Electrocardiographic predictors of future coronary heart disease:

a possible role of autonomic control

Jacqueline M. Dekker

STELLINGEN

1. Electrocardiogrammen van patiënten zeggen iets over het bestaan van hartafwijkingen, die van gezonden iets over het ontstaan.
dit proefschrift

2. Een lang QTc in het electrocardiogram gaat gepaard met een grotere kans op coronaire hartziekte.
dit proefschrift

3. Een te geringe aan de ademhaling gerelateerde fluctuatie van het hartritme is waarschijnlijk een indicatie van een matige gezondheid.
dit proefschrift

4. In hun hart verschillen mannen en vrouwen wel degelijk van elkaar.
Dekker JM, et al. Is QT interval a strong or a weak predictor of cardiac death? (letter to the editor) Circulation 1993;87:300

5. 'Of course, lion attacks are sporadic events, though sometimes in clusters, so control observations are needed to establish statistical significance of the protective properties of umbrellas.'
Anderson DA. Umbrellas and lions. J Clin Epidemiol 1991;44:335-7

6. Hardlopers zijn geen doodlopers.

7. Het gebruik van de promovendus als wegwerpartikel past niet in het wetenschappelijk pleidooi voor duurzaamheid.

8. Geloof in eigen superioriteit komt meestal voort uit onwetendheid.

9. De preoccupatie van artsen met ziekte weerklinkt in de commentaren van referenten van wetenschappelijke medische tijdschriften, waarin zij over patienten spreken als het onderzoek in de algemene populatie heeft plaatsgevonden.

10. Bezuiniging op de gezondheidszorg kan ook leiden tot besparing op de pensioenen.

11. Al te nuchter is niet goed voor je hart.

Stellingen behorend bij het proefschrift "Electrocardiographic predictors of future coronary heart disease: a possible role of autonomic control" van Jacqueline Dekker
Wageningen, 28 november 1994

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"Als ik het ongewone, het alledaagse, in dit nieuwe licht bezag stond ik vaak als aan de grond genageld. Zodra men nauwkeurig aandacht schenkt aan wat ook, zelfs aan een grasspriet, wordt dit een geheimzinnige, ontzagwekkende, onbeschrijflijk vergrote wereld op zich. Welhaast een 'onherkenbare' wereld."

Henry Miller in 'Plexus', 1953

Contents

Abstract

Electrocardiographic predictors of future coronary heart disease: a possible role of autonomic control

PhD Thesis, Department of Human Epidemiology and Public Health, Wageningen Agricultural University, Wageningen, The Netherlands, November 1994.

Jacqueline Dekker

This thesis presents a number of studies on the predictive value of electrocardiographic manifestations of autonomic control of the heart and of ischemic heart disease for coronary heart disease morbidity and mortality in the general population. The electrocardiograms of the Zutphen Study, a prospective study on cardiovascular disease in the general population, were used for this purpose. Physical examinations (including electrocardiography) were repeatedly carried out from 1960 to 1985, among 878 men from Zutphen, born between 1900 and 1920. In 1985 additional recruitment in the same birth cohort in Zutphen was performed. A cohort of 939 men, then aged 65 to 84, participated. These cohorts have been followed with respect to morbidity, vital status, and causes of death.

The results of these studies provide evidence that electrocardiographic characteristics (the Cardiac Infarction Injury Score, QTc duration, ST-T-characteristics, and heart rate variability) do predict the occurrence of future heart disease. Furthermore, there were indications that besides autonomic cardiac control, other determinants, like glucose tolerance, may affect ventricular electrical stability as well. In future research, determinants like glucose tolerance, physical activity, certain nutritional factors, and smoking, warrant further attention. Especially, it should be evaluated whether improvements in the electrocardiogram caused by interventions in these determinants are associated with a better prognosis.

1. Introduction

It is striking how much one can learn of a person's heart and its function by just placing some electrodes on the skin and amplifying the signal. An experienced cardiologist is able to diagnose many types of heart disease, just by inspection of the electrocardiogram. It is evident that this non-invasive technique since the invention in 1902 of the string galvanometer by Willem Einthoven (for which he received the Nobel Prize[1]), has gained a major place in medicine. The almost exclusive employment of electrocardiography in clinical practice however, has led to concentration on its diagnostic properties. Even in population studies, the focus has mainly been on early signs of heart disease[2-4]. The study of electrocardiograms of healthy people, however, may contribute to our understanding of the development of heart disease. In this thesis we present a number of studies on the predictive value of electrocardiographic characteristics, which reflect cardiac autonomic control, for coronary morbidity and mortality in middle-aged and elderly men.

From experimental studies and observations in myocardial infarction patients, it is known that the autonomic nervous system has a crucial function in cardiac control, including ventricular electrical stability[5-7]. In periods of high sympathetic stimulation, because of high physical or emotional stress, certain patients have high risk of developing life threatening arrhythmia and sudden death. This may be due to imbalance of sympathetic innervation by left and right ganglia stellata[8,9] or to predominance of sympathetic over parasympathetic activity[10,11]. Associated electrocardiographic manifestations are prolongation of the heart rate adjusted QT (QTc) and reduced heart rate variability[12-15]. More than twofold relative risks of sudden death for patients with QTc prolongation[13,14] and more than fivefold for patients with reduced heart rate variability[14,15] have been reported. In a previous study in Dutch middle-aged civil servants, Schouten et al. also found a higher risk of coronary heart disease mortality in apparently healthy subjects with prolonged QTc[16]. Furthermore, subjects with slight ST-elevation were shown to have reduced risk[17]. Possibly unfavourable autonomic control increased the risk of fatal events in subjects who, though being healthy at baseline, subsequently developed coronary heart disease. However, it may also be involved in the disease process, because high sympathetic

activity is associated with unfavourable levels of a number of coronary heart disease risk factors. In the latter case, an association with coronary heart disease morbidity is expected.

The aim of the present study was to determine the predictive value of electrocardiographic manifestations of autonomic control of the heart (QTc duration, T-wave amplitude, ST-segment level, and heart rate variability) for coronary heart disease morbidity and mortality in the general population. Because at old age the responsiveness to tests of autonomic function is reduced[18], and the prevalence of electrocardiographic abnormalities is higher[19], the associations were also studied in elderly people.

For this purpose, the electrocardiograms of the Zutphen Study, a prospective study on cardiovascular disease in the general population, were used. From 1960 to 1985, physical examinations (including electrocardiography) were repeatedly carried out among 878 men from Zutphen, born between 1900 and 1920. In 1985 additional recruitment in the same birth cohort in Zutphen was performed. A cohort of 939 men, then aged 65 to 84, participated. These cohorts have been followed with respect to morbidity, vital status, and causes of death.

Outline of the thesis

In chapter 2, the association of electrocardiographic signs of prevalent heart disease with coronary morbidity and mortality is described. The Cardiac Infarction Injury Score was used to quantify signs of a past myocardial infarction. In chapter 3 findings on the predictive value of a prolonged heart rate adjusted QT interval for coronary heart disease incidence are presented. The relationship of QT with carbohydrate metabolism is discussed in chapter 4. The associations of T-wave amplitude deviations and ST-segment with coronary morbidity and mortality are described in chapter 5. The results of a study on heart rate variability and mortality from different causes are presented in chapter 6.
Finally, in the general discussion, chapter 7, a number of methodological issues of the presented study are commented on, and the possible mechanisms and implications of these findings for future research are discussed.

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2. The cardiac infarction injury score as predictor of coronary heart disease in middle-aged and elderly men. The Zutphen Study[1]

Jacqueline M. Dekker, Evert G. Schouten, Daan Kromhout, Peter Klootwijk, Jan Pool

Abstract

The Cardiac Infarction Injury Score (CIIS), based on electrocardiographic characteristics, was developed as a measure to determine the presence of myocardial infarctions. In the present study the predictive value of the CIIS for coronary morbidity and mortality was investigated among middle-aged and elderly men.
A cohort of 877 men, born between 1900 and 1919, was followed and repeatedly examined from 1960 on. In 1985 the remaining cohort was extended to 836 elderly men from the same birth cohort, and followed until 1990. In both middle-aged and elderly men with high CIIS the prevalence of (silent) previous myocardial infarction and the occurrence of ST-T abnormalities were increased. Five-year relative risks of men with CIIS 20 or more relative to men with CIIS less than 5 were 2.2 (95% confidence interval: 1.2-4.1) for angina pectoris, 2.4 (1.4-4.0) for myocardial infarction and 5.8 (3.4-9.9) for coronary heart disease death.
Thus, the CIIS predicts coronary heart disease in apparently healthy middle-aged as well as elderly men.

