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Cardiac Autonomic Function and Incident Coronary Heart Disease: A Population-based Case-Cohort Study

The ARIC Study

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Cardiac autonomic activity, as assessed by heart rate variability, has been found to be associated with postmyocardial infarction mortality, sudden death, and all-cause mortality. However, the association of heart rate variability and the incidence of coronary heart disease (CHD) is not well described. The authors report on the association of baseline cardiac autonomic activity (1987–1989) with incident CHD after 3 years (1990–1992) of follow-up of the Atherosclerosis Risk in Communities Study cohort selected from four study centers in the United States by using a case-cohort design. The authors examined 137 incident cases of CHD and a stratified random sample of 2,252 examinees free of CHD at baseline. Baseline, supine, resting beat-to-beat heart rate data were collected. High- (0.16–0.35 Hz) and low- (0.025–0.15 Hz) frequency spectral powers and high-/low-frequency power ratio, estimated from spectral analysis, and standard deviation of all normal R-R intervals, calculated from time domain analysis, were used as the conventional indices of cardiac parasympathetic, sympatho-parasympathetic, and their balance, respectively. Incident CHD was defined as hospitalized myocardial infarction, fatal CHD, or cardiac revascularization procedures during 3 years of follow-up. The age, race, gender, and other CHD risk factor-adjusted relative risks (and 95% confidence intervals) of incident CHD comparing the lowest quartile with the upper three quartiles of high-frequency power, low-frequency power, high-/low-frequency power ratio, and standard deviation of R-R intervals were 1.72 (95% confidence interval (CI) 1.17–2.51), 1.09 (95% CI 0.72–1.64), 1.25 (95% CI 0.84–1.86), and 1.39 (95% CI 0.94–2.04), respectively. The findings from this population-based, prospective study suggest that altered cardiac autonomic activity, especially lower parasympathetic activity, is associated with the risk of developing CHD. *Am J Epidemiol* 1997;145:696–706.

autonomic nervous system; coronary disease; heart rate; risk factors

In recent years, analysis of beat-to-beat heart rate variability (HRV) has emerged as one of the noninvasive methods to assess cardiac autonomic activity quantitatively. As a result of the interaction between sympathetic and parasympathetic activity, beat-to-beat heart rate shows periodicities over time. These periodicities can be identified through spectral analysis whereby the observed heart rate is expressed mathematically by a function of time as the sum of a series of sine and cosine functions of varying amplitudes and frequencies (frequency domain analysis). Previous work has shown that cycles with a frequency of 0.025–0.15 Hz (called low-frequency component (or power) of HRV) are under the influence of both the sympathetic and parasympathetic nervous systems. Cycles with a frequency of 0.16–0.35 Hz (called high-frequency component (or power) of HRV) are under the influence of the parasympathetic system only and have been regarded as a marker of cardiac parasympathetic activity (1–9). Alternative techniques to estimate HRV from the summary statistics of beat-to-beat heart rate data have also been used extensively (time domain analysis) (8).

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CI, confidence interval; ECG, electrocardiogram; HDL cholesterol, high density lipoprotein cholesterol; HRV, heart rate variability; LDL cholesterol, low density lipoprotein cholesterol.

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Several clinically based studies have found that survivors of acute myocardial infarction who had a lower HRV had higher risk of all-cause mortality post-myocardial infarction compared with survivors with higher HRV (10) and that long-term survivors of acute myocardial infarction had significantly higher mean values of HRV compared with those who died during follow-up (11–13). Lower HRV has also been found to be related to sudden cardiac death (14). In the Framingham Study, it was found that both the time and frequency domains of HRV were inversely associated with the risk of all-cause mortality (15). Although biologically plausible and previously documented in postmyocardial infarction survivors, the hypothesis that reduced HRV is associated with increased risk of coronary heart disease (CHD) has not been tested at the population level, nor have data been available to investigate the temporal association of cardiac autonomic activity and the development of CHD. Therefore, this study is designed to test the hypothesis that cardiac autonomic activity is related to the development of incident CHD at the population level. Specifically, we hypothesized that a lower heart rate variability estimated from both frequency and time domain methods is associated with an increased risk of developing nonfatal and fatal ischemic heart disease manifestations.

MATERIALS AND METHODS

A case-cohort approach was used, based on the principles described by Prentice (16). The population for this study consisted of all cases of incident CHD and a stratified random sample of the cohort, drawn from the individuals who participated in the baseline examination of the Atherosclerosis Risk in Communities (ARIC) Study, which is a longitudinal study of cardiovascular and pulmonary diseases sponsored by the National Heart, Lung, and Blood Institute. It includes community surveillance and cohort components. The ARIC cohort was selected as a probability sample of 15,800 men and women between ages 45 and 64 years at four study centers in the United States, three of which enumerated and enrolled all age-eligible residents sampled from geographically defined areas (Washington County, Maryland; Forsyth County, North Carolina; and selected suburbs of Minneapolis, Minnesota). The fourth quarter of the ARIC cohort was sampled from black residents of Jackson, Mississippi. Details of sampling, study design, and cohort examination procedures have been published elsewhere (17). Eligible participants were interviewed at home and then invited to a baseline clinical examination. The baseline examination of the ARIC cohort was conducted in 1987–1989. Three years after the baseline examination, all participants were invited to a follow-up clinical examination, which was conducted in 1990–1992. The overall cohort follow-up rate has been better than 98 percent from the inception of the ARIC Study to the end of 1992.

