Impaired Autonomic Function Is Associated With Increased Mortality, Especially in Subjects With Diabetes, Hypertension, or a History of Cardiovascular Disease

The Hoorn Study

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OBJECTIVE — Measures of baroreflex sensitivity, heart rate variability (HRV), and the classical Ewing test parameters are currently used for the diagnosis of diabetic autonomic neuropathy and for mortality risk stratification after myocardial infarction. However, the strengths of the associations of these measures of autonomic function with risk of mortality have never been compared in one study population. Furthermore, no evidence is available on the possible effect of glucose tolerance on these associations.

RESEARCH DESIGN AND METHODS — The study population ($n = 605$) consisted of a glucose tolerance–stratified sample from a general population (50–75 years of age). Cardiac cycle duration and continuous finger arterial pressure were measured under two conditions: at rest and on metronome breathing. From these readings, seven parameters of autonomic function were assessed (one Ewing, five HRV, and one baroreflex sensitivity).

RESULTS — During 9 years of follow-up, 101 individuals died, 43 from cardiovascular causes. Subjects with diabetes and low levels of the autonomic function parameters, indicating impaired autonomic function, had an approximately doubled risk of mortality. This association was consistent, though not statistically significant, for all parameters. The elevated risk was not observed in subjects without diabetes, hypertension, or prevalent cardiovascular disease.

CONCLUSIONS — Impaired autonomic function is associated with all-cause and cardiovascular mortality. Moreover, the results of the present study suggest that cardiac autonomic dysfunction in patients already at risk (diabetes, hypertension, or history of cardiovascular disease) may be especially hazardous.

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Dysfunction of the autonomic nervous system is associated with increased risk of mortality in patients with diabetes (1,2), survivors of myocardial infarction (3,4), and unselected middle-aged and elderly subjects (5,6). This has been explained by the fact that autonomic imbalance predisposes individuals to cardiac arrhythmias (7). The association of autonomic imbalance with incident cardiovascular disease and all-cause mortality in the general population has been attributed to subclinical coronary artery disease or otherwise poor health (5,6). Another possibility, addressed only marginally in these studies, might be glucose intolerance. Subjects with diabetes are known be at high risk of developing autonomic dysfunction, and autonomic dysfunction is already present in patients with newly diagnosed diabetes (8). Glycemic parameters are associated with death from all causes in patients with diabetes, impaired glucose tolerance (IGT) (9), and even normal glucose tolerance (10,11). However, impaired autonomic function and mortality so far have not been studied in relation to glucose intolerance.

Numerous tests exist to assess cardiovascular autonomic function, based on measurement of beat-to-beat changes in heart rate and/or blood pressure. These tests may be classified into three groups: *1*) classical Ewing tests (12), including the deep breathing and lying-to-standing test; *2*) spectral analysis of spontaneous heart rate variability (HRV) (13,14); and *3*) baroreflex sensitivity (BRS), the heart rate response following a change in blood pressure. The different types of autonomic function measures so far have not been compared in one single study population.

Therefore, we studied the association

of several autonomic function measures with mortality in 50- to 75-year-old men and women, with special reference to the possible confounding or effect-modifying role of glucose intolerance and cardiovascular disease.

RESEARCH DESIGN AND METHODS

Study population
The present study is part of the Hoorn Study, a prospective study of glucose tolerance in a general population of Caucasian subjects (50–75 years of age) (11). The baseline examination was conducted in 1989–1992, as previously described in detail (15). Briefly, a random sample was drawn from the municipal population of Hoorn, the Netherlands. All 2,484 participants (71%), except those who were taking glucose-lowering medication, underwent 75-g oral glucose tolerance testing. A sample of 708 subjects, stratified by 2-h glucose values, age, and gender, was invited to undergo extensive examinations of diabetes-related complications, and 631 subjects (89%) participated. For the present analyses, we excluded subjects who had pacemakers ($n = 2$), who were taking antiarrhythmic medication ($n = 17$), or who had self-reported neurologic disease ($n = 8$), resulting in a study population of 605 subjects.