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[1] Journal of Clinical Epidemiology *in press*

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Introduction

The Cardiac Infarction Injury Score (CIIS) is an electrocardiogram based measure which was originally constructed as a diagnostic tool, to discriminate between presence or absence of myocardial infarction[1]. Furthermore, emphasis has been placed on the capacity of the CIIS to detect changes in the extent of cardiac injury in myocardial infarction patients, indicating recovery or exacerbation. A limited number of studies have reported on the predictive value of the CIIS for coronary heart disease mortality, in middle-aged men only[2-4]. However, since the prevalence of electrocardiographic abnormalities increases with age, whereas age-related selection results in survival of relatively healthy people, it may be questioned whether the CIIS is as discriminative of coronary heart disease risk in the elderly as it is in middle-aged persons. In addition, information on the predictive value of individual change of CIIS over time in apparently healthy people is not available at all.

The purpose of the present study was to investigate the predictive value of the CIIS and of temporal changes in it for angina pectoris, first myocardial infarction, and coronary heart disease mortality in both middle-aged and elderly men. This was studied in the Zutphen Study, the Dutch contribution to the Seven Countries Study.

Subjects and methods

Study Population

The Zutphen Study, which started in 1960, is a follow-up study of a cohort of men, born between 1900 and 1919 and living in Zutphen, The Netherlands. A sample of 1088 men was invited for a medical examination and a dietary survey. Of these, 32 (3%) refused to participate, while 178 (16%) only took part in the dietary survey or were examined later than 1960. A 12-lead electrocardiogram was recorded in 877 of the remaining 878 middle-aged men. Of this cohort electrocardiograms were made during follow-up medical examinations in 1965 and 1970 of 717 and 625 men respectively.

In 1985 the cohort was extended to form a new cohort of elderly persons. An additional sample of 711 elderly men was drawn from the same birth cohort,

in 1985 aged 65-85, and added to the remaining 555 members of the 1960 cohort. Of these, 384 were excluded: 109 (9%) could not be examined because of illness or death, 156 (12%) did not volunteer, and 62 (5%) could not participate for various reasons (moved out, could not be traced etc.). Finally 939 (74%) men participated in the study, 885 of whom had a 12-lead electrocardiogram recorded. Unfortunately, 49 of the paper recordings were lost, so the elderly cohort comprised 836 men. At the follow-up medical examination in 1990 electrocardiograms were made in 545 of 656 surviving men.

Data Collection

Electrocardiography and measurement of other cardiovascular risk factors were performed according to the protocol of the Seven Countries Study[5] in 1960, 1965, 1970, 1985 and 1990. The electrocardiograms were coded according to the Minnesota Code[6]. In 1992 all electrocardiograms were coded according to the CIIS as well. Coders were blinded for other information and survival.

Supine systolic and diastolic blood pressures were measured twice at the end of all physical examinations in the right arm. Between 1960 and 1970 the last value was recorded. In 1985 and 1990 duplicate measurements were recorded. Serum total cholesterol was determined in a standardized laboratory by the Abell-Kendall[7] method (1960 and 1965), by the method of Zlatkis[8] in 1970, by the enzymatic method of Siedel et al.[9] and Stahler et al.[10] in 1985 and 1990. All these methods provided Abell-Kendall equivalents. Body mass index (weight/height^2) was calculated from height and weight (height was measured in 1960 and 1985 only). At all examinations until 1985 subjects answered the Seven Countries Study questionnaire on smoking habits. In 1985 and 1990 a newly developed questionnaire[11] was used.

End points

Mortality was registered weekly by means of the municipal registry of the town of Zutphen. A small number of men who moved out of Zutphen were followed individually by means of questionnaires. Causes of death were obtained from the death certificates, and from the hospital and/or the general practitioner. Information on coronary disease (including the Rose questionnaire) was collected during the medical examinations. Between 1960 and 1973 medical examinations were performed

annually, and after that also in 1977/78 and in 1985. In addition questionnaires on health status were filled in in 1980 and 1982. The information on morbidity provided in these questionnaires was verified by contacting general practitioners. In the period 1985-1990 hospital discharge data of members of the cohort who had been hospitalized in Zutphen were made available as well. The follow-up of both the middle-aged and the elderly cohort is 100%.
Causes of death were coded according to the International Classification of Diseases[12] (8th revision or the period 1960 to 1985; 9th from 1985 to 1990), based on all available information on morbidity and mortality. Coronary heart disease mortality was defined as ICD-8 codes 410, 411.9-413.9, and as ICD-9 codes 410-414.
Angina pectoris was coded only in men without prior myocardial infarction, when the subject had complaints of chest pain during physical effort, relieved within 10 minutes by stopping the effort. Myocardial infarction was coded when 2 of the following 3 criteria were present: 1. a specific medical history, e.g. severe chest pain lasting for more than 20 minutes and not disappearing during rest; 2. electrocardiographic changes corresponding to Minnesota Codes 1.1 (major Q waves) code 1.2 accompanied by 5.1 or 5.2 (smaller Q waves and major T-wave abnormalities); 3. specific enzyme level elevations. In case of fatal events, myocardial infarction was coded when ICD code 410 was used. The year of the first occurrence of myocardial infarction (fatal or non fatal) and of angina pectoris was recorded.

Data Analysis

Subjects were categorized according to the CIIS in classes less than 5 (I), 5-9 (II), 10-19 (III), and 20 or more (IV). The lowest cutoff point was selected to separate approximately half of the population. The two upper cut-off points were selected in accordance with the 'severity levels' as defined by Rautaharju[1]. Mean values of CIIS and covariates at baseline and at repeated examinations were described in categories of CIIS at baseline.
The predictive value of CIIS for the incidence of angina pectoris and myocardial infarction, and for mortality of coronary heart disease was analyzed using Cox Proportional Hazards models. For the analyses using angina pectoris or myocardial infarction as end points, prevalent cases were excluded. Conventional analyses of long-term (15-year) predictive value were performed for each period of measurement

separately, viewing each follow-up exam as the baseline measurement of a separate 15-year follow-up study. Secondly, in order to make better use of the repeated measurements, each exam and subsequent 5-year follow up was regarded as one observation. These combined data were analyzed by Cox proportional hazards models, stratified for the periods of measurement. The resulting coefficients may be interpreted as short-term (5-year) rate ratios of the exposure[13,14].

In all regression analyses age was included to adjust for confounding. The effect of all other evaluated confounders (systolic blood pressure, total serum cholesterol, body mass index, and the product of number of cigarettes and years of smoking) was checked by including them simultaneously in multivariate models. Proportional hazards assumptions were verified by inspection of log-log-survival curves. All data analyses were performed on a VAX-computer with SAS software[15].

Results

The mean value of the CIIS was 4.4 in 1960 and 10.7 in 1970. In the elderly cohort the mean CIIS was 7.5 in 1985 and 10.8 in 1990. In 1960, men who had myocardial infarction before or in 1960 (n=21) had an average CIIS of 18.1 $\pm$ 13.6; men with prevalent angina pectoris (n=32) 9.1 $\pm$ 12.8. In 1985, men with a previous myocardial infarction (n=102) had CIIS of 17.7 $\pm$ 12.7 and men with angina pectoris (n=78) 13.7 $\pm$ 12.1. The sensitivity of CIIS of 20 or more to detect previous myocardial infarction at all repeated measurements was about 50%, with a specificity of 90%. The prevalence of angina pectoris and of ST-T abnormalities (Minnesota codes 4.1, 4.2, 5.1 or 5.2) in subjects without Q-waves was significantly associated with CIIS as well.

The characteristics of the middle-aged men in 1960 and the elderly men in 1985 are provided in table 1, in categories of the CIIS. Although age, systolic and diastolic blood pressure, and serum cholesterol showed a positive trend over categories of CIIS, the differences were not statistically significant. The cumulative incidence of angina pectoris, myocardial infarction and coronary heart disease mortality during follow-up increased continuously over CIIS categories.