Sampling of the cohort

The cohort for this study was drawn as a random sample of all ARIC cohort members who were free of any CHD manifestations at the baseline, stratified to include a high proportion of individuals with B-mode ultrasound studies indicative of carotid atherosclerosis (18), a group of individuals with thin carotid artery walls, suggesting that they were free of carotid atherosclerosis but comparable in other attributes to those with thick carotid artery walls (18), and a sample of the remaining examinees. The sampling process involved dividing the entire cohort free of CHD manifestations into 15 sampling strata defined by the three carotid atherosclerosis characteristics described above and five field center-race categories. From this total of 15 strata, 2,618 individuals free of any CHD manifestations at the baseline were selected, and the stratum-specific sampling fractions were calculated by dividing the total number of the ARIC participants in each stratum by the total number of participants sampled from that stratum.

Assessment and validation of incident CHD events (the case population)

CHD incidence was ascertained by active surveillance of the cohort participants (17, 19). Interviewers contacted participants annually by telephone to identify all hospitalizations and deaths during the follow-up period. In addition, ARIC staff surveyed death certificates and discharge lists from local hospitals. All participants from the ARIC cohort who developed incident CHD over 3 years of follow up (n = 167) were selected as the case population for this study (100 percent sample) and allocated to the corresponding sampling strata described above. Individuals were required to be free of CHD at the baseline examination, defined as a history of myocardial infarction, a history of cardiac revascularization procedures, or prevalent myocardial infarction documented by electrocardiogram (ECG) (major Q wave, or borderline Q wave with significant ST segment or T wave abnormalities, in the absence of ventricular conduction defects that interfere with Q wave coding). For hospitalized events identified by either annual telephone contact or survey of death certificates and hospital discharge lists, trained abstractors obtained the hospital chart and recorded the presenting signs and symp-

toms, including chest pain, cardiac enzymes, and related diagnostic and therapeutic information. Up to three 12-lead ECGs were photocopied and coded at the University of Minnesota, Minneapolis, Minnesota, using the Minnesota Code (19). Out-of-hospital deaths were investigated using death certificates, an interview with one or more next of kin, and a questionnaire completed by the patient's physician. Coroner reports and autopsy reports were also obtained when available. Incident CHD was defined as a CHD death or a subject hospitalized for a validated myocardial infarction or cardiac revascularization procedures (including percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery). The criteria for myocardial infarction diagnosis have been published elsewhere (19) and are based on a combination of chest pain, cardiac enzymes, electrocardiographic changes, and/or autopsy findings. These elements were then independently reviewed by two physicians on the ARIC morbidity and mortality classification panel, with discrepancies in the diagnostic classification adjudicated by a third panel member.

Heart rate variability data collection

At the baseline examination, study participants had three ECG electrodes placed on the epigastrium. Resting, supine, 2-minute beat-to-beat heart rate data were collected after participants remained comfortably in the supine position for 20 minutes during the B-mode ultrasound and arterial distensibility studies (20). A dedicated computer and software were used for continuous detecting and recording of ECG R waves. The system then converted the R-R interval into beat-to-beat heart rate, including a record of the clock time for each beat (20).

Spectral analysis

The data process and analysis have been published elsewhere (21). In brief, 2-minute raw heart rate data were first subjected by a single, trained operator to a filter program to remove any artifacts under visual control. A plot of the smoothed version of the heart rate data over time was then superimposed on the plot of the raw data to confirm a good fit of any segment of smoothed data. The procedure could be repeated until a satisfactory plot was obtained. After smoothing, linear interpolation was applied to neighboring heart rate data points, and 256 heart rate data points were resampled with an equal distance of 0.4685 seconds. These 256 data points were used to fit a quadratic least-squares model, so that any time trend in the data was removed by taking the residuals. From the residuals, Fast Fourier Transformation was performed to estimate the Fourier Transformation of the heart rate residuals, from which the power spectral density was computed. An example of the power spectral density curve, following the Fast Fourier Transformation, with corresponding time domain beat-to-beat heart rate data inserted, is shown in figure 1 for one participant. From the power spectral density curve, the high-frequency spectral power component, defined as the power (area) between 0.16 and 0.35 Hz, and the low-frequency

