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Both Decreased and Increased Heart Rate Variability on the Standard 10-Second Electrocardiogram Predict Cardiac Mortality in the Elderly

The Rotterdam Study

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Decreased heart rate variability has been associated with an adverse prognosis in patients after myocardial infarction. Studies carried out in the population at large show contradictory results. The authors examined the association between heart rate variability on a standard 10-second electrocardiogram and cardiac and all-cause mortality in the Rotterdam Study, a population-based cohort study of men and women aged ≥55 years, using data collected between 1990 and 1996 (mean follow-up = 4 years). Heart rate variability, taken as the standard deviation of normal R-R intervals (SDNN), was computed by means of the Modular ECG Analysis System. After exclusion of subjects with arrhythmia and those with fewer than six normal R-R intervals, the study population consisted of 2,088 men and 3,184 women. Cox's proportional hazards model was used to examine the age- and sex-adjusted risk for cardiac, noncardiac, and total mortality in relation to quartiles of SDNN, using the third quartile of SDNN as the reference category. Subjects in the lowest quartile of SDNN relative to those in the third quartile had an 80 percent age- and sex-adjusted increased risk for cardiac mortality (hazard ratio = 1.8; 95% confidence interval: 1.0, 3.2). Interestingly, for subjects in the highest quartile of SDNN, an even more pronounced risk for cardiac mortality was present (hazard ratio = 2.3; 95% confidence interval: 1.3, 4.0). Additional adjustment for possible confounders did not materially change the risk estimates. The authors conclude that heart rate variability measured on the standard 10-second electrocardiogram can be used to identify older men and women with an increased risk for cardiac mortality. In the elderly, increased heart rate variability is an even stronger indicator of cardiac mortality than decreased heart rate variability. Further studies are needed to confirm these findings and to elucidate their physiologic meaning. *Am J Epidemiol* 1999;150: 1282–8.

aged; cardiovascular diseases; electrocardiography; heart rate

Heart rate variability (HRV) has been put forward as a promising marker of autonomic activity (1). HRV is influenced by various physiologic and pathologic conditions, such as aging (2, 3), respiration (4), diabetic neuropathy (5), congestive heart failure (6), and coronary heart disease (7–9). In the last two decades, ample evidence has emerged that reduced HRV has adverse prognostic implications in patients after myocardial infarction (10–15).

Several studies reported an association between decreased HRV and all-cause and cardiac mortality in middle-aged and elderly subjects (16–20). However, no association of reduced HRV with cardiac and all-cause mortality was found in elderly men and women in the Bronx Aging Study (21). Surprisingly, in the latter study, an association of increased HRV with cardiac events was present in women. A similar association was reported for elderly men in the Zutphen Study (17).

The task force on HRV recommends that, in order to standardize clinical studies, only two types of HRV measurements should be used (1): 1) short term measurements on 5-minute electrocardiograms made under physiologically stable conditions, processed by frequency-domain methods, and 2) 24-hour recordings processed by time-domain methods. However, two prior population-based studies restricted to men

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Abbreviations: HRV, heart rate variability; ICD-10, *International Classification of Diseases*, Tenth Revision; SDNN, standard deviation of normal R-R intervals.

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reported an association between decreased HRV, measured in 10-beat electrocardiograms (18) and 20-second electrocardiograms (17), and total and cardiac mortality. Provided that the predictive value is established, the standard 12-lead electrocardiogram would offer a useful tool for risk stratification in large populations, as it is much easier and less costly to obtain than the standardized 5-minute electrocardiogram or the 24-hour Holter electrocardiogram.

In the present study, we examined the association between decreased and increased HRV on the standard 10-second electrocardiogram and cardiac and all-cause mortality in the Rotterdam Study, a population-based cohort study of men and women aged ≥55 years.