Table 1. Population characteristics and coronary heart disease in categories of Cardiac Infarction Injury Score. The Zutphen Study

	CIIS < 5	CIIS 5-9	CIIS 10-19	CIIS ≥ 20
1960 N	484	161	177	55
CIIS	-2.1±4.6	6.9±1.4	13.3±2.7	24.9±5.5
age (years)	49.8±5.5	50.0±5.7	50.1±5.1	52.4±5.6
systolic blood pressure (mm Hg)	142.8±19.0	143.3±19.6	143.3±21.3	147.0±22.6
serum cholesterol (mmol/l)	6.08±1.10	6.11±1.38	6.14±1.19	6.27±1.30
Body Mass Index (kg/m^2)	24.2±2.7	23.7±2.7	24.1±2.8	24.0±2.4
product of cigarettes and years smoking	367±284	400±267	381±285	322±269
Prevalent AP (%)	3.3	2.5	4.0	9.1
Prevalent MI (%)	0.8	1.2	4.0	14.6
Minnesota codes 4/5 without Q-waves (%)	0.6	3.1	3.0	21.8
25 year (15 year) AP (%)	11.9 (9.8)	21.7 (12.1)	21.2 (15.3)	20.0 (16.0)
25 year (15 year) MI (%)	23.1 (11.7)	18.2 (10.0)	21.2 (12.4)	23.4 (17.0)
25 year (15 year) CHD mortality (%)	16.1 (5.8)	16.2 (6.8)	14.7 (7.3)	25.5 (18.2)
1985 N	369	129	205	133
CIIS	3.0±5.0	6.8±1.3	13.6±2.7	28.2±6.9
age (years)	71.4±4.9	72.6±5.8	71.9±5.3	73.1±6.9
systolic blood pressure (mm Hg)	150.0±20.0	152.5±21.5	150.4±23.0	151.8±22.5
serum cholesterol (mmol/l)	6.11±1.07	6.12±1.10	6.04±1.07	6.11±1.08
Body Mass Index (kg/m^2)	25.5±3.0	25.7±3.2	25.4±3.2	25.4±3.3
product of cigarettes and years smoking	501±523	538±529	548±469	484±534
Prevalent AP (%)	7.1	10.1	15.1	25.6
Prevalent MI (%)	4.9	10.9	13.7	42.9
Minnesota codes 4/5 without Q-waves (%)	5.2	15.5	20.0	17.3
5 year AP (%)	3.3	2.8	1.3	5.9
5 year MI (%)	4.8	6.0	4.5	9.1
5 year CHD mortality (%)	3.0	7.0	5.9	15.0

AP: angina pectoris
MI: myocardial infarction
CHD: coronary heart disease
Values are mean ± sd

The age-adjusted hazard ratios for coronary end points in categories of CIIS are presented in table 2.

Table 2. The predictive value of the Cardiac Infarction Injury Score for angina pectoris (AP) myocardial infarction incidence (MI), and coronary heart disease (CHD) death. The Zutphen Study

CIIS category	N	AP	MI	CHD death
1960-1975	cases:	99	101	62
< 5	484	1	1	1
5-10	161	1.2 (0.7-2.1)*	0.9 (0.6-2.4)	1.2 (0.6-2.4)
10-20	177	1.6 (1.0-2.7)	1.1 (0.7-1.8)	1.4 (0.7-2.7)
≥ 20	55	1.9 (0.9-4.1)	1.7 (0.8-3.5)	3.4 (1.6-7.0)
1965-1980	cases:	92	99	67
< 5	307	1	1	1
5-10	146	1.2 (0.7-2.1)	1.2 (0.7-2.1)	1.2 (0.5-2.5)
10-20	208	1.3 (0.8-2.2)	1.5 (1.0-2.4)	1.9 (1.0-3.5)
≥ 20	56	1.2 (0.4-3.3)	1.8 (0.7-4.2)	6.7 (3.5-13.0)
1970-1985	cases:	85	96	89
< 5	164	1	1	1
5-10	138	0.6 (0.3-1.1)	0.8 (0.4-1.6)	1.2 (0.5-2.6)
10-20	216	1.0 (0.6-1.6)	1.5 (0.9-2.5)	2.0 (1.1-3.8)
≥ 20	106	0.6 (0.3-1.3)	1.8 (1.0-3.3)	3.6 (1.9-7.1)
1985-1990	cases:	20	39	52
< 5	369	1	1	1
5-10	129	0.9 (0.2-3.1)	1.3 (0.5-3.1)	2.3 (1.0-5.6)
10-20	205	0.4 (0.1-1.9)	1.0 (0.4-2.3)	2.0 (0.9-4.5)
≥ 20	133	1.7 (0.5-5.4)	1.9 (0.8-4.7)	5.1 (2.4-10.7)
Pooled data†	cases:	100	133	113
< 5	1324	1	1	1
5-10	574	1.1 (0.6-1.9)	0.8 (0.5-1.3)	1.8 (0.9-3.1)
10-20	806	1.3 (0.8-2.1)	1.6 (1.1-2.4)	2.3 (1.3-4.0)
≥ 20	350	2.2 (1.2-4.1)	2.4 (1.4-4.0)	5.8 (3.4-9.9)

* Age adjusted hazard ratios (95% confidence interval)

† Taking each measurement and subsequent 5-years of follow up as 1 observation, stratified for period

The 15-year hazard ratios, whether starting from 1960, 1965 or 1970, showed a similar pattern of steadily increasing relative risk for the categories II to IV relative to category I. The association was apparent for angina pectoris and myocardial infarction incidence, but strongest for coronary heart disease mortality. Although tests of a linear trend of risk of coronary heart disease mortality over these categories were significant, there was no continuous increase, because men who had very low CIIS (less than -10) did not have lower risk than men with CIIS between -10 and 5.

In the elderly cohort, the 5-year relative rates of coronary heart disease mortality showed a similar pattern. A predictive value for first myocardial infarction or angina pectoris however, is not apparent.

The analysis of the pooled data of the repeated measurements showed that the 5-year incidence rates of angina pectoris and myocardial infarction were not clearly higher in CIIS category II compared to category I. The age-adjusted hazard ratios of angina pectoris for category III and IV relative to the lowest category were 1.3 (95% confidence interval: 0.8-2.1) and 2.2 (1.2-4.1); for myocardial infarction 1.6 (1.1-2.4) and 2.4 (1.4-4.0) respectively. The hazard ratio of coronary heart disease mortality was 1.8 in category II, though not significant. In category III and IV hazard ratios were observed of 2.3 (1.3-4.0) and 5.8 (3.4-9.9). If prevalent cases of angina pectoris or known myocardial infarction and cases occurring in the year of the medical examination were excluded (leaving 55 coronary heart disease deaths) the relative risks for coronary heart disease mortality were only slightly lower.

Inclusion of other possible confounders into the models did not markedly change the associations.

In addition to level, the predictive value of change of the CIIS in the periods 1960-1965 and 1965-1970 for the 5-year period to follow (1965-1970 and 1970-1975 respectively) was studied. The average change during these 5-year periods was 3.6 ± 9.5. There was no clear association of this change with the occurrence of angina pectoris during the 5 years to follow. Risk of myocardial infarction incidence and coronary heart disease death was higher among men increasing 15 CIIS points or more (table 3), even when the final value was lower than 15. Also men with more than 5 CIIS-points decrease had higher risk of coronary heart disease death.

The high risk was attributable to those in whom the initial level of the CIIS was high. This was supported by the finding that the high initial level itself (CIIS 15 or more) was associated with coronary heart disease mortality in the period between 5 and 10 years later.

Table 3. Level and 5-year change of the Cardiac Infarction Injury Score and angina pectoris (AP), myocardial infarction incidence (MI) and coronary heart disease (CHD) death in the subsequent 5 years*. The Zutphen Study

	AP	MI	CHD death
current CIIS			
< 15	1	1	1
≥ 15	1.3 (0.7-2.5)†	1.6 (0.9-2.7)	2.5 (1.4-4.6)
CIIS 5 years previously			
< 15	1	1	1
≥ 15	0.8 (0.4-1.9)	1.0 (0.5-2.1)	3.4 (1.8-6.3)
change of CIIS between previous and current exam			
δ‡ < -5	1.0 (0.5-2.2)	0.6 (0.3-1.5)	1.7 (0.8-3.7)
δ -5-14	1	1	1
δ ≥ 15	1.6 (0.8-3.4)	2.3 (1.3-4.3)	2.9 (1.4-5.9)

* Pooled observations of the periods 1965 and 1970, total number is 1327
† Age adjusted hazard ratio (95% confidence interval)
‡ δ= difference between current CIIS and previous CIIS

Discussion

In this study the Cardiac Infarction Injury Score predicts coronary heart disease morbidity, and even more so mortality. This association is observed in both middle-aged and in elderly men.