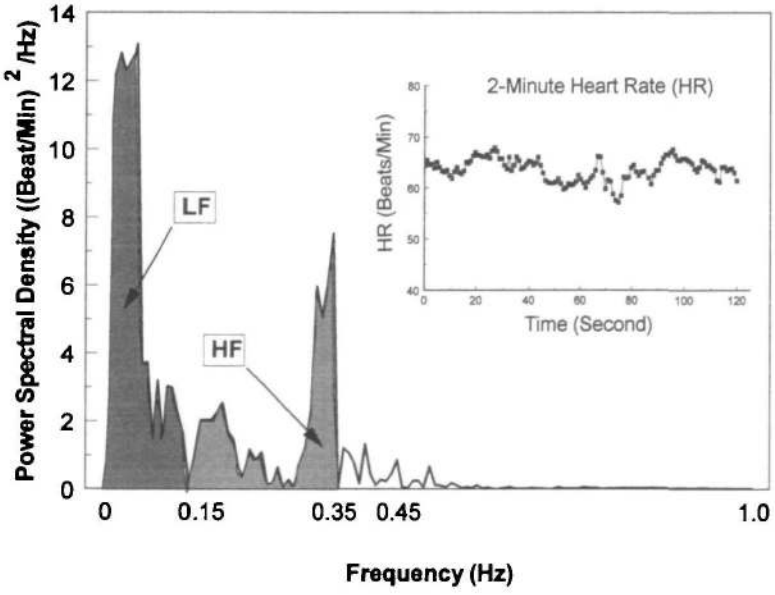

FIGURE 1. An example of a power spectral density curve following Fast Fourier Transformation, derived from time domain heart rate (HR) data (upper right panel), ARIC baseline survey examination, 1987–1989. Low-frequency (LF) power (0.04–0.15 Hz), 3.25 beats/minute^2; high-frequency (HF) power (0.15–0.35 Hz), 1.10 beats/minute^2; high-/low-frequency power ratio = 0.34; standard deviation of all normal R-R intervals, 40.20 msec.

spectral power component, defined as the power (area) between 0.025 and 0.15 Hz under the power spectral density curve, respectively, were calculated based on a rectangular method. The ratio of high- to low-frequency powers was also derived. The standard deviation of all normal R-R intervals was calculated from the time domain data after elimination of artifacts.

The short-term (blinded, measured 6 minutes apart) intraparticipant reliability coefficients, defined as one minus the proportion of total variance explained by intraparticipant variance, were 0.82, 0.56, 0.64, and 0.70 for high-frequency power, low-frequency power, high-/low-frequency power ratio, and standard deviation of R-R intervals, respectively, suggesting good-to-fair intraparticipant repeatability. Processing of HRV data and indices was performed blinded to CHD events status as well as to any personal identifiers. The intra-and interdata operator reliability coefficients for the high-frequency power, low-frequency power, high-/low-frequency power ratio, and standard deviation of R-R intervals were greater than 0.95, indicating high repeatability (21).

Covariates

Demographic variables and risk factors of CHD were obtained according to standardized protocols common to all ARIC study sites and subject to regular quality-control checks (21). In brief, age, race, gender, education level, and cigarette smoking status were obtained by trained and certified interviewers by a home interview using a standardized questionnaire. Body mass index was calculated as the measured weight (kg)/height $(m)^2$. Total cholesterol (fasting), triglyceride, and high density lipoprotein cholesterol (HDL cholesterol) were measured by an enzymatic procedure using a Cobas centrifuge analyzer (Hoffman-La Roche, Basel, Switzerland). HDL cholesterol was measured after precipitation of apolipoprotein B-containing lipoproteins. Low density lipoprotein cholesterol (LDL cholesterol) was calculated in participants with a triglyceride level of less than 400 mg/dl as total cholesterol minus HDL cholesterol and one-fifth of triglyceride. Sitting blood pressure was measured three times on each participant with a random zero sphygmomanometer after a 5-minute rest by trained technicians following a standardized protocol. The average of the second and the third readings of systolic and fifth-phase diastolic blood pressures was used in this report. Hypertension was defined as diastolic pressure of 90 mmHg or greater, systolic pressure of 140 mmHg or greater, or self-reported use of antihypertensive medication for treatment of hypertension. Diabetes mellitus was defined as fasting (8 hours) serum glucose of greater than 140 mg/dl or glucose greater than 200 mg/dl if fasting for less than 8 hours, or use of an oral hypoglycemic agent or insulin. β-Blocker usage was defined by coding all of the medications, vitamins, and supplements taken in the 2 weeks prior to the clinical examination. Heart rate was determined from the standard ECG measurement.