MATERIALS AND METHODS

Study population and baseline data collection

This study was part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk factors for chronic diseases in the elderly. The objectives and methods of the Rotterdam Study are described in detail elsewhere (22). Briefly, all men and women aged ≥55 years living in the Rotterdam district of Ommoord were invited to participate (response rate = 78 percent). Baseline data on 7,129 participants, collected from 1990 to 1993, included an electrocardiogram and information on history of cardiovascular disease, cardiovascular disease risk factors, and use of coffee, alcohol, and medications.

Digitally stored electrocardiographic data were available for 6,160 (86 percent) participants. Electrocardiographic data were missing for 14 percent of the participants, mainly because of temporary technical problems with the electrocardiographic recorder. Blood pressure was calculated as the average of two consecutive measurements taken with a random-zero mercury manometer. Body mass index was calculated as weight (kg)/height $(m)^2$. Hypertension was defined as a systolic blood pressure greater than 160 mmHg or a diastolic blood pressure greater than 95 mmHg or use of antihypertensive medication. Diabetes mellitus was defined as a nonfasting blood glucose level greater than 11.1 mmol/liter or use of antidiabetic medication. History of myocardial infarction was defined as self-reported myocardial infarction with hospital admission, or a myocardial infarction indicated on the electrocardiogram. The presence of angina pectoris was established through the Rose questionnaire (23).

Subjects with arrhythmia (n = 232 (162 with atrial fibrillation, 14 with atrial flutter, 23 with atrial rhythm, 32 with ideoventricular rhythm, and one with supraventricular tachycardia)) and subjects for whom less than six R-R intervals on the electrocardiogram could be analyzed for HRV measurements (n = 251) were excluded. In addition, 345 subjects without follow-up data (mainly because they had moved to unknown locations) and 60 subjects with electrocardiograms of poor technical quality in which cardiac rhythm could not be analyzed were excluded. The final study population consisted of 2,088 men and 3,184 women.

Follow-up procedures

The follow-up period, starting at the baseline examination and lasting until April 1996 for the present analysis, was 3–6 (mean = 4) years. Information on the vital status of participants was obtained at regular intervals from the municipal authorities in Rotterdam. Information on fatal and nonfatal endpoints was obtained from the general practitioners working in the study district of Ommoord. These general practitioners, covering about 85 percent of the cohort, all have their practice computerized, and they report possible fatal and nonfatal events among participants to the Rotterdam Study data center in computer files on a regular basis. All possible events reported by the general practitioners are verified by research physicians from the Rotterdam Study, through review of patient records of the participating general practitioners and of medical specialists. In April 1996, the medical records of those participants with general practitioners from outside the Ommoord area (~15 percent of the cohort) were checked by research physicians, and additional information for coding was collected on all possible events.

For deceased participants, information on the cause and circumstances of death was obtained shortly after the death was reported by the general practitioner or municipal authorities. The information was obtained from the general practitioner by questionnaire and by scrutinizing hospital discharge records in cases of hospital admittance or referral.

Complete follow-up information was available for 94 percent of the Rotterdam Study population. Differences in baseline characteristics between participants with and without follow-up data were examined using one-way analysis of covariance, adjusting for age and sex when appropriate. Persons without follow-up data were, on average, older (73.9 years vs. 70.4 years) and had lower prevalences of hypertension (25 percent vs. 30 percent) and diabetes mellitus (10 percent vs. 14 percent). No other differences in baseline characteristics were found.

Classification of fatal and nonfatal events was based on the *International Classification of Diseases*, Tenth Revision (ICD-10) (24). We defined cardiac mortality as death from myocardial infarction (ICD-10 codes 121–124), chronic ischemic heart disease (ICD-10 code

125), pulmonary embolism or other pulmonary heart disease (ICD-10 codes 126–128), cardiomyopathy (ICD-10 codes 142–143), cardiac arrest (ICD-10 code 146), arrhythmia (ICD-10 codes 147–149), heart failure (ICD-10 code 150), or sudden cardiac death. Sudden cardiac death was defined as death occurring within 1 hour after onset of symptoms or unwitnessed death in which a cardiac cause could not be excluded (25, 26).