The present study was conducted in the general population of 1960. At that time motivation for participation in medical research was very high, which is reflected in a low non-response and virtually no loss to follow-up. Even in 1985 only 12% of the invited subjects actually refused. However, 9% was too ill to participate.

It is therefore likely, that the men who eventually participated (74%) represent relatively healthy elderly.

The original aim of the Seven Countries Study was to study risk factors for coronary disease. Consequently, coronary end points were well defined and much emphasis was given to their definite ascertainment. Because diagnosis was established by personnel unaware of the present hypothesis, and because the coders of the CIIS were blinded with respect to the disease status of the subjects, the potential for differential misclassification is very limited. On the other hand, especially because the electrocardiograms were paper recordings and had to be coded visually, random misclassification may have occurred.

As another source of bias, confounding must be considered. Age, systolic blood pressure, serum cholesterol, smoking habits and Body Mass Index were considered as possible confounding factors because of the slightly higher values of most factors in the high CIIS category. Only age appeared to be a definite confounder and was therefore included in all analyses. Neither adjusting for one additional possible confounder at a time, nor including all variables in one model changed the observed associations in a relevant way.

In long lasting studies, like the Zutphen Study, in which competing mortality may become substantial, analysis of person-time data, like Cox proportional hazards, is preferable[16]. Usually the association between one baseline measurement and disease or mortality during the follow-up period is studied. However, change over time may occur and a single characterization of exposure may not represent the real exposure category during a large part of the observation period. The possible differences in results from single-baseline or repeated-measurements analyses were demonstrated in the Framingham Study, where examinations were repeated biennially. The 30-year predictive value of baseline electrocardiographic abnormalities for sudden death was low and nonsignificant, whereas the hazard ratio, based on all repeated measurements and the incidence in the subsequent 2-year period, was more than two-fold and highly significant[13]. Similarly, in the present study the relative rates resulting from pooled analysis of 5-year periods were higher than the long-term estimates.

In three previous studies[2-4], high CIIS was also associated with coronary mortality. In hypertensive men in the Multiple Risk Factor Intervention Trial[2] a CIIS of 10 or more was associated with coronary heart disease mortality in the intervention

group only. In this study among a high risk population, also other electrocardiographic abnormalities in the resting electrocardiogram (known to be associated with increased coronary heart disease risk in the general population) were predictive exclusively in the intervention group[17]. Among Finnish men, aged 50-69, without coronary heart disease at baseline, the CIIS was associated with 15-year coronary heart disease mortality[3]. In this Finnish study the CIIS was treated as a continuous variable. The regression coefficient observed in this study means a relative risk of 2 for subjects differing 10 CIIS points. This type of analysis requires the assumption of continuously increasing risk. In the Zutphen Study this appeared not to be the case in the lower range of the distribution (J-shape). When the analysis nevertheless was carried out with CIIS as a continuous variable, the coefficients were virtually identical to those reported in the Finnish men. We have previously reported on the predictive value of the CIIS for coronary heart disease mortality among apparently healthy middle-aged Dutch civil servants[4]. Both men and women with a CIIS of more than 10 had higher risk of coronary heart disease death.

We are not aware of studies on the association of the CIIS and angina pectoris or myocardial infarction incidence, or on the predictive value of change of the CIIS over time in the literature.

It has been suggested that changes of the CIIS after a myocardial infarction may be a sensitive measure for recovery or reinfarctions. In the present study of apparently healthy men, subjects who increased 15 CIIS points or more during a 5-year period had higher risk of myocardial infarction and coronary heart disease death in de subsequent period. Coronary heart disease mortality risk remained elevated in men with initial high CIIS (indicating a possible underlying ischemic event) even after normalization of the CIIS. This may be in agreement with the elevated mortality risk that is generally observed in patients with previous myocardial infarction[18]. Although information of change of the CIIS did contribute, the absolute level provided the largest contribution to risk stratification for coronary heart disease.

In the elderly men intermediate CIIS did not predict angina pectoris and myocardial infarction incidence. This may partly be explained by small numbers. More than 10% of the elderly population had prevalent coronary disease and were thus excluded from these analyses. In the short follow-up period, only 20 incident cases of angina pectoris and 31 of myocardial infarction occurred. It is also possible

that survival to old age produces a selection of relatively insusceptible persons.

Because the CIIS was constructed to detect myocardial infarction, it may be questioned whether the high risk in men with high CIIS is a consequence of previous silent myocardial infarction, with associated increased risk of new coronary events. Although men with known myocardial infarction were excluded from these analyses, still a small number of subjects with Q waves or ST-T abnormalities (Minnesota codes 1.1, 1.2 or 1.3 in combination with 4.1, 4.2, 5.1, 5.2) were present. These men may have had a silent myocardial infarction. This observation is in line with previous studies by Mittelmark et al.[19] and Kannel et al.[20], who reported that 25% of myocardial infarctions were not recognized. If this percentage is true, in elderly men the presence of silent myocardial infarction in men with high CIIS might have been responsible for the increased risk. However, in the middle-aged cohort, the prevalence was very low, and further exclusion of men with possible infarction according to the Minnesota code did not produce different results. The interpretation of the CIIS in apparently healthy men is difficult, since the CIIS is a summary measure, and most of the contributing items are rather non-specific. Possibly elevated CIIS may result from small infarctions, not leading to clear electrocardiographic abnormalities according to the Minnesota code. Because of the association of the CIIS with ST and T abnormalities in men without signs of previous infarction, and with the incidence of angina pectoris and first myocardial infarction, it may also be speculated that to some extend CIIS could reflect early signs of myocardial ischemia in apparently healthy individuals.

In conclusion, the CIIS is predictive of both coronary morbidity and mortality in middle-aged and in elderly men, the association being the strongest for mortality.

Acknowledgements

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Appendix. Composing items of the Cardiac Infarction Injury Score

Component number		Contribution
1	duration of Q in lead AVL (msec)	Q absent: 5 10 msec: 1 20 msec: 3 30 msec: 9 40 msec: 10 50 msec: 12
2a	amplitude of positive T in lead AVL $\leq$ 0.5 mm or $>$ 3 mm (Y/N)	Y: 3
2b	amplitude of negative T in lead AVL (mm)	number of mm x 2
3	amplitude of negative QRS in lead AVR $<$ 5 mm (Y/N)	number of mm x -1
4	amplitude of negative T in lead AVR (mm)	no negative phase: 6 1 mm: 3 2 mm: -5 3 mm: -8 4 mm: -10 5 mm: -12 6 mm: -14 7 mm: -16 8 mm: -18
5	largest Q/R amplitude ratio in lead II or AVF $\geq$ 1/5 (Y/N)	Y: 12
6	duration of Q in lead III or AVL $\geq$ 40 ms (Y/N)	Y: 5
7	amplitude if T in lead III $>$ 1 mm (Y/N)	Y: 7
8	amplitude of positive T in lead V1 $>$ 2 mm (Y/N)	Y: 4
9	amplitude of R in lead V2 $<$ 3 or $>$ 14 mm (Y/N)	Y: 5
10	amplitude of negative T in lead V2 $\geq$ 1/4 mm (Y/N)	Y: 5
11	largest Q/R amplitude ratio in lead V3 $>$ 1/20 (Y/N)	Y: 9
12	amplitude of S in lead V5 $<$ 2 mm (Y/N)	Y: 5

Cardiac Infarction Injury Score for visual coding, revised version in consultation with dr. Rautaharju

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3. The association between QT interval and coronary heart disease in middle-aged and elderly men. The Zutphen Study[2]

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Abstract

Heart-rate adjusted QT-interval (QTc) is prognostic of sudden death in myocardial infarction patients. So far, population studies have yielded conflicting results on the predictive value of QTc for coronary heart disease morbidity and mortality. Therefore this was studied in a longitudinal study of middle-aged and elderly men.

From 1960 to 1985, 877 middle-aged men were followed and repeatedly examined in the Zutphen Study. In 1985 the remaining cohort was extended to 835 elderly men from the same birth cohort, and followed until 1990. Men with prolonged QTc (420 msec or more) had higher risk of myocardial infarction and coronary heart disease death relative to men with QTc less than 385 msec. Age adjusted coronary heart disease mortality rate ratios were 4.3 (95% confidence interval [CI], 1.3 to 13.8) in middle aged, and 3.3 (95% CI, 1.0 to 11.6) in elderly men. These associations could not be attributed to prevalent heart disease, and were independent of other cardiovascular risk factors.