Statistical analysis

To make inferences to the population from which this study sample was drawn, weighted analyses were performed taking into consideration the sampling weight in each stratum. Survey Data Analysis Software (SUDAAN, Research Triangle Institute, Research Triangle Park, North Carolina) and SAS (SAS Institute, Inc., Cary, North Carolina) were utilized. A total of 396 individuals (366 from the cohort group and 30 from the case group) were excluded from this analysis for one or more of the following reasons: race other than black or white (n = 10 in cohort group/n = 0 in case group); age less than 44 years (n = 8 in cohort group/n = 0 in case group); heart rate data collected before May 15, 1987 (n = 0 in cohort group/n = 7 in case group), indicating possible data collection error; prevalent CHD in the cohort group (n = 117); and a high degree of artifacts in the heart rate record (n = 231 in cohort group/n = 23 in case group), defined by total spectral power greater than 321 or high-frequency power greater than 27 $(\text{beats/minute})^2$, with the former corresponding to three times the variance of heart rate in the ARIC cohort and the latter approximating the upper 96 percentile of the study population. The final sample size for this report is 2,389 (137 in the case group and 2,252 in the cohort group). Of the 137 cases, 36 were also included in the cohort group due to random selection of the cohort population from the entire ARIC cohort, which is a feature of case-cohort design (16).

Mean values and standard errors/proportions and 95 percent confidence intervals for major covariates were obtained by contrasting the case and the cohort groups. Since HRV indices showed a distribution skewed to the right, a natural logarithmic transformation was used to normalize their distributions. Consequently, geometric means and standard errors of HRV indices were obtained. Incident odds ratios from logistic regression models were used to estimate the relative risks and their 95 percent confidence intervals by applying the method described in detail by Prentice (16) to stratified case-cohort design. Cubic spline method was used to determine the shape of the relation between incident odds ratios and HRV indices.

RESULTS

The baseline characteristics of the population from which this study sample was drawn are presented in table 1, stratified by the CHD case and the cohort groups. There were 137 incident CHD cases and 2,252 cohort participants (36 of whom were also incident CHD cases), with a 3-year, weighted cumulative incidence of 1.5 percent (95 percent confidence interval (CI) 0.94–1.96). Overall, compared with the cohort, the incident CHD cases were older and more likely to be white, to be male, to have less than a high school education, to be diabetic, to be hypertensive, and to be using β-blockers. Cases also had higher total cholesterol, LDL cholesterol, triglyceride, heart rate, and cigarette-years of smoking, and they had lower levels of HDL cholesterol. Of the 137 incident CHD cases, 82 (60 percent) had an acute myocardial infarction during the 3 years of follow-up, 44 (32 percent) had cardiac revascularization procedures, and 11 (8 percent) were diagnosed with fatal CHD.

The baseline characteristics of the cohort sample by quartiles of HRV indices are presented in table 2. As can be seen from this table, the HRV indices were negatively associated with age; HRV indices also showed associations with race, gender, hypertension, diabetes, and β-blocker usage. Body mass index, heart rate, cigarette-years of smoking, total cholesterol, and educational level were similar across quartiles of HRV indices.

The sampling weight-adjusted geometric mean values (and their standard errors) of high-frequency power, low-frequency power, high-/low-frequency power ratio, and standard deviation of R-R intervals for the CHD case group were 0.84 ± 0.10, 2.46 ± 0.23, 0.34 ± 0.03, and 32.26 ± 1.90, respectively, in contrast to 1.29 ± 0.03, 3.16 ± 0.07, 0.41 ± 0.01, and 37.79 ± 0.60 for the cohort group. The PP-plots of HRV indices comparing the distributions of the case group with the cohort-representative group are presented in figure 2. It can be observed from the mean values and the PP-plots that the distribution of HRV indices in the case group was shifted to the left relative to the cohort-representative group, indicating lower HRV indices in the case group. Differences in the geometric means between these two groups were not tested because of lack of independence (36 cases of incident CHD were also in the cohort group).

Cubic spline models were fit to determine the shapes of the association between HRV indices and incident CHD. The likelihood ratio tests indicated a statistically significant nonlinear relation (p for high-frequency power, low-frequency power, high-/low-frequency power ratio, and standard deviation of R-R intervals all less than 0.001). The cubic spline logistic regression estimates for high-frequency power and standard deviation of R-R intervals are graphically presented in figure 3 as examples of frequency and time domain HRV indices and incident CHD risk function, respectively. The cubic spline models also suggested a threshold in the association of HRV indices to CHD with the threshold at about the 25th percentile cutpoint. Consequently, models to assess the relative risk of incident CHD were set up to compare the lowest quartile of HRV indices with the upper three quartiles (reference group). The results from the logistic regression models are presented in table 3. As

TABLE 1. *Baseline characteristics* of the study population, comparing incident coronary heart disease cases and the cohort, the ARIC Study, 1987–1989*