Baseline examination
Fasting and 2-h plasma glucose levels were determined with a glucose dehydrogenase method (Merck, Darmstadt, Germany). Subjects were classified into glucose tolerance groups, based on the mean values of two oral glucose tolerance tests (16). A total of 282 individuals had normal glucose tolerance (NGT), 164 had IGT, 85 had newly diagnosed diabetes, and 74 had known type 2 diabetes, as defined by the use of a diet or glucose-lowering medication. HbA$_{1c}$ was determined by ion-exchange high-performance liquid chromatography (Bio-Rad, Veenendaal, the Netherlands).

Blood pressure was measured in duplicate on two separate occasions on the right arm of seated subjects after at least 5 min of rest, by means of a random-zero sphygmomanometer (Hawksley-Gelman, Lancing, Sussex, U.K.). The averages of the four blood pressure readings were calculated. Hypertension was defined as a systolic blood pressure ≥160 mmHg, a

diastolic blood pressure ≥95 mmHg, and/or the use of antihypertensives (17). These cutoff points were used because of the definition of hypertension at the time of the data collection. Use of antihypertensives was defined as current treatment with alpha blockers, beta blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, diuretics, and/or a rest group including centrally acting antihypertensives.

Cardiovascular disease was defined as coronary artery, cerebrovascular, and/or peripheral arterial disease. Coronary artery disease was defined as self-reported history of myocardial infarction, coronary artery bypass grafting, or Minnesota codes 1-1 or 1-2 on electrocardiography. Peripheral arterial disease was defined as self-reported peripheral arterial reconstruction, nontraumatic limb amputation, and/or an ankle brachial pressure index <0.50 (18). Cerebrovascular disease was defined as self-reported history of stroke or carotid stenosis >80% (19,20).

For assessment of cardiac autonomic function, participants were asked to refrain from smoking and drinking coffee for 2 h before the tests. Tests took place between 8:30 A.M. and 4:00 P.M., at least 1 h after participants ate a light meal, in a quiet ambience with room temperature of 19–22°C. Cardiac cycle duration (R-R interval) and continuous finger arterial pressure were continuously recorded on a PC-based data-acquisition system, in supine position *1*) during spontaneous breathing for 3 min and *2*) during metronome breathing at six breaths/min for 1 min. When off-line spectral analysis showed that breathing was not performed at the appropriate frequency, the record was discarded. The test session started with a resting period of at least 10 min. R-R intervals were obtained by electrocardiography using a QRS detector with an accuracy of 1 ms. Blood pressure was recorded using the Finapres method (finger arterial blood pressure, model BP2000; Ohmeda, Englewood, CO) (20). Systolic blood pressure values were obtained from the sampled blood pressure signal by means of an automatic procedure, which was verified by visual inspection.

Seven measures of cardiovascular autonomic function were computed, as previously described in detail (14,18,21,22) (Table 1). Individual data were missing (57 for spectral measures, 51 for Ewing

tests, 87 for BRS) because the test schedule was not completed, because the test was not performed correctly, or because the quality of the data were insufficient for processing.

Follow-up examination
Information on vital status was obtained from the population register of the city of Hoorn. Causes of death were obtained from the medical records at the general practices, the local hospital, and the local nursing home and coded according to the *International Classification of Diseases, Injuries and Causes of Death, 9th Revision* (ICD-9) (23). Cardiovascular disease mortality, including sudden death, was defined by the ICD-9 codes 390-459 and 798.

The study protocol was approved by the Ethics Committee of the University Hospital of the Vrije Universiteit. All study participants gave informed consent.

