenetic factors that are shared more closely by individuals living within the same household than by individuals living in different households. These corre-
lations between spouse pairs were adjusted for several clinical measures that can influence HRV, for example, age, sex, body mass index, systolic and diastolic blood pressure, coffee and alcohol consumption, and cigarette smoking.

After accounting for covariate, genetic, and household effects, the proportion of the variance that remains unexplained for most of the phenotypes in this study ranged from 40% to 64%. For many of the traits, some of this unexplained phenotypic variance can be attributed to the nonlinear effects of environmental risk factors on specific genotypes. Although such genotype-environment interaction effects may be difficult to detect, these interactions may nevertheless profoundly influence many of these phenotypes.

**Strengths and Limitations**

This is the first study to examine the heritability of HR and HRV. An important strength of this study is the well-characterized study sample through the many years of follow-up. This information allowed us to select subjects who were free of clinically apparent cardiovascular disease, which can alter autonomic function and HRV measurements.

This study was based on intermediate duration recordings, which yield different values for SDNN than shorter or longer recordings. The recordings were obtained when subjects underwent an extensive clinic evaluation and are not representative of basal resting conditions. Such activity can precipitate short-term changes in autonomic activity confounding the correlations, thereby biasing the results toward the null. Our findings of significant correlations among siblings despite unmeasurable environmental influences enhance the significance of our study. Also, our findings must be interpreted in light of the high correlations among the HRV phenotypes. In a secondary analysis, parent-offspring HRV correlations were observed to be lower than that observed among spouses; this analyses was limited in its power and biased by survival-effect among the parents.

It is likely that we have underestimated the effects of some environmental covariates. We did not account for the effect of physical activity, which has a conditioning effect on autonomic nervous system activity. The likely effect of these shortcomings would be to underattribute variance to the measured environmental factors and overattribute variance to the unmeasured (residual) environmental factors. In addition, there may be important environmental determinants of autonomic activity that we have not measured. The sample enrolled in the Framingham Heart Study was predominantly white, and it is possible that results from the present study may not apply to other ethnic and racial groups.

**Clinical Implications**

Hereditability may explain a substantial proportion of the variance in heart rate and HRV. Studies are currently underway to identify genetic loci associated with these markers of autonomic activity. This knowledge will provide additional insight into the pathophysiology of the autonomic nervous system and offer clues toward its modulation. Further studies in this direction will lead to a better understanding of the complex interplay of heritable and environmental factors affecting autonomic activity.

**References**


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Circulation. 1999;99:2251-2254
doi: 10.1161/01.CIR.99.17.2251

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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