These results indicate that within the normal range of QTc in the general population, men with long QTc are at higher risk. Because QTc is easily determined, it may provide a valuable contribution to risk stratification.

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Introduction

Long QT syndrome patients are at high risk of malignant ventricular arrhythmia and sudden death[1]. Also in myocardial infarction patients and patients who had diagnostic 24-hour electrocardiography[2,3] an association of heart-rate adjusted QT-interval (QTc) with sudden death has been observed, although not in all studies[4]. This elevated risk has been attributed to predominance of left sympathetic nerve activity[5-7], or myocardial membrane defects[8,9] leading to electrical instability in situations of high sympathetic activity.

Whether QTc prolongation predicts coronary heart disease mortality in healthy persons remains to be clarified. Recently, two studies in the general population came to contradictory conclusions. In the Framingham Heart Study[10] no significant associations with mortality were observed, whereas in the Dutch Civil Servants Study[11] men and women with QTc prolongation had about twofold risk of coronary heart disease death. In the present study the predictive value of QTc for 25-year coronary heart disease morbidity and mortality was investigated in a prospective cohort study of middle-aged men from the general population. As QT-interval duration gradually increases with age[12], and autonomic function alters as well[13], the same associations were evaluated in a five-year follow-up of a cohort of elderly men.

Methods

Study population

From 1960 on the Zutphen Study, a prospective study on coronary heart disease, has been carried out in the frame of the Seven Countries Study[14]. In 1960 a random sample of 1088 men, residents of the town of Zutphen, the Netherlands, and born between 1900 and 1920, were invited for a medical examination and a dietary survey. Thirty two men refused to participate, while 178 only took part in the dietary survey or were examined later than 1960. In 877 of the remaining 878 participants a 12-lead electrocardiogram was recorded. During follow-up examinations in 1965 and 1970, 717 and 625 men took part respectively. After exclusion of men who had previous myocardial infarction (see 'endpoints' for the definition), the resulting study population

consisted of 851 middle-aged men in 1960, 685 in 1965, and 582 in 1970. In 1985 the 555 survivors and an additional sample of 711 men, drawn from the same birth cohort (then aged 65-85) were invited to take part in the elderly study. Of these, 156 did not volunteer and 171 did not participate for various reasons (illness or death, could not be traced, etc.). In 54 men no electrocardiogram was made, 49 recordings were lost during follow up, and in one the QT interval could not be determined accurately. Of the remaining 835 men 115 were excluded because of previously diagnosed myocardial infarction, thus the final study population comprised 720 elderly men in 1985. At the follow-up medical examination in 1990 552 of 656 surviving participants took part. Exclusion of 78 men with previous myocardial infarctions left a study population of 474 men in 1990.

Electrocardiography

Standard resting 12-lead electrocardiographic recording and assessment of cardiovascular risk factors were performed according to the protocol of the Seven Countries Study[14] in 1960, 1965, 1970, 1985 and 1990. The electrocardiograms were classified and coded according to the Minnesota Code[15]. In 1992 QT and RR intervals were measured, using a digitizing tablet (Calcomp) and a personal computer. The resolution of the tablet is 100 lines/mm and the reproducibility is 0.25 mm (corresponding to 10 msec). QT-intervals were read from three leads: V2, V6 and of I, II, or III the lead with the longest QT. In each lead, QT-intervals and the preceding RR-intervals were measured in three consecutive normal complexes, in order to reduce measurement error, and because QT-duration may slightly vary from beat to beat due to concomitant variability of heart frequency[16]. The beginning of the QT-interval was defined as the first deflection of the QRS complex, the end as the point of maximal change in the slope as the T-wave merges with the baseline[9]. All intervals were measured by one observer who was blinded for other baseline information and survival.

Information on other variables

At all examinations systolic and diastolic blood pressure were measured twice at the end of the physical examination on the right arm in supine position. Between 1960 and 1970 only the last value was recorded. For 1985 and 1990 the mean of

duplicate readings was calculated. Serum total cholesterol was determined in a standardized laboratory by the Abell-Kendall[17] method in 1960 and 1965, by the method of Zlatkis[18] in 1970, and by the enzymatic method of Siedel et al.[19] and Stahler et al.[20] in 1985 and 1990. All methods produced Abell-Kendall equivalents. The Body Mass Index was calculated from height and weight (height was measured in 1960 and 1985 only). Before 1985 smoking was assessed by the Seven Countries Study questionnaire on smoking habits. From 1985 on a newly developed questionnaire[21] was used.

Endpoints

Mortality was registered weekly by means of the municipal registry of the town of Zutphen. Causes of death were obtained from the death certificates, the hospital and/or the general practitioner. Follow-up was complete for all participants. Information on cardiovascular disease was collected during the medical examinations. Between 1960 and 1973 medical examinations were performed annually, and after that period in 1977/1978, 1985 and 1990. In addition, questionnaires on health status were filled in by the survivors in 1980 and 1982. The information on morbidity provided was verified by contacting the general practitioner. For the period 1985-1990, hospital discharge data of the members of the cohort who were hospitalized in Zutphen were made available as well. Coding of causes of death was performed according to the International Classification of Diseases[22] (8th revision in the period of 1960 to 1985, 9th from 1985 to 1990). Coronary heart disease mortality was defined as ICD-8 codes 410, 411.9-413.9 and as ICD-9 codes 410-414. Myocardial infarction was coded when 2 of the following 3 criteria were present: 1. a specific medical history, e.g. severe chest pain lasting for more than 20 minutes and not disappearing during rest; 2. electrocardiographic changes corresponding to Minnesota Codes 1.1 (major Q waves) code 1.2 accompanied by 5.1 or 5.2 (lesser Q waves and major T-wave findings); or 3. specific enzyme level elevations. Only first occurrence of myocardial infarction (fatal or non fatal) was recorded. Sudden cardiac death was not coded until recently by one of the authors (JD). Because of the limitations of the available information, sudden cardiac death in this study was coded in two situations: 1. when it was documented that death occurred within two hours after onset of typical symptoms, and no other causes of death were known; or 2. in subjects

with a history of heart disease: when "mors subita" was notified by the physician or death occurred unwitnessed (within 12 hours after men had been observed to be well).

Data analysis

QT-intervals were adjusted for heart rate according to Bazett's formula[23]. Means of three consecutive heart-rate adjusted QT-intervals were calculated from leads V2, V6, and either lead I, II or III. The greatest from these was used for the analyses.

Subjects were categorized into three groups: short, intermediate, and long QTc, with cut-off points 385 msec and 420 msec respectively. The first cut-off point separates the lowest tertile in 1960 and the lowest quartile in 1985. In order to have a sufficient number of middle-aged men in the upper category, the second cut-off point was 420 msec instead of 440 msec, which is the usual criterium for definitely prolonged QTc.

The predictive value of QTc for the incidence of a first myocardial infarction, coronary heart disease mortality, and sudden death was analyzed using Cox proportional hazards models. Rate ratios for three, partly overlapping, 15-year periods were estimated using 1960, 1965, and 1970 as baseline respectively. In order to have full profit of the repeated measurements, in the middle-aged population a time-dependent Cox model was fitted. The resulting coefficients are to be interpreted as short-term (5-year) rate ratios[24,25].

In all regression analyses, age was included to adjust for confounding. The effect of all other possible confounders (systolic blood pressure, serum total cholesterol, Body Mass Index, and the product of number of cigarettes and years of smoking) was checked by including them simultaneously in multivariate models.

Analyses were repeated after exclusion of subjects with angina pectoris or with electrocardiographic signs of heart disease (Minnesota codes 1.1, 1.2, 3.1, 3.2, 4.1, 4.2, 5.1, 5.2, 7.1- 7.4) to study the possibility that observed associations are a consequence of detectable prevalent heart disease (men with prevalent myocardial infarction were excluded from the beginning).

Proportional hazards assumptions were verified by inspection of log-log-survival curves. All data analyses were performed on a VAX-computer with SAS software[26].

Results

In figure 1 the distribution of QTc at repeated measurements is plotted. With time, the mean of the distribution is shifting to longer QTc, and the standard deviation is increasing. The mean QTc increased from 395 ± 23 msec (mean ± SD) in middle-aged men in 1960 to 410 ± 26 msec in the elderly in 1985. The proportion of men in the long QTc-category was 12 percent in 1960 and 35 percent in 1985.