Statistical analysis
All analyses were performed using SPSS statistical software (SPSS, Chicago, IL). For survival analyses, the lowest 25th percentile values of the autonomic function measures in the NGT group were considered the cutoff to define autonomic dysfunction. There are no generally accepted cutoff points to define impaired autonomic function, and furthermore, there are indications that the association with mortality risk may not be continuous. The lower quartile was selected to have substantial numbers in each group for the statistical analysis. Hazard ratios (relative risk) and 95% CIs for determinants of cardiovascular and all-cause mortality were determined by Cox's proportional hazards analysis. All analyses were adjusted for age, gender, and glucose tolerance because of the stratification procedure. We primarily adjusted for other risk factors that were statistically significantly associated with mortality and secondarily for all other risk factors. As possible confounders, we considered BMI, HbA$_{1c}$, fasting insulin, total cholesterol, HDL cholesterol, current smoking (yes/no), and alcohol consumption (yes/no). To test for possible effect modification, the risk factor of interest, the autonomic function measure under consideration, and the product term were included in the model. A significant product term was interpreted as effect modification by that risk factor. Whenever effect modification was

Table 1—*Overview of the seven measures of cardiovascular autonomic function*

Measure	Unit	Definition
During spontaneous breathing for 3 min in the supine position:		
Mean NN	ms	The mean of all normal-to-normal (sinus rhythm) R-R intervals*
SDNN	ms	The standard deviation of all normal-to-normal (sinus rhythm) R-R intervals*
LF power	ms^2	Low-frequency power, in absolute units: energy in the power spectrum between 0.04 and 0.12 Hz*
HF power	ms^2	High frequency power, in absolute units: energy in the power spectrum between 0.12 and 0.40 Hz*
LF/(LF + HF)		The ratio of low-frequency power to the sum of the low- and high-frequency power*
During six deep breaths for 1 min in the supine position:		
EI difference	ms	The mean expiration-inspiration difference in R-R intervals over the six consecutive breaths†
BRS	ms/mmHg	A measure of baroreflex sensitivity, computed as gain, i.e., ratio of the energy, in the cross-spectrum of systolic blood pressure and R-R intervals and the energy in the power spectrum of the R-R interval, all between 0.05 and 0.15 Hz and with a squared coherence (γ^2) of 0.5 or higher‡

*See reference no. 14; †see reference no. 12; ‡see reference no. 21.

likely, a stratified analysis was performed. For all analyses, two-sided probability values <0.05 were considered statistically significant.

RESULTS — Follow-up continued until January 1999. Median follow-up was 7.9 years (range 0.5–9.2). During the follow-up period, 101 of the 605 persons died. Information on cause of death could not be obtained for 14 of the subjects who had died, because the individuals had moved and medical records could not be retrieved. The baseline characteristics for survivors ($n = 504$) and nonsurvivors are shown in Table 2 . Subjects who died had significantly lower scores on all parameters of autonomic function, except for the HRV power ratio, than those who survived (Table 2).

Cutoff points for impaired autonomic function, taken from the lowest 25th percentile in the NGT group, were 878 ms for the mean of all normal-to-normal (NN) (sinus rhythm) R-R intervals, 25.7 ms for the standard deviation of all NN (sinus rhythm) R-R intervals (SDNN), 125 ms^2 for low-frequency (LF) power in the R-R–interval spectrum between 0.04 and 0.12 Hz, 93 ms^2 for high-frequency (HF) power in the R-R interval spectrum between 0.12 and 0.40 Hz, 0.41 for LF/(LF + HF), 107 ms for expiration-inspiration (EI) difference in R-R intervals during

breathing at six breaths/min, and 6.1 ms/mmHg for BRS.

The survival analyses, shown in Table 3, yielded systematically different results for subjects with and without diabetes. In diabetic subjects, but not in nondiabetic subjects, impaired autonomic function was consistently associated with an approximately doubled risk of mortality but was not statistically significant for all parameters. Of these seven parameters of autonomic function, EI difference was significantly associated with all-cause mortality, after adjustment for age, gender, and glucose tolerance, and an additional four parameters showed a tendency ($P < 0.10$): mean NN, LF power, HF power, and BRS. A survival curve of categories of the EI difference is shown in Fig. 1. For six of the seven measures of autonomic function, the relative risks were slightly higher in diabetic subjects than in nondiabetic subjects; for SDNN, the product term was significant. The associations with cardiovascular disease mortality were similar.

