Low Heart Rate Variability in a 2-Minute Rhythm Strip Predicts Risk of Coronary Heart Disease and Mortality From Several Causes

The ARIC Study

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Background—Low heart rate variability (HRV) is associated with a higher risk of death in patients with heart disease and in elderly subjects and with a higher incidence of coronary heart disease (CHD) in the general population.

Methods and Results—We studied the predictive value of HRV for CHD and death from several causes in a population study of 14 672 men and women without CHD, aged 45 to 65, by using the case-cohort design. At baseline, in 1987 to 1989, 2-minute rhythm strips were recorded. Time-domain measures of HRV were determined in a random sample of 900 subjects, for all subjects with incident CHD (395 subjects), and for all deaths (443 subjects) that occurred through 1993. Relative rates of incident CHD and cause-specific death in tertiles of HRV were computed with Poisson regression for the case-cohort design. Subjects with low HRV had an adverse cardiovascular risk profile and an elevated risk of incident CHD and death. The increased risk of death could not be attributed to a specific cause and could not be explained by other risk factors.

Conclusions—Low HRV was associated with increased risk of CHD and death from several causes. It is hypothesized that low HRV is a marker of less favorable health. **(*Circulation*. 2000;102:1239-1244.)**

Key Words: heart rate ■ nervous system, autonomic ■ coronary disease ■ mortality ■ heart diseases

The heart rate of healthy persons displays beat-to-beat variations that result from fluctuations in autonomic nervous system activity at the sinus node. Heart rate variability (HRV) decreases under situations of stress, either emotional or physical, whereas it increases with rest. Therefore, HRV is considered a noninvasive marker of autonomic nervous system function.[1,2] The lack of HRV has long been used for the diagnosis of diabetic neuropathy. In more recent years, low HRV has been shown to have prognostic value in patients with myocardial infarction.[3] Also, in the general population, low HRV is associated with death[4,5] and with the risk of cardiac events.[6,7] Because low HRV has been reported in patients with diabetes, hypertensive cardiac hypertrophy, and atherosclerosis,[1,8,9] prevalent disease may account for these findings. It is questioned whether, in the general population, low HRV is a consequence of disease or an indicator of an underlying mechanism for future disease; therefore, we studied HRV in relation to total and CHD mortality risk in the Atherosclerosis Risk In Communities (ARIC) Study.

Methods

Study Population and Baseline Measurements

The ARIC Study follows a cohort of 15 792 middle-aged men and women.[10] During 1987 to 1989, population samples were drawn from the 45- to 64-year-old inhabitants of Forsyth County, NC; Jackson, Miss; suburban Minneapolis, Minn; and Washington County, Md; and they were invited for a home interview and a clinical examination.

In the home interview, questions were asked about health behaviors, sociodemographics, and disease history. The clinical examination included an ECG recording. After a 5- to 10-minute rest period, during which electrodes were placed, each subject had a standard 12-lead ECG and a 2-minute rhythm strip recorded. Plasma total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels were determined with standard methodology. Serum insulin

Received January 7, 2000; revision received March 27, 2000; accepted April 13, 2000.

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was measured with a radioimmunoassay (^{125}I Insulin Kit; Cambridge Medical Diagnostics). Serum glucose was assessed with the hexokinase method. Prevalent diabetes mellitus was defined as a fasting glucose level of ≥140 mg/dL (≥7.8 mmol/L), a nonfasting glucose level of ≥200 mg/dL (≥11.1 mmol/L), or a history of, or treatment for, diabetes. Three seated blood pressure measurements were taken on the right arm with a random-zero sphygmomanometer. The mean of the last 2 measurements was used. Hypertension was defined as systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or the use of antihypertensive agents. The ratio of waist (umbilical level) and hip (maximum buttocks) circumferences was calculated as a measure of fat distribution. The average carotid intima-media thickness was assessed with a standardized B-mode ultrasonic technique.[11]