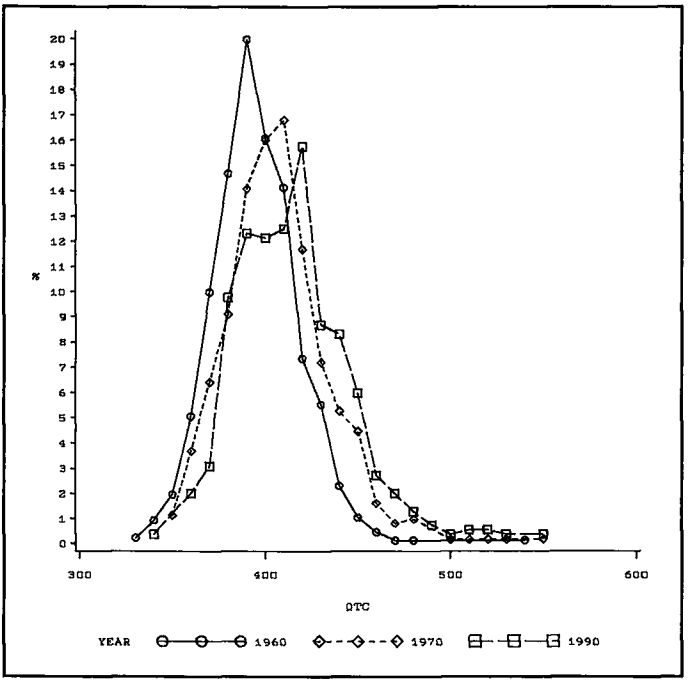

Figure 1. Graph of the population distributions of QTc in the electrocardiograms recorded in 1960 through 1990

As shown in table 1, mean age, blood pressure, serum cholesterol and Body Mass Index showed a positive trend over QTc categories in 1960 as well as in 1985.

This was similar in the other follow-up examinations. The cumulative incidences of myocardial infarction, coronary heart disease mortality, and sudden death were all higher in the intermediate- and highest in the long-QTc category (table 1). Men

who had a first myocardial infarction in the period 1960 to 1975, had mean QTc in 1960 of 399 ± 20 msec, men who died of coronary heart disease 404 ± 20 msec, and men who died suddenly 401 ± 21 msec. In the remaining group mean QTc was 394 ± 23 msec, which was significantly different from the other categories.

Table 1. Population characteristics (mean ± sd) and coronary heart disease (%) in categories of QTc interval length. The Zutphen Study

		QTc < 385	QTc 385-420	QTc ≥ 420
1960	N	278	468	105
age (years)		49.7±5.5	49.9±5.5	50.9±5.5
systolic blood pressure (mm Hg)		139.9±17.4	143.8±20.4†	150.1±22.2†
serum cholesterol (mmol/l)		6.00±1.19	6.09±1.14	6.30±1.33
Body Mass Index (kg/m^2)		23.8±2.6	24.1±2.8	24.7±2.7†
product of cigarettes and years smoking		373±287	367±281	389±279
25 year (15 year) incidence MI (%)		19.1 (7.6)	22.7 (13.3)	26.7 (17.1)
25 year (15 year) CHD mortality (%)		11.1 (2.5)	16.7 (6.8)	21.9 (13.3)
25 year (15 year) sudden death (%)		9.4 (3.6)	13.0 (7.1)	18.1 (10.5)
1985	N	170	299	251
age (years)		70.7±4.8	72.0±5.1†	72.6±5.5†
systolic blood pressure (mm Hg)		148.5±20.8	150.4±21.1	154.0±21.5†
serum cholesterol (mmol/l)		6.07±1.04	6.03±1.05	6.09±1.05
Body Mass Index (kg/m^2)		25.1±2.8	25.4±3.0	26.0±3.5†
product of cigarettes and years smoking		518±551	485±462	516±508
5 year MI incidence (%)		3.5	4.4	7.6
5 year CHD mortality (%)		1.8	2.0	6.0
5 year sudden death (%)		1.8	2.0	5.2

MI: myocardial infarction
CHD: coronary heart disease
* Individual parameters have missing data
† Significant F-test ($p < 0.05$) over the QTc categories; indicated value significantly different from lowest category (Tukey-Kramer test, $p < 0.05$)

Risk analysis for middle-aged men is presented in table 2. For each of the three periods, the rate of myocardial infarction occurrence in the long-QTc category was about twice that of the short category (not significant for the period 1970-1985 only). Both risk of fatal and non-fatal myocardial infarctions were associated with QTc.

Table 2. Relative rates of coronary heart disease in categories of QTc in middle-aged men. The Zutphen Study

	N	MI incidence	CHD death	sudden death
1960-1975		n=101*	n=58	n=54
QTc < 385	278	1.0	1.0	1.0
QTc 385-420	468	1.8 (1.1-3.0)†	2.7 (1.2-6.2)	2.1 (1.0-4.2)
		1.9 (1.1-3.2)‡	2.6 (1.1-6.2)	1.7 (0.8-3.4)
QTc ≥ 420	105	2.3 (1.2-4.4)	5.1 (2.1-12.8)	3.2 (1.4-7.6)
		1.9 (1.0-3.7)	4.2 (1.6-11.4)	2.6 (1.1-6.1)
1965-1980		n=98	n=53	n=55
QTc < 385	240	1.0	1.0	1.0
QTc 385-420	353	1.2 (0.7-1.8)	1.9 (0.9-3.7)	1.5 (0.8-2.8)
		1.0 (0.7-1.6)	1.6 (0.9-3.0)	1.4 (0.8-2.5)
QTc ≥ 420	92	1.8 (1.0-3.2)	3.0 (1.3-6.9)	1.5 (0.6-3.6)
		1.4 (0.8-2.6)	2.1 (0.9-4.8)	0.9 (0.4-2.3)
1970- 1985		n=98	n=68	n=60
QTc < 385	120	1.0	1.0	1.0
QTc 385-420	315	1.3 (0.7-2.2)	1.6 (0.8-3.4)	2.6 (1.0-6.7)
		1.1 (0.6-2.0)	1.4 (0.7-3.0)	2.2 (0.9-5.8)
QTc ≥ 420	147	1.5 (0.8-2.8)	2.2 (1.0-4.8)	4.8 (1.8-12.7)
		1.3 (0.7-2.4)	1.8 (0.8-4.0)	3.8 (1.4-10.1)
Pooled data§		n=94	n=39	n=23
QTc < 385		1.0	1.0	1.0
QTc 385-420		1.4 (0.9-2.4)	3.3 (1.2-9.6)	2.1 (0.7-6.3)
		1.4 (0.8-2.3)	4.0 (1.2-13.4)	1.6 (0.5-5.1)
QTc ≥ 420		1.5 (0.8-2.8)	4.3 (1.3-13.8)	1.8 (0.5-7.5)
		1.3 (0.7-2.5)	4.4 (1.2-16.4)	1.4 (0.3-5.7)

* Number of cases

† Age adjusted hazard ratio

‡ Hazard ratio adjusted for age, systolic blood pressure, body mass index, total serum cholesterol, and product of number of cigarettes and years smoked

§ Taking measurements from 1960, 1965, and 1970 and subsequent 5-years of follow up as separate observations, stratified for period

For coronary heart disease death and sudden death rate ratios were more than 2 in the intermediate- and more than 3 in the long-QTc category. The 5-year rate ratios of coronary heart disease mortality resulting from time-dependent analysis were somewhat higher. The short-term occurrence of myocardial infarction was not clearly associated with QTc. Adjustment for age, systolic blood pressure, body mass index, total serum cholesterol, and smoking only slightly lowered the observed rate ratios.

Mean QTc in subjects with angina pectoris or electrocardiographic signs of possible heart disease at baseline (13 percent in 1960, 22 percent in 1970) was approximately 10 msec longer than in men without signs of heart disease. Exclusion of these subjects, however, left the estimates essentially unchanged. Also exclusion of men who had QTc increase of 20 msec or more between repeated measurements did not change the relationships.

In the elderly men similar associations for long QTc were observed during the available 5 years of follow-up, but not for intermediate QTc. A change of the upper cut-off point to 440 msec left 19 percent of the elderly men in the long-QTc category. Age adjusted rate ratios for myocardial infarction incidence and coronary heart disease mortality this more extreme category were 2.8 (95 percent confidence interval, 1.0 to 7.5), and 5.0 (1.4 to 18.0) and respectively.