Further stratified analyses showed an elevated risk of mortality associated with low autonomic function in subjects with hypertension, subjects taking antihypertensive medication, or subjects with a history of cardiovascular disease (data not shown). Therefore, a stratified analysis was performed for subjects at low or high

risk, with high risk defined as the presence of diabetes and/or hypertension and/or a history of cardiovascular disease. In subjects at low risk, impaired autonomic function did not seem to be associated with all-cause or cardiovascular mortality. In the high-risk group, however, autonomic dysfunction showed a consistent association with mortality but was not statistically significant for all parameters (Table 3). For the EI difference, the product term, indicative of effect-modification by baseline risk, was significant.

Potentially confounding variables that were statistically significantly associated with all-cause mortality were BMI, smoking, and fasting insulin (data not shown). Including these potentially confounding variables into the models did not materially change the estimated relative risks for impaired autonomic function.

CONCLUSIONS — This study shows that autonomic function parameters are associated with risk of all-cause and cardiovascular death, even after adjustment for age, gender, glucose tolerance, and use of antihypertensive medication. The strength of the relation between survival and autonomic function was generally stronger in subjects with diabetes, hyper-

Table 2—*Baseline characteristics and measures of autonomic function*

| | Survivors ($n = 504$) | Nonsurvivors ($n = 101$) | |
		Deaths from all causes ($n = 101$)	Cardiovascular deaths ($n = 43$)
Age (years)	63.5 (7.0)	68.5 (6.3)	68.7 (6.6)
Sex (% male)	47.8	49.5	53.5
Type 2 diabetes (%)	22.8	43.6	46.5
Impaired glucose tolerance (%)	27.6	24.8	23.3
BMI (kg/m^2)	27.0 (3.9)	28.5 (4.4)	28.7 (4.7)
Current smokers (%)	25.6	30.7	30.2
Alcohol consumption (%)	64.3	60.4	58.1
Prevalence of cardiovascular disease (%)	30.6	57.4	67.4
Hypertension (%)	34.5	57.4	65.1
Antihypertensive drug treatment (%)	24.2	42.6	48.8
Total cholesterol (mmol/l)	6.65 ± 1.18	6.71 ± 1.16	6.77 ± 1.21
HDL cholesterol (mmol/l)	1.29 ± 0.36	1.23 ± 0.35	1.19 ± 0.35
HbA$_{1c}$ (%)	5.8 ± 1.2	6.4 ± 1.6	6.5 ± 1.3
Fasting insulin (pmol/l)*	82 (46–151)	93 (44–197)	100 (45–191)
Autonomic function measures			
Mean NN (ms)	953 ± 150	902 ± 144†	903 ± 127†
SDNN (ms)*	33.2 (18.8–56.5)	27.7 (13.7–55.8)†	26.0 (9.4–55.4)†
LF power (ms^2)*	233 (61–945)	153 (18–640)†	134 (15–519)†
HF power (ms^2)*	183 (37–835)	123 (16–747)†	137 (15–1022)†
LF/(LF + HF)	0.58 ± 0.19	0.53 ± 0.22	0.49 ± 0.23
EI difference (ms)*	158 (74–336)	126 (45–318)†	113 (46–329)†
BRS (ms/mmHg)*	7.8 (3.4–14.4)	6.4 (2.2–13.3)†	6.3 (2.2–14.2)†

Data are means ± SD, %, and 95% CI unless otherwise indicated. *Given are the median (10th to 90th percentiles); †nonsurvivors differed from the survivors, Student's t test $P < 0.05$ (only autonomic function measures were tested; Student's t tests were performed using the ln-transformed values). See Table 1 for definition of autonomic function measures.

tension, and/or a history of cardiovascular disease.