Study Design and Methods of Follow-Up

Because it was not feasible to determine HRV for all participants, the case-cohort design was applied, in which data are collected in the complete cohort before disease occurs. At a later stage, the available data are processed for the cases that occurred during follow-up and in a random sample (including a number of future cases), which is used to reflect the total cohort. This design provides estimates of relative risks.[12]

For the present study, a random sample of 900 subjects was selected in 1995 from the 14 672 subjects without prevalent coronary heart disease (CHD) at baseline, combined with all incident CHD cases and all deaths that occurred through 1993. Prevalent CHD was defined as self-reported history of physician-diagnosed heart attack, 12-lead Minnesota Code evidence of prior myocardial infarction (MI), prior cardiovascular surgery, or prior coronary angioplasty.

The method of follow-up has been described previously.[13] Briefly, interviewers contacted participants annually by telephone to identify hospitalizations and deaths. For hospitalized patients with potential acute CHD events, trained abstractors recorded the presenting signs and symptoms, including chest pain, cardiac enzyme levels, and related clinical information. As many as three 12-lead ECGs were visually coded with the Minnesota Code, and waveform evolution was evaluated with side-by-side comparisons.[14] Out-of hospital deaths were investigated by means of the death certificate, an interview with the next-of-kin, and questionnaires completed by the patients' physicians. Coroner reports and autopsy reports, when available, were used for validation.

CHD incidence was defined as definite or probable MI, cardiac revascularization procedures (excluding thrombolytic therapy), or definite CHD death. Cause-specific death was based on the underlying cause given on the death certificate: cardiovascular disease (CVD) (ICD-9 codes 390 to 459) and cancer (ICD-9 codes 140 to 240). After the exclusion of subjects with missing data, the study population consisted of 856 subjects in the random sample combined with 395 incident CHD cases (29 were also part of the sample) and 443 deaths (21 were also part of the sample), of whom 140 died from CVD and 209 died from cancer. Of the subjects who died from cancer, 36 reported a history of cancer at baseline.

Data analysis

In 1995 to 1996, the duration of all normal sinus intervals (R-R intervals) was measured at the University of Minnesota ECG Coding Center by coders who were blinded with respect to disease occurrence during follow up. A digitizing tablet (Calcomp) and a personal computer were used. Coders mounted the 2-minute rhythm strip on the tablet and used the mouse to successively mark the top of all of the R peaks. The *X-Y* coordinates were transmitted to the personal computer, and the duration of the R-R interval was computed on the basis of the difference between coordinates. To reduce measurement error, the procedure was performed in duplicate, and the mean of the 2 measurements of each R-R interval was used for the analyses. Abnormal beats were marked by the coders. The 2 intervals after a single abnormal beat were excluded for analysis of HRV. Subjects with >2 abnormal beats in the rhythm strip were excluded from the analyses (36 in the random sample, 98 cases), because the presence of multiple ventricular extrasystoles is known to be associated with elevated mortality risk,[15] and it is accompanied with higher HRV.

Four measures of HRV were determined: the standard deviation of all R-R intervals (SDNN), the mean of absolute successive differences (rMSSD), the standard deviation of absolute differences between successive intervals (SDSD), and the percentage of intervals differing by >50 ms from the preceding interval (pNN50). In addition, heart rate was calculated from the mean duration of R-R intervals. HRV could not be determined for 4 subjects in the random sample, and rhythm strips were missing for 3 subjects in the random sample and for 23 cases.

The intercoder and intracoder variabilities were evaluated in a set of 10 rhythm strips, which were measured 3 times by each coder. HRV measures were used as the dependent variables. For the SDNN, the between-subject variance was 310 ms^2, the between-coder variance was 0.04 ms^2, and the intercoder variance was 3.24 ms^2. The correlation of all HRV measures between coders was >0.99.

Subjects were categorized a priori into 3 groups according to HRV and heart rate. Categories were based on the tertile cut points of the distribution of subjects in the random sample. The cut points were 23.9 and 35.4 ms for SDNN, 14.7 and 22.3 ms for rMSSD, 11.3 and 16.4 ms for SDSD, 0.8% and 5.9% for pNN50, and 63 and 72 bpm for heart rate.