Variable	Cohort group (n = 2,253)			Case group (n = 137)		
	Mean ± standard error	Proportion	95% confidence interval	Mean ± standard error	Proportion	95% confidence interval
Age (years)	54 ± 0.13			56 ± 0.44		
Race (% black)		27.3	27.0–27.6		23.6	13.5–33.8
Gender (% male)		45.0	42.8–47.2		72.1	61.4–82.9
High school or higher education (%)		76.4	74.6–78.2		74.3	63.8–84.7
Body mass index (kg/m^2)	27.30 ± 0.11			27.47 ± 0.41		
Hypertension (%)		33.6	31.6–35.6		51.1	39.1–63.0
Heart rate (beats/minute)	66 ± 0.23			69 ± 0.98		
Smoking (cigarette-years)	306 ± 9.91			544 ± 44.5		
Total cholesterol (mg/dl)	214 ± 0.94			231 ± 3.10		
HDL cholesterol† (mg/dl)	53 ± 0.39			42 ± 1.16		
LDL cholesterol† (mg/dl)	136 ± 0.90			157 ± 3.02		
Triglyceride (mg/dl)	126 ± 1.79			169 ± 8.43		
Diabetes (%)		8.2	7.0–9.4		25.8	15.3–36.3
β-Blocker usage (%)		8.7	7.5–9.9		15.2	6.6–23.8

* Adjusted for sampling weight.
† HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol.

TABLE 2. Baseline characteristics* of the cohort population across quartiles of heart rate variability indices, the ARIC Study, 1987–1989

	Age (years) (mean ± SE†)	Race (% black)	Gender (% male)	High school education or more (%)	Body mass index (kg/m²) (mean ± SE)	Hypertension (%)	Heart rate (beats/minute)	Smoking (cigarette-years)	Total cholesterol (mg/dl)	Diabetes (%)	β-blocker usage (%)
HF† (quartiles)											
1	56 ± 0.24	19.6	52.4	75.0	27.6 ± 0.24	39.8	67 ± 0.50	348 ± 20.7	218 ± 1.95	11.7	12.3
2	54 ± 0.25	22.2	48.3	77.2	27.1 ± 0.22	28.8	66 ± 0.45	301 ± 23.3	216 ± 1.86	6.1	7.3
3	53 ± 0.24	30.5	36.5	78.4	27.2 ± 0.26	32.8	66 ± 0.43	270 ± 16.9	213 ± 2.08	7.7	7.3
4	54 ± 0.27	36.1	43.5	74.9	27.3 ± 0.25	33.2	67 ± 0.45	308 ± 18.6	211 ± 1.64	7.3	8.1
LF†(quartiles)											
1	55 ± 0.25	31.9	41.1	71.8	27.8 ± 0.24	40.0	65 ± 0.52	324 ± 20.2	215 ± 1.96	11.6	14.2
2	54 ± 0.26	25.3	40.8	76.7	27.4 ± 0.24	31.2	66 ± 0.42	322 ± 22.7	217 ± 1.99	7.9	7.0
3	54 ± 0.25	23.6	46.0	78.4	27.1 ± 0.22	28.7	67 ± 0.42	284 ± 19.8	215 ± 1.90	6.2	8.0
4	54 ± 0.26	28.6	51.7	78.4	26.9 ± 0.23	30.7	67 ± 0.45	295 ± 17.2	209 ± 1.69	7.0	6.0
HF/LF ratio (quartiles)											
1	54 ± 0.24	13.3	59.0	77.5	27.0 ± 0.20	30.0	68 ± 0.44	310 ± 19.7	216 ± 1.88	7.5	8.2
2	54 ± 0.25	24.1	50.2	80.6	27.4 ± 0.24	32.8	67 ± 0.45	316 ± 22.8	213 ± 1.89	8.1	7.9
3	54 ± 0.26	31.5	39.2	76.6	27.3 ± 0.24	34.0	66 ± 0.45	278 ± 17.7	213 ± 1.89	8.1	6.7
4	54 ± 0.26	39.6	32.3	71.0	27.5 ± 0.23	37.3	65 ± 0.49	321 ± 19.4	215 ± 1.90	8.9	12.1
SDNN† (quartiles)											
1	56 ± 0.24	28.0	40.6	71.3	28.1 ± 0.23	50.1	73 ± 0.51	363 ± 21.0	220 ± 2.00	15.9	13.1
2	54 ± 0.24	24.4	40.4	77.6	27.3 ± 0.22	29.8	68 ± 0.46	300 ± 20.2	219 ± 1.89	7.7	6.4
3	54 ± 0.25	27.6	44.7	79.2	27.0 ± 0.25	29.2	65 ± 0.42	296 ± 17.2	211 ± 2.01	6.8	7.4
4	54 ± 0.24	30.3	52.8	75.1	27.1 ± 0.24	32.0	62 ± 0.44	285 ± 18.6	209 ± 1.65	5.8	9.4

* Adjusted for sampling weight.
† SE, standard error; HF, high-frequency power; LF, low-frequency power; SDNN, standard deviation of all normal R-R intervals.