Methodological issues

Relatively short recordings of heart rate variability (15 s to 15 min) have been shown to be predictive for both cardiovascular and all-cause mortality in post-myocardial infarction patients and also in the general population (3,5). Autonomic function assessment is used mainly in two clinical fields: in cardiology for risk-stratification after myocardial infarction and in internal medicine to assess (diabetic) autonomic neuropathy. Cardiologists tend to use HRV measures (SDNN, LF power, and HF power) as obtained from 24-h Holter monitor recordings (14), whereas internists tend to use controlled breathing and the lying-to-standing maneuver (12,24), both known as Ewing tests, although HRV analysis has been introduced as well. Recently, the BRS has gained more interest (4,25). The current study is the first to address all these measures of autonomic function: Ewing test, HRV, and BRS. In general, the measures

obtained from the deep-breathing test (EI difference and BRS) showed the highest relative risks, especially in individuals with hypertension or diabetes. However, the measures obtained during spontaneous breathing also showed a clear association with mortality. Use of certain medication, such as beta blockers and sympaticomimetics, may be confounding because they affect autonomic nervous system function (14,18). Therefore, additional stratified analyses were performed, and indeed, hypertension and use of antihypertensives were effect modifiers. This finding has not been reported before and has not been taken into account in previous studies (3–5). In the present study, a large proportion of the diabetic subjects were taking antihypertensive medication; the initial tendency of effect modification by diabetes was partly attributable to the differences in use of antihypertensives in the diabetic subjects (40 vs. 23% in nondiabetic subjects).

In the present study, the lowest quartiles of the distribution of autonomic function parameters were taken as indica-

tions for impaired autonomic function. In this population-based study, few subjects had levels lower than previously reported cutoff points. However, when we did apply these cutoff points to our data, the estimated relative risks were not consistently higher, and the results with respect to the observed interaction with high-risk status were similar.

Previous studies

Studies on the relation between autonomic function and survival in diabetes are scarce (2,26). This is the first study to address the influence of diabetes on the association between autonomic function parameters and mortality in a large cohort, stratified by glucose intolerance. The Framingham Heart Study (6), the Zutphen study (5), and the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study (4) have shown that impaired autonomic function is predictive for (cardiovascular) death, both in the general population and after myocardial infarction. In the Zutphen Study (5), these possible effect modifiers (4,5) were

Table 3—*Relative risks (95% CI) of autonomic dysfunction* for all-cause and cardiovascular mortality in subjects without (n = 446) and with diabetes (n = 159) and in subjects at low risk (n = 271) and high risk (diabetes and/or hypertension and/or cardiovascular disease) (n = 334)*

Parameter*	Without diabetes		With diabetes	
	All cause	Cardiovascular	All cause	Cardiovascular
Mean NN	1.43 (0.79–2.58)	1.21 (0.46–3.18)	1.69 (0.90–3.18)	1.29 (0.50–3.32)
SDNN	0.99 (0.54–1.84)†	1.33 (0.52–3.39)	1.72 (0.89–3.31)†	1.32 (0.51–3.42)
LF power	1.29 (0.70–2.36)	1.23 (0.46–3.31)	1.89 (0.98–3.65)	2.30 (0.82–6.43)
HF power	1.69 (0.94–3.02)	1.57 (0.61–4.02)	1.36 (0.72–2.59)	1.03 (0.40–2.67)
LF/(LF + HF)	0.67 (0.31–1.44)	1.29 (0.46–3.61)	1.73 (0.86–3.46)	1.90 (0.72–5.06)
EI difference	1.21 (0.66–2.21)	1.64 (0.64–4.17)	2.25 (1.13–4.45)	2.04 (0.74–5.65)
BRS	1.32 (0.72–2.41)	1.28 (0.47–3.53)	2.19 (1.11–4.34)	2.98 (1.08–8.25)