All events were classified independently by two research physicians. If there was disagreement, a consensus was reached in a separate session. Finally, all events were verified by a medical expert in the field of cardiovascular disease. In cases of discrepancies, the judgment of this expert was considered definite.

Electrocardiogram interpretation and measurements

A 12-lead resting electrocardiogram was recorded using an ACTA cardiograph (Esaote Biomedica, Florence, Italy) with a sampling frequency of 500 Hz, and results were stored digitally. All electrocardiograms were processed by the Modular ECG Analysis System to obtain electrocardiographic measurements and diagnostic interpretations. The Modular ECG Analysis System has been evaluated extensively (27–30).

Only R-R intervals between two adjacent normal dominant beats were used to compute mean heart rate and HRV, taken as the standard deviation of normal R-R intervals (SDNN). Both premature ventricular and supraventricular complexes were considered abnormal. The overall Q-T interval was determined on a representative beat for all 12 leads together. To adjust the Q-T interval for heart rate, we calculated Q-T_c according to Bazett's formula (31). Left ventricular hypertrophy was determined using voltage as well as repolarization criteria. Negative T waves were defined as negative T-wave deflections of at least 1.0 mm in any of the following leads: I–III, aVR, aVF, and V2–V6.

Data analysis

SDNN was categorized into quartiles, with 25th, 50th, and 75th percentile values of 9.6, 15.2, and 25.9 ms, respectively.

To evaluate the association between HRV and potentially confounding factors and other electrocardiographic factors, we examined differences in the distribution of selected baseline characteristics between subjects in quartiles of SDNN by one-way analysis of covariance, adjusting for age and sex when appropriate. Because a U-shaped relation was apparent between several determinants and SDNN in which the lowest risk was present in the third quartile, we performed separate analyses for decreased HRV (analyzing the lowest three quartiles) and increased HRV (analyzing the highest two quartiles). All determinants that showed a statistically significant ($p < 0.05$) association with SDNN in one of these analyses was considered a possible confounder.

Cox's proportional hazards model was used to examine the risk for cardiac, noncardiac, and total mortality in relation to quartiles of SDNN, adjusted for two sets of confounders: 1) age and sex and 2) all possible confounders resulting from the analysis of covariance. The third quartile of SDNN was taken as the reference category. To minimize the effect of missing data in the multivariate analysis, we replaced missing values for categorical variables with dummy variables (32). Missing values for continuous variables were replaced by the variable's average value and a dummy variable to indicate whether an imputed value was added to the model.

Subgroup analyses were performed to examine whether age (≤75 years vs. >75 years), sex, history of myocardial infarction, and presence of ectopic beats influenced the association between SDNN and cardiac mortality.

RESULTS

Baseline characteristics of participants are presented by quartile of SDNN in table 1. In the analysis of determinants of decreased HRV, statistically significant differences existed between the three groups with regard to age, sex, body mass index, and diabetes mellitus. The electrocardiographic characteristics associated with decreased SDNN were mean R-R interval and overall Q-T_c interval. Increased HRV, comparing the highest two quartiles, was associated with age, sex, mean R-R interval, the presence of negative T waves, and premature ventricular and supraventricular complexes.

During follow-up, 222 (10.6 percent) men and 238 (7.5 percent) women died; 69 (3.3 percent) men and 63 (2.0 percent) women died from a cardiac cause. Subjects in the lowest quartile of SDNN relative to those in the third quartile had an 80 percent age- and sex-adjusted increased risk for cardiac mortality (hazard ratio = 1.8; 95 percent confidence interval: 1.0, 3.2) (table 2). The corresponding hazard ratios for noncardiac mortality and all-cause mortality were 1.3 (95 percent confidence interval: 0.9, 1.8) and 1.4 (95 percent confidence interval: 1.0, 1.8), respectively. Interestingly, for subjects in the highest quartile of SDNN compared with those in the third quartile, we found an even more pronounced risk for cardiac mortality (hazard ratio = 2.3; 95 percent confidence interval: 1.3, 4.0).