Relative incidence rates of CHD, total mortality, and cause-specific mortality, in categories of all measures of HRV and of heart rate, were computed with Poisson regression for the case-cohort design.[12] In line with previous work, the intermediate category was taken as the reference.[5] Subjects with a self-reported history of cancer at baseline were excluded from the analyses of cancer risk.

Two models were used for the regression analyses. The first model adjusted for age, sex, race group, and ARIC recruitment center; the multivariable model also adjusted for variables that were associated with HRV: current smoking, cigarette-years, triglycerides, HDL cholesterol, diabetes, hypertension, body mass index, waist-to-hip ratio, and carotid intima-media thickness. For cancer mortality, current smoking and cigarette-years were added in the multivariable model.

Results

In the random sample of this population of middle-aged men and women, mean±SD values were 34±17 ms for SDNN, 22±12 ms for rMSSD, 17±12 ms for SDSD, 8±12% for pNN50, and 68±10 bpm for heart rate. All measures of HRV were significantly correlated, ranging from 0.70 between pNN50 and SDNN to 0.95 between rMSSD and SDSD. The correlations with heart rate were lower: −0.43 (SDNN and pNN50) and −0.50 (SDSD and rMSSD).

In Table 1, population characteristics are shown in the random sample in tertiles of SDNN. Age, male sex, heart rate, body mass index, ratio of waist to hip circumferences, insulin level, triglyceride level, HDL cholesterol level, blood pressure, carotid intima-media thickness, and the prevalence of hypertension and diabetes differed significantly for the HRV categories, with subjects with low HRV in general having a worse cardiovascular risk profile. Therefore, these variables were considered possible confounding or mediating factors.

In the survival analysis (Table 2), low HRV and high heart rate were associated with elevated risk of all end points. The age-, sex-, race-, and field center–adjusted relative risks of cardiovascular mortality in the lowest compared with the intermediary tertile of SDNN was 2.10 (95% CI 1.21 to 3.64) For rMSSD, SDSD, and pNN50, the relative risks of all end points were higher than those observed for SDNN. The relative risks were less favorable in the high than in the intermediate tertile. A U shape was observed for cancer mortality; the relative rates in the lowest and highest tertiles of pNN50 were 1.95 (1.27 to 2.92) and 1.53 (0.97 to 2.41),

TABLE 1. Baseline Characteristics in Tertiles of 2-Minute SDNN in the Random Sample

	Low (<23.9 ms)	Intermediate (23.9–35.4 ms)	High (≥35.4 ms)	*P* (ANOVA)
n	280	281	295	
Age, y	55.1	53.7	52.0	0.0001
Sex, % men	44	40	51	0.0243
Race, % black	28	29	27	0.208
Heart rate, bpm	74	67	63	0.0001
Current smoking, %	30	29	26	0.461
Smoking, cigarette-y	341	290	247	0.050
Body mass index, kg/m^2	28.9	28.0	27.3	0.002
Waist/hip ratio	0.947	0.931	0.923	0.0001
Insulin, pmol/L*†	77.2	66.7	60.4	0.001
Triglycerides, mmol/L†	1.32	1.17	1.15	0.002
HDL cholesterol, mmol/L	1.29	1.34	1.40	0.009
LDL cholesterol, mmol/L	3.63	3.64	3.47	0.117
Systolic blood pressure, mm Hg	125	122	121	0.011
Carotid intima-media thickness, mm	0.75	0.74	0.72	0.038
Hypertension, %	36	34	28	0.076
Diabetes, %	13	9	6	0.012

Values are least-squares adjusted mean values, adjusted for age, sex, race, and field center. Age, sex, race, and field center were adjusted for the other 3.

*Subjects with diabetes and subjects who did not fast 12 hours before blood sampling were excluded for this analysis.