	Low risk		High risk	
	All cause	Cardiovascular	All cause	Cardiovascular
Mean NN	1.14 (0.44–3.00)	0.96 (0.19–4.77)	1.66 (1.03–2.67)	1.46 (0.70–3.04)
SDNN	0.57 (0.19–1.73)	0.83 (0.16–4.22)	1.41 (0.88–2.28)	1.56 (0.75–3.24)
LF power	0.87 (0.31–2.47)	0.42 (0.05–3.55)	1.49 (0.92–2.42)	2.13 (1.01–4.49)
HF power	1.08 (0.40–2.90)	0.87 (0.17–4.52)	1.52 (0.94–2.45)	1.37 (0.66–2.85)
LF/(LF + HF)	0.20 (0.03–1.51)	0.50 (0.06–4.17)	1.33 (0.78–2.25)	2.09 (0.99–4.42)
EI difference	0.80 (0.29–2.24)†	0.82 (0.16–4.14)†	1.69 (1.02–2.80)†	1.75 (0.80–3.86)†
BRS	1.61 (0.63–4.10)	0.49 (0.06–4.14)	1.45 (0.88–2.40)	2.02 (0.93–4.39)

*The lowest 25th percentile values of the autonomic function parameters in the NGT group were considered the cutoff to define autonomic dysfunction: mean NN 878 ms; SDNN 25.7 ms; LF power 125 ms^2. HF power 93 ms^2; LF/(LF + HF) 0.41; EI difference 107 ms; BRS 6.1 ms/mmHg. See Table 1 for definition of autonomic function measures. Models in subjects without diabetes were adjusted for age, gender, and impaired glucose tolerance; models for subjects with diabetes were adjusted for age, gender, and known diabetes; models for both low-risk and high-risk subjects were adjusted for age and gender. †Product-term (glucose tolerance times autonomic function), $P < 0.05$.

not taken into account, whereas in the Framingham Heart Study, data have been adjusted for diabetes and use of diuretics. However, as we observed in our study, diabetes and hypertension may be effect modifiers, and in that case, a stratified analysis is indicated to present the results. In the ATRAMI study, subjects with type 1 diabetes were excluded, but hyperten-
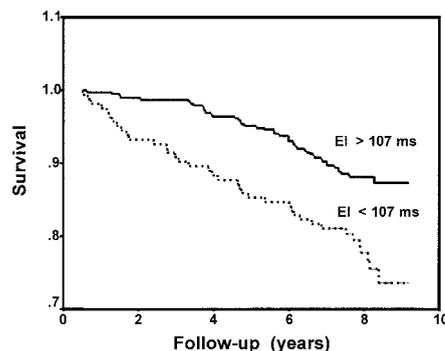

Figure 1—*Kaplan-Meier curve stratified for EI difference, based on the results of all subjects for whom measurements were available (n = 554). The dotted line represents an EI difference >107 ms, and the solid line represents an EI difference ≤107 ms, indicative of autonomic dysfunction.*

sion or use of antihypertensives was not accounted for. These differences of accounting for diabetes and use of antihypertensives, together with the different ways of assessing autonomic function, the different cutoff points used, and the different populations, limit detailed comparison with previous results. However, the association of autonomic dysfunction with mortality risk is consistent. Our study confirms this for a Ewing test measure, HRV measures, and BRS. We showed that these associations were especially strong in a high-risk population, defined by the presence of diabetes, hypertension, and/or a history of cardiovascular disease.

Possible mechanisms

The increased risk of mortality in myocardial patients with impaired autonomic function can be attributed to the elevated risk of life-threatening arrhythmia (3,14). In the general population, impaired autonomic function by low HRV or low BRS is also associated with nonfatal cardiovascular events and even with future risk of hypertension (27–29); therefore, other mechanisms must be involved. Autonomic dysfunction could be a marker or

even a risk factor for endothelial dysfunction and atherosclerotic disease. The present finding that impaired autonomic function is especially harmful in subjects at high risk may add strength to the hypothesis that impaired autonomic function may complicate underlying cardiovascular disease rather than being a risk factor. However, further studies are needed to elucidate the involved mechanisms.

The strength of the relation between survival and autonomic function was dependent on the presence of diabetes, hypertension, or a history of cardiovascular disease. This suggests that in subjects already at high risk, cardiovascular autonomic dysfunction may be especially hazardous.

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