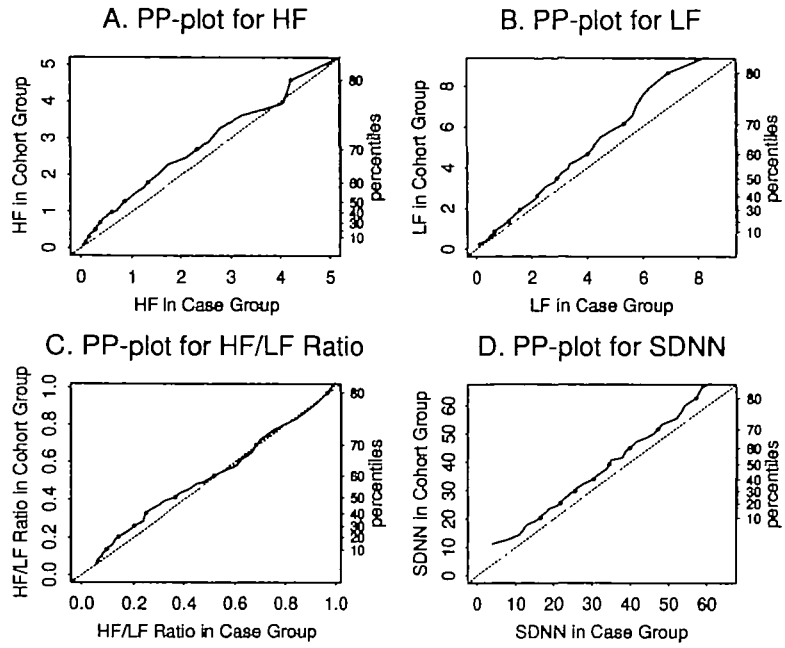

FIGURE 2. PP-plots of heart rate variability indices according to incident CHD and cohort status of the study population adjusted for sampling weight, the ARIC Study, 1987–1992. HF, high-frequency power (beats/minute)^2; LF, low-frequency power (beats/minute)^2; HF/LF, ratio of HF to LF; SDNN, standard deviation of all normal R-R intervals (msec).

shown in the table, individuals with the lowest HRV had an increased risk of incident CHD. For the high-frequency power, the relative risks were 2.25 (95 percent CI 1.57–3.23) and 1.72 (95 percent CI 1.17–2.51) in an unadjusted and a multivariable-adjusted model, respectively, and for the low-frequency power, they were 1.35 (95 percent CI 0.92–1.99) and 1.09 (95 percent CI 0.72–1.64), respectively. For the high-/low-frequency power ratio, the relative risks were 1.48 (95 percent CI 1.01–2.16) and 1.25 (95 percent CI 0.84–1.86), respectively, and for the standard deviation of R-R intervals, they were 1.70 (95 percent CI 1.79–2.43) and 1.39 (95 percent CI 0.94–2.04), respectively. The interactions between age, race, gender, heart rate, hypertension, severity of carotid atherosclerosis measured by B-mode ultrasound, diabetes, β-blocker, education, and each of the HRV indices were tested and found to be not statistically significant at the $p \leq 0.20$ level. Adding heart rate, cigarette smoking, and total cholesterol to the multivariable adjusted model did not meaningfully alter the HRV and incident CHD associations.

To determine whether the CHD risk associated with lower HRV varied across the 3 years of follow-up, we repeated the age-, race-, and gender-adjusted models presented in table 3, stratified by years of follow-up. The relative risks of incident CHD comparing the lowest with the upper three quartiles of high-frequency power for the first, second, and third follow-up years were 1.83 (95 percent CI 1.04–3.21), 1.67 (95 percent CI 0.91–3.05), and 2.16 (95 percent CI 1.17–3.98), respectively; those for low-frequency power were 1.33 (95 percent CI 0.73–2.42), 1.19 (95 percent CI 0.62–2.30), and 1.67 (95 percent CI 0.87–3.22), respectively; those for high-/low-frequency power ratio were 1.52 (95 percent CI 0.86–2.70), 0.94 (95 percent CI 0.48–1.81), and 1.52 (95 percent CI 0.81–2.84); and the corresponding values for standard deviation of R-R intervals were 1.74 (95 percent CI 0.98–3.09), 1.39 (95 percent CI 0.75–2.59), and 2.11 (95 percent CI 1.15–3.88). These results reflect homogeneity over this short period of follow-up in the associations estimated from all four HRV indices.

DISCUSSION

A case-cohort design was used, as proposed by Prentice (16), that involves assembling information on all individuals identified as cases and on a randomly selected subcohort of a cohort. The motivation for using the case-cohort design was to reduce the cost of assembling information for the entire cohort population given that the outcomes are rare, while taking advantage of the prospective study design. A key advantage of the case-cohort design is that the same subcohort can be used to study different outcomes. Since the subcohort is a random sample of the entire cohort population, it can be used to estimate the incidence of the events (outcomes) and the population