The risks for cardiac and noncardiac mortality associated with both decreased and increased SDNN were

TABLE 1. Baseline characteristics of participants, by quartile of SDNN†: The Rotterdam Study, 1990–1993‡

Characteristic	All subjects (n = 5,272)	Quartile of SDNN			
		1 (<9.6)	2 (9.6–<15.2)	3 (15.2–<25.9)	4 (≥25.9)
Mean age (years)	68.7 (8.8)§	70.6**	69.1	67.4	68.0*
Sex (% women)	60.4	59.9*	64.4	62.1	54.9**
Mean systolic blood pressure (mmHg)	139.4 (22.3)	140.7	139.7	139.5	137.2
Mean diastolic blood pressure (mmHg)	73.6 (11.5)	74.2	73.7	73.5	73.0
Mean body mass index¶	26.4 (3.7)	26.7*	26.4	26.3	26.1
Mean serum cholesterol level (mmol/liter)	6.6 (1.2)	6.7	6.6	6.6	6.7
Cigarette smoking (%)	21.4	21.4	20.8	20.7	22.7
Mean coffee intake (mg/day)	482 (238)	483	481	474	490
Mean alcohol intake (mg/day)	10.3 (15.3)	10.7	9.9	10.0	10.9
Hypertension (%)	29.3	31.5	30.1	29.4	26.0
Diabetes mellitus (%)	12.3	14.8*	12.0	11.3	10.9
Angina pectoris (%)	6.7	6.9	7.0	7.0	5.7
Myocardial infarction (%)	12.1	13.3	11.4	11.3	12.0
Use of cardiovascular medication (%)	33.9	34.6	34.2	34.5	32.2
Negative T waves (%)	6.8	7.5**	8.4	5.2	7.4**
Left ventricular hypertrophy on electrocardiogram (%)	4.4	4.0	4.9	4.3	4.3
Mean R-R interval (ms)	867 (140)	801**	858	898	911*
Overall Q-T_c interval (ms)	430.9 (26.2)	438**	432	428	426
Presence of premature ventricular complex (%)	2.8	2.9	2.2	2.6	3.9*
Presence of premature supraventricular complex (%)	2.7	0.6	0.2	0.2	10.3*

* $p < 0.05$; ** $p < 0.01$.
† SDNN, standard deviation of normal R-R intervals (in ms).
‡ p values are for equality of quartile-specific values in quartiles of SDNN, adjusted for age and sex.
§ Numbers in parentheses, standard deviation.
¶ Weight (kg)/height (m)^2.

more pronounced in women than in men. The risks for cardiac mortality associated with increased HRV were more pronounced in subjects with a history of myocardial infarction and in subjects aged ≤75 years (table 2).

Because premature ventricular or supraventricular complexes occurred more frequently in persons with increased SDNN, we performed a separate analysis excluding subjects with premature complexes on their electrocardiogram. However, this did not change the results (data not shown).

We carried out analyses with additional adjustment for body mass index, diastolic blood pressure, diabetes mellitus, overall Q-T_c interval, mean R-R interval, and the presence of negative T waves (table 3). The hazard ratios did not change substantially for any endpoints.

DISCUSSION

This study showed that both decreased HRV and increased HRV, as measured by the standard 10-second electrocardiogram, are associated with cardiac mortality in the elderly. These risks were more pronounced in elderly people aged ≤75 years, in women, and in subjects with a history of myocardial infarction. In addition, the results indicate that both decreased HRV and increased HRV are associated with death from noncardiac causes in women.