†Because triglycerides and insulin were not normally distributed, log transformation was performed, and the antilog of the mean is presented.

respectively. Adjustment for possible confounders slightly decreased the increased risks for the low SDNN and high heart rate categories and increased the risks in the lowest tertiles of rMSSD, SDSD, and pNN50 and in the high tertiles of all measures of HRV.

Adjustment for insulin or glucose level in subjects without diabetes did not affect the associations. Stratified analysis was performed to evaluate possible confounding and interaction. Stratification did not show appreciably different relative risk estimates within subgroups of heart rate, age, sex, race, hypertension, diabetes, smoking, or body mass index. Furthermore, when analyses were restricted to subjects without hypertension, diabetes, cancer, or symptomatic heart disease at baseline, the associations with death remained virtually unchanged (Table 3).

Discussion

In this population study, middle-aged men and women with low HRV, as determined from a 2 minute-rhythm strip, had an adverse cardiovascular risk profile and elevated risk of death from all causes, including cancer, and of incident CHD. The elevated risk could not be attributed to other risk factors.

Methodological Issues

In the present study, the case-cohort design was used. To evaluate whether the cohort sample was a representative sample, we compared mean values for cardiovascular risk factors of the cohort sample versus those of the full cohort. None of these values were significantly different, and they never differed by >1%. It is therefore likely that the distributions of measures of HRV in the cohort sample also are representative of the distributions in the full cohort, thus justifying the estimates of relative risks.

The use of certain medication was considered as a possible confounding factor, because many drugs affect autonomic nervous system function. The analyses for subjects without chronic diseases (subjects who used antihypertensive, glucose-lowering, or other cardioactive medication were excluded) showed similar results. When the analyses were restricted to persons not using any medication, the associations did not change.

Two-minute rhythm strips were used for the determination of HRV. It is known from 24-hour Holter recordings that HRV changes during the day.[1] However, short-term HRV measurements during the daytime are correlated with 24-hour HRV measures, and in patients with myocardial infarction, such short-term HRV measurements predict future mortality rates.[3]

Heart rate was correlated with measures of HRV and associated with mortality risk and therefore may be considered a possible confounding variable. Because both heart rate and HRV reflect autonomic function, the inclusion of both parameters was regarded as an overadjustment. When the coefficient of variation was used, SDNN divided by mean R-R interval, the age-, sex-, race-, and field center–adjusted relative risks of the lowest versus the intermediate tertile were 1.82 (1.07 to 3.09) for CVD mortality and 1.45 (1.04 to 2.03) for CHD incidence.

Previous Studies

Previous work in the ARIC study, with spectral analysis of heart rate, has shown low HRV to predict incident CHD.[7] The results of the present study confirmed this association over a

TABLE 2. Relative Rates (95% CIs) of Death From Several Causes and CHD Incidence in Tertiles of HRV and Heart Rate in a 2-Minute Rhythm Strip