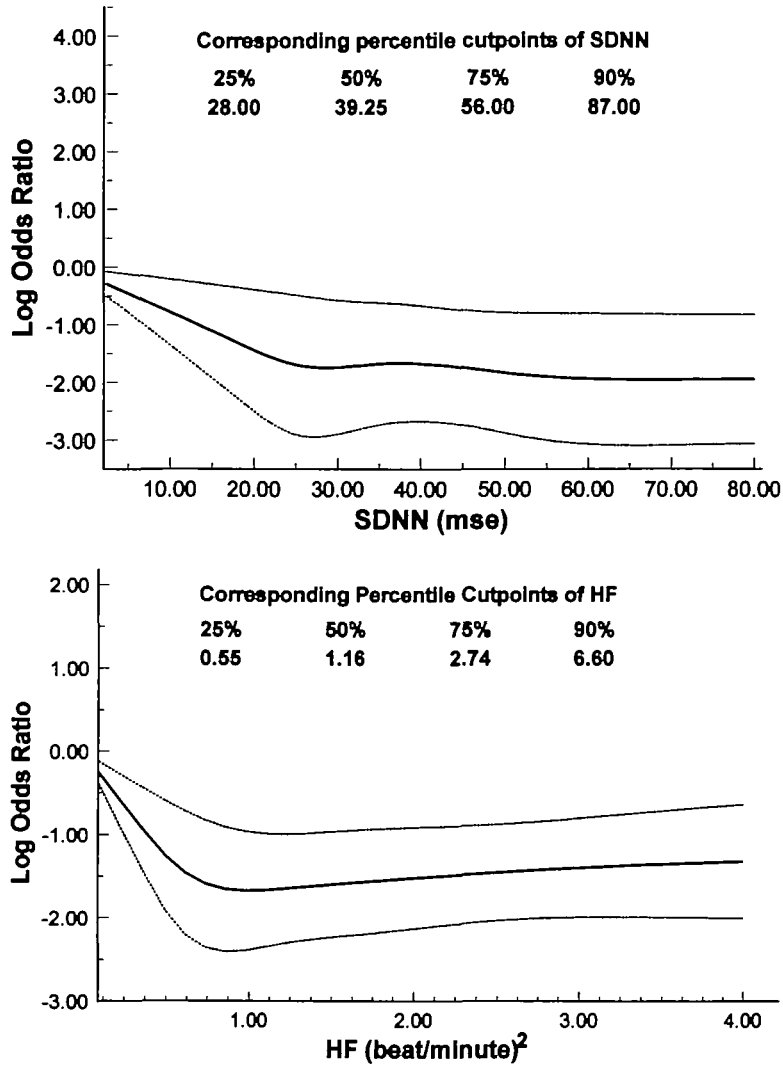

FIGURE 3. Cubic spline logistic regression estimates of HRV indices and incident CHD risk, the ARIC Study, 1987–1992. Top, cubic spline plot for high-frequency power (HF) and incident CHD. bottom, cubic spline plot for standard deviation of R-R intervals (SDNN) and incident CHD. Solid line, log odds ratio; dotted lines, 95% confidence intervals.

distribution and correlates of the key variables collected on the subcohort.

Analysis of beat-to-beat HRV has been widely used as a method to evaluate sympathetic and parasympathetic influence on the cardiac system in various scientific applications. It has become well established that HRV indices derived from spectral analysis, namely high-frequency power, low-frequency power, and high-/low-frequency power ratio, are reflective of parasympathetic activity, sympathetic and parasympathetic activity, and parasympathetic-sympathetic activity balance, respectively (1–9). Traditionally, HRV analyses have been based on heart rate data recorded over several hours. This provides a wealth of data (and high degrees of precision), but also introduces costs and logistic complexities that are particularly burdensome for population-based, epidemiologic research. In this report. we applied spectral analysis to 2-minute heart rate data collected according to a standardized protocol by trained and certified technicians, subject to well-established quality-control monitoring. Although caution needs to be exercised when estimating the low-frequency component of HRV from heart rate records of short duration, sufficient documentation exists today to support the use of records of 5 minutes duration or less. For frequency domain analysis, Bigger (2) indicated that estimates of high-frequency power centered around 0.25 Hz should be based on records of approximately 1 minute duration; low-frequency power estimates (0.04–0.15 Hz) require about 2.5 minutes of beat-to-beat data. Additional, supportive findings have been reported by other investigators in this field (8, 22). As demonstrated by Bigger (2), our 2-minute records collected on the

TABLE 3. Adjusted* relative risk and 95% confidence interval (CI) of incident coronary heart disease comparing the lowest quartiles of heart rate variability (HRV) indices with the upper three quartiles of HRV (as a reference), the ARIC Study, 1987–1992

HRV indices	Unadjusted			Adjusted model 1†			Adjusted model 2‡		
	Quartiles 2–4	Quartile 1		Quartiles 2–4	Quartile 1		Quartiles 2–4	Quartile 1	
		Relative risk	95% CI		Relative risk	95% CI		Relative risk	95% CI
High-frequency power (beats/minute)²	1.00	2.25	1.57–3.23	1.00	2.01	1.39–2.91	1.00	1.72	1.17–2.51
Low-frequency power (beats/minute)²	1.00	1.35	0.92–1.99	1.00	1.35	0.91–2.01	1.00	1.09	0.72–1.64
High-/low-frequency power ratio	1.00	1.48	1.01–2.16	1.00	1.27	0.86–1.86	1.00	1.25	0.84–1.86
Standard deviation of all normal R-R intervals (msec)	1.00	1.70	1.79–2.43	1.00	1.76	1.22–2.54	1.00	1.39	0.94–2.04

* Adjusted for sampling weight.
† Adjusted model 1: adjusted for age, race, and gender.
‡ Adjusted model 2: adjusted for age, race, gender, education, diabetes mellitus, hypertension, and β-blocker medication usage.