Sex differences in the mortality risk associated with decreased and increased HRV in the elderly may partly be explained by selective survival. Men with heart disease die at a younger age than women, and men who live to an older age may be healthier than women of the same age. Moreover, the risks associated with decreased and increased HRV were more pronounced in those aged ≤75 years, suggesting that those who survive to older ages are less susceptible to disturbances of HRV, possibly because of other unknown characteristics. The risks of both decreased HRV and increased HRV for cardiac mortality were more clear in subjects with a history of myocardial infarction. This suggests that ischemic heart disease is involved in the mechanism controlling HRV. However, HRV was also associated with cardiac death in subjects without a history of myocardial infarction,

TABLE 2. Age-adjusted hazard ratios for cardiac, noncardiac, and all-cause mortality, by quartile of heart rate variability (defined as SDNN*), relative to the third quartile: The Rotterdam Study, 1990–1996

Outcome	Group	Quartile of SDNN						
		1 (<9.6)		2 (9.6–<15.2)		3† (15.2–<25.9)	4 (≥25.9)	
		HR*	95% CI*	HR	95% CI		HR	95% CI
Cardiac mortality	All subjects	1.8	1.0, 3.2	1.7	1.0, 3.1	1	2.3	1.3, 4.0
	Men	1.3	0.6, 2.8	1.6	0.7, 3.4	1	2.0	1.0, 4.2
	Women	2.5	1.1, 5.8	2.0	0.8, 4.8	1	2.7	1.1, 6.4
	No myocardial infarction	1.6	0.8, 3.0	1.3	0.6, 2.5	1	2.0	1.0, 3.9
	Myocardial infarction	2.4	0.8, 7.2	3.2	1.0, 9.6	1	3.2	1.1, 9.8
	Age ≤75 years	2.0	0.8, 5.4	2.8	1.1, 7.2	1	3.8	1.6, 9.5
	Age >75 years	1.6	0.8, 3.2	1.2	0.6, 2.5	1	1.6	0.8, 3.2
Noncardiac mortality	All subjects	1.3	0.9, 1.8	1.2	0.9, 1.7	1	1.1	0.8, 1.6
	Men	1.1	0.7, 1.7	0.8	0.5, 1.3	1	0.9	0.5, 1.4
	Women	1.5	0.9, 2.5	1.7	1.1, 2.8	1	1.6	1.0, 2.7
All-cause mortality	All subjects	1.4	1.0, 1.8	1.3	1.0, 1.8	1	1.4	1.0, 1.9
	Men	1.1	0.8, 1.7	1.0	0.7, 1.5	1	1.1	0.7, 1.6
	Women	1.7	1.1, 2.6	1.8	1.2, 2.7	1	1.9	1.2, 2.9

* SDNN, standard deviation of normal R-R intervals (in ms); HR, hazard ratio; CI, confidence interval.
† Reference category.

which may indicate that HRV is also a marker for subclinical disease.

Prior studies assessing the risk for future morbidity and mortality associated with HRV in the general population have consistently shown an association of decreased HRV with cardiac and all-cause mortality in middle-aged persons (17, 18–20). An association between increased HRV and mortality has never been reported for middle-aged subjects. In elderly populations, however, contradictory results have been reported for the risks associated with both decreased HRV and increased HRV. In the Framingham Heart Study (16), a linear association between decreased SDNN and all-cause mortality was present in men and

TABLE 3. Adjusted* hazard ratios for cardiac, noncardiac, and all-cause mortality, by quartile of heart rate variability (defined as SDNN†), relative to the third quartile: The Rotterdam Study, 1990–1996

Outcome	Group	Quartile of SDNN						
		1 (<9.6)		2 (9.6–<15.2)		3‡ (15.2–<25.9)	4 (≥25.9)	
		HR*	95% CI*	HR	95% CI		HR	95% CI
Cardiac mortality	All subjects	1.8	1.0, 3.3	1.7	1.0, 3.1	1	2.3	1.3, 3.9
	Men	1.4	0.6, 3.0	1.6	0.7, 3.5	1	2.0	1.0, 4.2
	Women	2.4	1.0, 5.6	2.0	0.8, 5.0	1	2.4	1.0, 5.8
Noncardiac mortality	All subjects	1.2	0.9, 1.7	1.2	0.9, 1.7	1	1.1	0.8, 1.6
	Men	0.8	0.5, 1.3	0.8	0.5, 1.3	1	1.0	0.6, 1.6
	Women	1.4	0.9, 2.4	1.7	1.1, 2.8	1	1.4	0.9, 2.4
All-cause mortality	All subjects	1.3	1.0, 1.8	1.3	1.0, 1.8	1	1.4	1.0, 1.8
	Men	1.1	0.7, 1.6	1.0	0.7, 1.5	1	1.1	0.7, 1.6
	Women	1.6	1.1, 2.5	1.8	1.2, 2.8	1	1.7	1.1, 2.6