Measure	Tertile*	All-Cause Death	CVD Mortality	Cancer Mortality‡	CHD Incidence
No. of events		443	140	173	395
SDNN	1	†1.51 (1.08–2.18)	2.10 (1.21–3.64)	1.20 (0.79–1.82)	1.18 (0.84–1.64)
		1.50 (1.02–2.21)	1.98 (1.06–3.70)	1.18 (0.72–1.92)	1.09 (0.73–1.64)
	2	1	1	1	1
	3	1.03 (0.72–1.48)	1.20 (0.66–2.18)	1.08 (0.70–1.70)	0.72 (0.51–1.03)
		1.23 (0.80–1.89)	1.61 (0.78–3.34)	1.37 (0.83–2.28)	0.92 (0.58–1.91)
rMSSD	1	1.73 (1.22–2.44)	2.60 (1.48–4.59)	1.47 (0.96–2.25)	1.36 (0.97–1.92)
		1.95 (1.30–2.93)	2.80 (1.36–5.75)	1.70 (1.02–2.84)	1.49 (0.99–2.25)
	2	1	1	1	1
	3	1.09 (0.76–1.56)	1.06 (0.59–1.93)	1.17 (0.75–1.83)	0.98 (0.69–1.40)
		1.13 (0.72–1.77)	0.97 (0.44–2.16)	1.49 (0.88–2.52)	1.10 (0.70–1.71)
SDSD	1	1.90 (1.33–2.69)	2.83 (1.59–5.03)	1.56 (1.00–2.42)	1.43 (1.01–2.03)
		1.97 (1.30–2.97)	3.18 (1.47–6.90)	1.90 (1.13–3.21)	1.42 (0.92–2.17)
	2	1	1	1	1
	3	1.37 (0.96–1.96)	1.52 (0.84–2.74)	1.35 (0.87–2.11)	1.04 (0.73–1.48)
		1.41 (0.91–2.20)	1.43 (0.66–3.11)	1.90 (1.13–3.20)	1.16 (0.74–1.79)
pNN50	1	2.16 (1.53–3.02)	2.87 (1.59–5.03)	1.95 (1.27–2.92)	1.61 (1.15–2.26)
		2.35 (1.57–3.50)	3.44 (1.69–7.02)	2.48 (1.48–4.15)	1.69 (1.12–2.55)
	2	1	1	1	1
	3	1.40 (0.97–2.02)	1.33 (0.73–2.44)	1.53 (0.97–2.41)	1.16 (0.81–1.65)
		1.46 (0.92–2.32)	1.24 (0.55–2.79)	2.10 (1.23–3.81)	1.29 (0.82–2.03)
Heart rate	1	1	1	1	1
	2	1.26 (0.88–1.80)	1.35 (0.77–2.38)	1.22 (0.79–1.90)	1.25 (0.88–1.77)
		1.02 (0.66–1.58)	1.06 (0.52–2.17)	1.04 (0.62–1.76)	1.03 (0.66–1.61)
	3	1.82 (1.29–2.57)	1.93 (1.13–3.30)	1.61 (1.05–2.48)	1.35 (0.95–1.91)
		1.71 (1.14–2.55)	1.84 (0.94–3.59)	1.39 (0.86–2.25)	1.09 (0.72–1.66)

*Categories are based on the tertile cut points of the distribution of subjects in the random sample. The cut points were 23.9 and 35.4 ms for SDNN, 14.7 and 22.3 ms for rMSSD, 11.3 and 16.4 ms for SDSD, 0.8% and 5.9% for pNN50, and 63 and 72 bpm for heart rate.

†Relative incidence rates were calculated by Poisson regression for the case-cohort design. Rates are relative to the intermediate HRV categories and the low heart rate category (indicated by relative rate=1). Two rows of relative rates are given. The first row shows the relative rates adjusted for age, sex, race, and field center. The second row shows the relative rates adjusted for age, sex, race, field center, current smoking, cigarette-years, triglycerides, HDL cholesterol, diabetes, hypertension, body mass index, waist/hip ratio, and carotid intima-media thickness.

‡For cancer mortality, the multivariable model adjusts for age, sex, race, field center, current smoking, and cigarette-years.

longer follow-up period with the use of different methodology (time domain) and a different subset of the ARIC cohort. The consistency of these results strengthens confidence that low HRV is an important predictor of CHD events. In addition, Tsuji et al[6] reported low HRV, as determined in 2-hour ambulatory ECG recordings, to be a risk indicator for incident CHD in the elderly participants of the original Framingham Heart Study, combined with the younger subjects from the Framingham Offspring Study. In the elderly cohort, low HRV was a strong predictor of death,[4] but because of the limited number of cases, the relation with specific causes of death could not be analyzed. In the Zutphen Study,[5] a prospective study in middle-aged and elderly Dutch men, HRV was determined from 15- to 30-second recordings. A strong association between low HRV and death from all causes, including cancer, was observed. The results of the present study are in line with these findings. Furthermore, we were able to show that the predictive value of HRV for death cannot be attributed to known underlying disease. The higher risk of death in the high-HRV group observed in the present study was also reported in the Zutphen Study.