Table 3. The predictive value of QTc-interval length for coronary heart disease in elderly men. The Zutphen Study

	N	MI incidence	CHD death	sudden death
1985-1990		n=38*	n=24	n=22
QTc < 385	170	1.0	1.0	1.0
QTc 385-420	299	1.2 (0.5-3.3)†	1.3 (0.4-3.3)	1.8 (0.6-5.6)
		1.3 (0.5-3.4)‡	1.3 (0.5-3.3)	1.7 (0.5-5.1)
QTc ≥ 420	251	2.3 (0.9-5.7)	3.1 (1.3-7.6)	3.7 (1.3-10.9)
		2.4 (0.9-6.1)	3.0 (1.2-7.3)	3.0 (1.0-8.9)

* Number of cases

† Age adjusted hazard ratio

‡ Hazard ratio adjusted for age, systolic blood pressure, body mass index, total serum cholesterol, and product of number of cigarettes and years smoked

In 1985 one third of all subjects had angina pectoris or electrocardiographic signs of heart disease. Their mean QTc was 425 ± 39 msec, which was significantly different from the other men (402 ± 30 msec). After excluding them, the relative rates of myocardial infarction, coronary heart disease death, and sudden death in the long QTc category (25% of the remaining men) were even higher.

Discussion

In this prospective cohort study in the general population, men with heart-rate adjusted QT-interval (QTc) of 420 msec or more had elevated risk for myocardial infarction, and even more so for coronary heart disease mortality and sudden death. The association could not be attributed to subjects with signs of prevalent heart disease and was independent of other risk factors for coronary heart disease.

The study, being an observational epidemiologic investigation, is subject to a number of potential errors. Evidently error may have occurred in the measurement of QT-interval length. The measurements were performed by only one observer who was blinded for the outcome. Therefore bias because of differential error in QT measurement and interobserver differences is impossible.

We did not follow the recommendation of Campbell[27] to measure QT in all available leads. In order to limit the number of QT-intervals to be measured, in the present study leads I, II or III, lead V2 and lead V6 were selected. The axes of these leads are nearly orthogonal, optimizing the ability to detect electrical activity in any direction.

The end of the T-wave was defined as the point of maximal change in the slope of the curve as it merges with the baseline. In previous studies the endpoint has often been defined as the point where the T-wave merges with the electrical baseline. However, especially in the chest leads, U-waves often obscure the end of the T. As a consequence the intervals measured in the present study may be slightly shorter, but precision will be greater.

Misclassification of the study end points is another possible source of bias. Information on morbidity and mortality from specialists and family practitioners was thoroughly checked and was evaluated by physicians who were not aware of

the present hypothesis. The ascertainment of sudden death was especially prone to misclassification because sudden death was not an item of interest in the Zutphen Study before, and detailed information on time between the first occurrence of symptoms and death was not systematically obtained. Since there is no reason to suspect the presence of differential error in the assessment of exposure or endpoints, information bias is not a likely explanation for the observed findings.

The use of certain drugs, which affect the length of the QT-interval could cause bias. Unfortunately information about use of drugs was not available before 1985. However, drugs which may influence QT-interval length were not frequently prescribed in the sixties. Therefore we do not expect a substantial drug effect on the observed QT-intervals for the periods 1960-1970. In the elderly population, exclusion of men using anti-arrhythmics, ß-blocking agents or diuretics did not change the associations.

Because men with angina pectoris or electrocardiographic signs of heart disease had longer QTc, it may be questioned whether the observed associations resulted from prevalent heart disease. However, exclusion of these men or of men with large increases of QTc between the consecutive measurements did not weaken the relative rates. Still, the possibility of subclinical heart disease underlying QTc-prolongation cannot be completely ruled out.

The presently reported results confirm previous findings from our group by Schouten et al.[11] In a study among 3000 healthy middle-aged men and women, significant 15-year relative risks of death of ischemic heart disease of 1.8 and 2.1 in men with intermediate prolongation (QTc 420-440 msec) and definite prolongation (QTc 440 msec or more) respectively were reported. In women, only total mortality was significantly associated with QTc. Goldberg et al. did not observe an association between QTc and 30-year total and coronary artery disease mortality or sudden death in the Framingham Heart Study[10]. However, the categorization of QTc in their study was based on quintiles of QTc distribution of both sexes combined. Because in general women have longer QTc and the association with coronary heart disease mortality seems weaker than in men, this may have weakened the power of their study[28]. In addition, a follow-up period of 30 years after a single baseline measurement is very long. In general, even when person-time analysis is used to account for competing mortality, the predictive value of one baseline classification will diminish

with time. In the present study, as well as in the study by Schouten and coworkers, the associations were clearly stronger when a shorter follow-up period was considered. The finding of a J-shaped relation in the Framingham Heart Study could not be confirmed in the Zutphen Study. Instead, men with QTc of 385 msec or less had the lowest risk.

Several studies have reported increased risk of ventricular arrhythmias and sudden death in subjects with prolonged QTc in patient populations[1,7,8]. In the present study, subjects with previous myocardial infarction were excluded. Indeed their mean QTc was higher, and including them in the analysis produced even higher relative rates.

Only very few middle-aged men had a clearly abnormal QTc (e.g. 440 msec or more). Nevertheless, a considerably elevated risk was observed in the category of QTc 420 msec or more. The present findings do not warrant a clear cut-off point. Instead, risk seems to gradually increase within the normal values in the population.

It has been suggested that determination of QT dispersion among the leads may be more informative than QT-length per se[29]. Therefore, we also checked the greatest difference between any two leads and the differences between specific leads. Indeed, subjects who had more than 40 msec difference between any lead had higher risk of coronary heart disease mortality, but these associations were weaker and less consistent than the associations with QTc length. No association was observed with myocardial infarction incidence.

The predictive value of prolonged QTc for sudden death and coronary heart disease death can be explained by ventricular electrical instability, particularly in the presence of high sympathetic activity. Such instability is hypothesized to result from left sympathetic predominance, accompanied by dispersion of repolarization[5-7] or from myocardial membrane properties that give rise to early afterdepolarizations[8,9,30]. In both mechanisms parasympathetic activity exhibits beneficial effects[31,32]. It is conceivable that QTc is especially prolonged in persons with an unfavourable balance between sympathetic and parasympathetic activity. The presently observed increased blood pressure in men with long QTc is in line with this reasoning. If QTc reflects autonomic balance, this might explain the association between QTc and non-fatal myocardial infarction incidence, because persons with high sympathetic drive may be more prone to coronary atherosclerosis or symptoms may occur earlier[33].

Furthermore, norepinephrine levels have been reported to increase with ageing[34], possibly because of reduced physical activity[13]. It could be speculated that such a change of autonomic balance contributes to the age-related prolongation of QTc.

If our finding is confirmed, it may be of importance with regard to preventive strategies, since the balance between sympathetic and parasympathetic activity can be improved by physical activity[35] and cessation of smoking[36].

In conclusion, QTc prolongation predicts coronary heart disease and sudden death in apparently healthy men. Because QT-interval length is easily determined, it may contribute to cardiovascular risk stratification. In addition subjects with prolonged QTc may especially benefit from preventive measures which affect autonomic balance.

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4. QTc prolongation: another component of the insulin resistance syndrome? The Zutphen Elderly Study[3]

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Abstract

Prolongation of heart rate adjusted QT-length (QTc) is associated with elevated risk of coronary heart disease and sudden death. This may have to do with autonomic cardiac control. Because insulin is known to stimulate sympathetic activity, we studied the association between insulin level and glucose tolerance with QTc.

In 1990, 383 men, aged 70-89, without previous myocardial infarctions or known diabetes had a 12-lead electrocardiogram recorded and glucose tolerance determined in the frame of an ongoing follow-up study. QTc was significantly associated with fasting glucose, insulin and C-peptide, and glucose level 60 and 120 minutes after an oral glucose load. For fasting C-peptide and the area under the glucose curve (AUGC) this association could not be explained by the concomitant occurrence of other risk factors of coronary heart disease. Furthermore, fasting C-peptide and AUGC were independent, additive predictors of QTc-duration. The difference of QTc between men in the extreme quintiles of both variables was 22 msec.

QTc-prolongation seems to be part of the insulin-resistance syndrome. The association may be explained by increased sympathetic activity, induced by high insulin levels. An additional explanation could be an effect of high insulin, impaired glucose utilization, or both on membrane activity of myocardial cells.