* Adjusted for age, sex (if applicable), diastolic blood pressure, body mass index, diabetes mellitus, negative T waves, mean R-R interval, and overall Q-T_c interval.
† SDNN, standard deviation of normal R-R intervals (in ms); HR, hazard ratio; CI, confidence interval.
‡ Reference category.

women aged ≥63 years, suggesting the absence of an association of increased HRV with mortality. In the Zutphen Study (17), the risk associated with reduced HRV was less pronounced in men aged ≥65 years than in middle-aged men, and an association of increased HRV with all-cause mortality was present only in elderly men. Finally, in the Bronx Aging Study (21), among men and women aged 75–85 years, no association was present between decreased HRV and cardiac or all-cause mortality, but an association of increased HRV with cardiac events was present in women.

The absence of an association of increased HRV with mortality in some of these studies may partly be explained by exclusion criteria and procedures used to measure HRV. Upon visual inspection, one can clearly see that increased HRV is accompanied by irregular sinus arrhythmia. However, using the conventional editing rules and measures for HRV, this irregular HRV cannot be distinguished from normal sinus arrhythmia. When these irregular sinus beats are considered abnormal, the risk associated with increased HRV might be reduced, but proper definitions for abnormal sinus beats are lacking. In addition, age differences between study populations are likely to account for part of the discrepancies.

In the present study, we analyzed HRV in quartiles of SDNN. The fact that the third quartile was associated with the lowest mortality may only be an approximate indication of the true underlying relation. The nonlinear association between HRV and cardiac outcome could be studied in more detail by using finer categories of SDNN. In this study, however, the numbers were too small to allow for a sophisticated analysis.

Presumably, increased HRV, unlike decreased HRV, is hardly influenced by the autonomic nervous system but rather may be due to sinus node dysfunction (33, 34). With increasing age, pathologic changes occur in the sinoatrial node, including an increase in collagen and elastic fibers (35). Pathologic studies performed in patients with sick sinus syndrome showed that an increased amount of fibrous tissue was present in the sinus node, apart from defects due to coronary arteriosclerosis (36). It has been shown that intrinsic sinus node function, which is measured after autonomic blockade, deteriorates with age, resulting in prolonged R-R intervals and increased, irregular HRV (37, 38). In the present study, persons with increased HRV had longer R-R intervals, on average. The finding that the risk associated with increased HRV was more pronounced for cardiac mortality than for noncardiac and all-cause mortality indicates that increased HRV is influenced by ischemic heart disease.

Standard measures of decreased HRV mainly reflect changes in autonomic balance (39, 40). Autonomic dysfunction, i.e., sympathetic overactivity and a decrease in vagal activity, results in increased heart rate and, consequently, decreased HRV. Changes in autonomic balance result from coronary heart disease, but they can also be due to other disease processes (2, 3, 31–43), as is suggested by the increased risk of noncardiac mortality with decreased HRV observed in our study. The biologic meaning of SDNN measured in electrocardiographic recordings of 10 seconds will only partly match that of SDNN derived from longer periods, since some physiologic determinants simply cannot be measured within 10 seconds. Further studies are needed to clarify what these short term measures reflect physiologically.

In conclusion, HRV measured on the standard 10-second electrocardiogram can be used to identify older men and women with increased risk for cardiac mortality. In the elderly, increased HRV is an even stronger indicator of cardiac mortality than decreased HRV. Further studies are needed to confirm these findings and to elucidate their biologic meaning.

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