Mechanisms

Heart rate and HRV are influenced by the autonomic nervous system. The rMSSD, SDSD, and pNN50 mostly reflect fast breathing–related beat-to-beat changes and are measures of

TABLE 3. HRV and Heart Rate in a 2-Minute Rhythm Strip in Relation to Death From Several Causes and CHD Incidence According to Health Status

Measure	Tertile*	All-Cause Death	CVD Mortality	Cancer Mortality	CHD Incidence
Subjects without hypertension, diabetes, symptomatic heart disease, or cancer (n=532)					
SDNN	1	†1.69 (1.11–2.57)	1.77 (0.99–3.14)	1.34 (0.77–2.34)	1.25 (0.83–1.88)
	2	1	1	1	1
	3	1.47 (0.80–2.40)	1.30 (0.59–2.43)	1.64 (0.89–3.00)	0.94 (0.58–1.52)
rMSSD	1	1.58 (1.02–2.43)	2.29 (1.24–4.25)	1.13 (0.64–1.98)	1.62 (1.05–2.51)
	2	1	1	1	1
	3	1.00 (0.62–1.61)	1.08 (0.48–2.12)	1.02 (0.56–1.86)	1.14 (0.71–1.84)
SDSD	1	1.91 (1.19–3.06)	3.04 (1.51–6.11)	1.31 (0.72–2.36)	1.44 (0.90–2.32)
	2	1	1	1	1
	3	1.29 (0.79–2.08)	1.69 (0.84–3.38)	1.12 (0.61–2.05)	0.96 (0.59–1.57)
pNN50	1	2.08 (1.34–3.23)	2.80 (1.52–5.14)	1.77 (1.00–3.13)	2.30 (1.46–3.65)
	2	1	1	1	1
	3	1.30 (0.81–2.07)	1.28 (0.66–2.47)	1.47 (0.80–2.70)	1.52 (0.94–2.47)
Heart rate	1	1	1	1	1
	2	1.02 (0.63–1.64)	1.13 (0.30–1.73)	0.89 (0.48–1.62)	1.16 (0.73–1.84)
	3	2.19 (1.38–3.47)	2.35 (1.27–4.36)	1.86 (1.05–2.31)	1.61 (1.02–2.56)
Subjects with hypertension, diabetes, symptomatic heart disease, or cancer (n=321)					
SDNN	1	†1.36 (0.87–2.14)	2.38 (0.95–5.93)	1.07 (0.61–1.87)	0.92 (0.56–1.49)
	2	1	1	1	1
	3	0.97 (0.47–1.22)	0.80 (0.29–2.22)	0.86 (0.48–1.53)	0.59 (0.36–0.96)
rMSSD	1	1.98 (1.23–3.30)	3.27 (1.23–8.68)	1.58 (0.89–2.81)	1.09 (0.67–1.77)
	2	1	1	1	1
	3	1.37 (0.85–2.20)	1.09 (0.39–3.06)	1.28 (0.71–2.31)	0.96 (0.59–1.57)
SDSD	1	2.01 (1.25–3.23)	2.29 (0.97–5.42)	1.63 (0.90–2.95)	1.29 (0.79–2.10)
	2	1	1	1	1
	3	1.60 (0.99–2.59)	0.82 (0.30–2.27)	1.67 (0.93–2.99)	1.17 (0.72–1.90)
pNN50	1	2.75 (1.70–2.37)	3.81 (1.46–9.96)	2.07 (1.15–3.72)	1.08 (0.67–1.73)
	2	1	1	1	1
	3	1.99 (1.19–3.22)	1.56 (0.52–4.69)	1.82 (0.98–3.38)	1.01 (0.62–1.64)
Heart rate	1	1	1	1	1
	2	1.48 (0.92–2.37)	1.40 (0.59–3.30)	1.58 (0.89–2.78)	1.35 (0.84–2.19)
	3	1.41 (0.88–2.35)	1.38 (0.57–3.33)	1.13 (0.62–2.06)	0.90 (0.55–1.48)

*Categories were based on the tertile cut points of the distribution of subjects in the random sample. The cut points were 23.9 and 35.4 ms for SDNN, 14.7 and 22.3 ms for rMSSD, 11.3 and 16.4 ms for SDSD, 0.8% and 5.9% for pNN50, and 63 and 72 bpm for heart rate.