ARIC cohort during its baseline examination are informative since they included at least 10–15 times the period of the heart rate fluctuation being estimated. A single, trained technician, blinded to CHD events status, processed all HRV data for this study. Standardized data collection and processing protocols were used in this study, as reflected in reasonably high short-term intraparticipant reliability coefficients and intrareader and interreader reliability coefficients for all HRV indices used in this study.

Clinically based studies have shown that survivors of acute myocardial infarction with lower HRV had a higher risk of all-cause mortality compared with post-myocardial infarction patients with higher HRV (10). Lower HRV has also been found to be related to sudden cardiac death (14). Notably, an impairment of cardiac autonomic activity also appears to carry an increased risk of noncardiovascular fatal outcomes. Specifically, it was observed in a subsample of the Framingham Study that HRV—both from time and frequency domain estimates—was inversely associated with the risk of all-cause mortality (15). Although the biological mechanisms for a link between imbalance of cardiac autonomic activity and the development of CHD is not fully understood, sufficient clinical and cardiophysiologic literature exists to indicate that imbalance of cardiac autonomic activity, mainly reduced parasympathetic activity and/or increased sympathetic activity, plays an important role in the development of coronary heart disease through (at least) six possible mechanisms: 1) increased heart rate, with consequent increase in oxygen consumption (23); 2) increased ventricular excitability with lower threshold to ventricular fibrillation (23, 24); 3) increased coronary vasoconstriction with greater risk of myocardial ischemia (25–27); 4) increased shear stress leading to plaque fissure (24); 5) enhanced atherosclerosis through increased macrophage-LDL cholesterol oxidation (28–30); and 6) decreased arrhythmia threshold, with consequent increased risk of sudden cardiac death (24).

While these mechanisms are plausible, the hypothesis that an altered cardiac autonomic activity is associated with the risk of developing CHD had not been tested in the general population. When overall HRV was expressed as the standard deviation of R-R intervals, we found a trend toward a significant association between standard deviation of R-R intervals and incident CHD, suggesting that the imbalance of sympathetic and parasympathetic activity is associated with increased risk of CHD. The significant inverse association between the high-frequency component of HRV and incident CHD observed in this study provides support for the hypothesis that links a reduced parasympathetic activity to CHD. These results also extend the previously extant literature to newly occurring CHD and to the general population. Our findings of a threshold effect of HRV indices of autonomic activity on the risk of developing CHD are consistent with the findings by Kleiger et al. (10), who reported that only the group with the lowest HRV measured by the time domain method was at significantly increased risk of mortality after an acute myocardial infarction.

In our data, an inverse, but not statistically significant, association between low-frequency power and the risk of incident CHD was observed, a finding that is consistent with reports from other studies (11, 16). With different data-collection protocols, a positive relation between low-frequency power and incident CHD could have been observed if low-frequency power were predominantly a measure of sympathetic activity. For instance, under experimental conditions of psychologic challenge, the low-frequency component is primarily subject to sympathetic control (31),

and data collected in this manner could have show a positive relation between low-frequency power and incident CHD. Several factors can account for the pattern observed in our data. First, our study protocol required participants to rest in a quiet environment in a supine position for at least 20 minutes prior to beat-to-beat heart rate data collection. Under these conditions, the parasympathetic activity is predominant, and sympathetic activity is at its minimum. This may apply to our particular case, since the low-frequency power is influenced by both the sympathetic and parasympathetic activity, and our low-frequency power measurements may reflect strong parasympathetic contribution. Further, low-frequency power estimates require records of beat-to-beat data of approximately 2.5 minutes (2). The 2-minute, beat-to-beat heart rate data collected in our study are only long enough to capture a few cycles of low-frequency heart rate fluctuation, leading to the possibility that the low-frequency power estimated in our study may not be an accurate reflection of the sympathetic activity expressed in the heart rate variability.

Since the follow-up period of our study is short (3 years) and the source population is relatively young, the number of incident CHD cases is small ($n = 137$). Nevertheless, this study represents the first population-based, prospective study to identify HRV as a potentially important risk factor of newly developed coronary heart disease. Other population-based studies are needed to confirm our findings before we can conclude that reduced HRV plays a causal role in the development of coronary heart disease.

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