†Relative incidence rates were calculated by Poisson regression for the case-cohort design. Rates are relative to the intermediate HRV categories and the low heart rate category (indicated by relative rate=1). Relative rates are adjusted for age, sex, race, and field center.

parasympathetic involvement in circulatory control.[2] The SDNN in a 2-minute recording contains both Mayer waves (10-second fluctuations) and fast fluctuations in heart rate and reflects sympathetic as well as parasympathetic involvement.[2]

In general, with sympathetic predominance, HRV is reduced, and the risk of (fatal) arrhythmias is elevated,[1] which may explain mortality risk in patients with myocardial infarction who have low HRV.[3] However, this cannot account for

the observed adverse cardiovascular risk profile and greater incidence of nonfatal CHD in subjects with low HRV in the present study, so other explanations are needed.

Many other factors affect autonomic nervous system function and, thus, HRV. HRV decreases with age,[7] high insulin level,[16] reduced baroreflex sensitivity,[17] physical inactivity,[18] rapid and shallow breathing,[19] smoking,[20] depression,[21] atherosclerosis,[9] obstructive sleep apnea,[22] and diabetic autonomic neuropathy.[1] Autonomic nervous system function affects all organ systems, including the immune system. Direct effects of sympathetic activity on the function, number, and subset distribution of circulating lymphocytes have been described.[23,24] All of these mechanisms may have contributed to the observed associations. However, our measures of age, insulin, smoking, hypertension, physical activity, atherosclerosis, diabetes, and cancer did not explain these relationships. In addition, the association was present in subjects without known disease. This suggests that low HRV precedes manifest disease. Possibly, sympathetic predominance, as reflected in low HRV and high heart rate, may be indicative of less favorable general health, with HRV being a more sensitive indicator than heart rate.

In conclusion, in a population-based study of middle-aged men and women, high heart rate and, especially, low HRV were predictive of increased mortality rates. For HRV, this relation could not be attributed to cardiovascular risk factors or to underlying disease. It may be hypothesized that low HRV is an indicator of poor general health.

Acknowledgments

This work was supported by grants from the Netherlands Organization for Scientific Research (NWO) (Dr Dekker). The authors thank the staff of the University of Minnesota ECG Coding Center and the contributors of the local centers: University of North Carolina, Chapel Hill (Phyllis Johnson, Marily Knowles, Catherine Paton); University of North Carolina, Forsyth County (Dawn Scott, Nadine Shelton, Carol Smith, Pamela Williams); University of Mississippi Medical Center (Jackson) (Virginia Overman, Stephanie Parker, Liza Sullivan, Cora Walls); University of Minnesota (Minneapolis) (Todd Avant, Joe Bjorklundx, Carolyne Campbell, Maxine Dammen); Johns Hopkins University, Baltimore, Md (Joan Nelling, Dorothy Nixon, Thelma Oliver, Rodney Palmer); University of Texas Medical School (Houston) (Valerie Stinson, Pam Pfile, Hogan Pham, Teri Trevino); The Methodist Hospital, Atherosclerosis Clinical Laboratory, Houston, Tex (Wanda R. Alexander, Doris J. Harper, Charles E. Rhodes, Selma M. Soyal); Bowman-Gray School of Medicine, Ultrasound Reading Center, Winston-Salem, NC (Bon Ellison, Julie Fleshman, Kathy Joyce, Mary Lauffer); and University of North Carolina, Chapel Hill, Coordinating Center (Hope Bryan, Myra Carpenter, Limin Clegg, Peter De Saix).

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