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[3] Submitted for publication

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Introduction

A prolonged heart-rate adjusted QT (QTc) is a risk factor for sudden death in patients with the long QT syndrome[1], in myocardial infarction patients[2,3], and in healthy men and women[4,5]. The length of the QT interval, which is easily obtained from the standard resting electrocardiogram, represents the time interval between the start of activation of the ventricle and completion of its repolarization. Two mechanisms have been formulated to explain the elevated risk in the presence of QTc-prolongation. In the first, dispersion of repolarization as a consequence of predominance of left sympathetic nerve activity is held responsible for high risk of ventricular fibrillation. In the second mechanism, disturbed myocardial membrane function is believed to lead to electrical instability. Whatever the underlying mechanism, sympathetic stimulation, unopposed by vagal activity, may induce ventricular electrical instability, resulting in high risk of arrhythmia and sudden death[6]. Since insulin is known to increase sympathetic activity[7], hyperinsulinemia and impaired glucose tolerance may be determinants of QTc prolongation.

Hyperinsulinemia and insulin resistance have been indicated as key factors in coronary heart disease etiology. They provide a basis for the clustering of several risk factors. Genetic predisposition, lack of physical activity and a positive energy balance, followed by increased body weight, result in high insulin levels. Hyperinsulinemia notably increases triglyceride level, lowers HDL-cholesterol[8] and stimulates sympathetic nervous activity[7]. This type of risk factor clustering is now often referred to as the insulin-resistance syndrome[8]. QTc prolongation and its sequelae may be an additional feature of this syndrome. Therefore we studied QTc in relation to insulin level and glucose tolerance in a cohort of Dutch elderly men.

Subjects and methods

Subjects

In 1985, 939 men, born between 1900 and 1920, have been examined in the Zutphen Elderly Study. This study is the continuation of the Zutphen Study, which is the Dutch contribution to the Seven Countries Study[9]. In 1985 the survivors of

the original cohort (555 men) and an additional sample of 711 men, then aged 65 to 84, were invited to take part in the elderly study. At the follow-up medical examination in 1990, 560 of 718 (76%) surviving men took part, of whom 478 both completed an oral glucose tolerance test and had a 12-lead resting electrocardiogram recorded. Because the QT-interval prolongation may be a consequence of a myocardial infarction, men with previous myocardial infarction (64 men) were excluded. The remaining study population consists of 414 elderly men.

Examinations

An oral glucose tolerance (OGTT) test was performed, according to WHO guidelines[10]. In the morning a fasting blood sample was obtained. Then a glucose load of 75 g was given, and additional blood samples were taken after 1 and 2 hours. Men using insulin or hypoglycaemic agents were excluded from the OGTT, one man did not complete the OGTT. Samples were collected in tubes with sodium fluoride. Plasma glucose was determined using the hexokinase method. Insulin was measured in serum using a radio- immune assay from Pharmacia Diagnostics, Uppsala, Sweden. Within- and between-run coefficients of variation ranged from 6 to 7%. Levels of fasting C-peptide, a measure of insulin secretion, were determined in serum using a ^{125}I-radio-immune assay from Incstar Corp., Minnesota, USA, after treatment with 25% polyethyleneglycol. The within-run coefficient of variation was 6.5% and the between-run coefficient was 14%.

The area under the post-load glucose and insulin curves were calculated using the trapezoidal rule ((fasting level * 30 min) + (1-hr level * 60 min) + (2-hr level * 30 min)).

In 1985 and 1990 standard resting 12-lead electrocardiographic recording and assessment of cardiovascular risk factors were performed according to the protocol of the Seven Countries Study[9]. The electrocardiograms were classified and coded according to the Minnesota Code[11]. QT and RR intervals were measured of 12-lead resting electrocardiograms, using a digitizing tablet (Calcomp) and a personal computer. The resolution of the tablet is 100 lines/mm and the reproducibility is 0.25 mm (corresponding to 10 msec). QT-intervals were read from three leads: V2, V6 and either I, II, or III, in whichever the longest QT was observed. In each lead, QT-intervals and the preceding RR-intervals were measured in three consecutive normal complexes. The beginning of the QT-interval was defined as the first deflection

of the QRS complex, the end of the T-wave was defined as the point of maximal change in the slope as the T-wave merges with the baseline[12]. All electrocardiograms were measured by one observer who was blinded for other information.

Systolic and diastolic blood pressure were measured twice at the end of the physical examination on the right arm in supine position[9]. The mean of duplicate measurements was used in the analyses. Non-fasting serum total and HDL-cholesterol, and fasting triglycerides were determined enzymatically at the standardized Lipid Laboratory at the Department of Human Nutrition, Agricultural University Wageningen, The Netherlands[13-15]. Body Mass Index (weight/height^2) was calculated. Subscapular skinfold thickness was measured in duplicate with a Harpenden caliper at the right side of the body[9]. Smoking habits were assessed using a standardized questionnaire. A 15-item questionnaire on physical activities, designed for retired men[16], was used to calculate minutes per week spent on activities like walking, gardening, doing odd jobs, sports, hobbies and work.

Data analysis

QT-intervals were adjusted for heart rate according to Bazett's formula[17]. The means of three consecutive heart-rate adjusted QT-intervals were calculated from each lead. The longest mean QTc of these three leads (V2, V6, and either lead I, II or III) was used for the analysis. QTc was described in categories of glucose tolerance. Because a treatment effect was observed among men with known diabetes, they were excluded from the remaining analyses (31 men).

Regression analysis was carried out using QTc as dependent variable. First age and indicators of carbohydrate metabolism (fasting glucose, insulin, and C-peptide, and glucose and insulin responses to the glucose load respectively) were evaluated one at a time. Because of being possible determinants of insulin level, Body Mass Index, subscapular skinfold thickness, smoking, and physical activity were further included in the models. Subsequently, diastolic blood pressure, total- and HDL cholesterol, and triglycerides were added as well. Finally the variables which significantly (p-value Wald test <0.05) contributed to the QTc variation in the different models were combined in one model. Because some variables were not normally distributed, analyses were repeated after log-transformation. The results were almost identical, therefore only the coefficients of the non-transformed analyzed

are presented. All data analyses were performed on a VAX-computer with SAS software[18].

Results

In the present study among healthy elderly men, aged 70-89, without previous myocardial infarctions, coronary heart disease risk factor levels were most favourable in men with normal glucose tolerance, and least favourable in newly diagnosed diabetic patients. In men with known diabetes mean levels of most risk factors were comparable to the normal category (table 1).

Table 1. Population characteristics according to diabetic category*

	Normal	IGT	NDD	KD
N	306	43	34	31
age (yr)	75.4±4.4	77.7±5.3	74.4±4.0	76.6 ± 5.0
Body Mass Index (kg/m^2)	25.4±3.1	26.6±4.2	26.7±3.2	24.8 ± 2.4
subscapular skinfold (mm)	16.8±6.0	19.8±6.8	20.9±6.6	17.6 ± 6.3
systolic blood pressure (mm Hg)	149±22	155±19	158±21	153 ± 23
diastolic blood pressure (mm Hg)	82±11	84±12	87±14	82 ± 11
HDL cholesterol (mmol/l)	1.18±0.28	1.16±0.34	1.05±0.23	1.11 ± 80.28
total cholesterol (mmol/l)	6.10±1.06	5.83±1.18	6.07±1.28	6.04 ± 1.16
serum triglycerides (mmol/l)	1.35±0.71	1.55±0.85	1.75±0.72	1.56 ± 0.87
physical activity (min/wk)	649±551	456±418	477±388	446 ± 490
heart rate (beats/min)	74±13.2	78±15	79±17	72 ± 15
smoking (# cigarettes/day)	2.66±5.76	2.21±5.29	2.56±7.33	3.32 ± 6.34

IGT: Impaired Glucose Tolerance
NDD: Newly Diagnosed Diabetes
KD: Known Diabetes
* According to the guidelines of the WHO, men with previous myocardial infarctions excluded

The mean heart-rate adjusted QT (QTc) was 413 ± 29 msec. QTc was longer in men with impaired glucose tolerance and newly diagnosed diabetes compared to men with normal glucose tolerance (table 2). These differences were virtually

absent in electrocardiograms of the same men recorded five years earlier. In men with known diabetes the five-year QTc-increase was similar to the normal group.

Table 2. QTc and indicators of carbohydrate metabolism according to diabetic category*

	Normal	IGT	NDD	KD
QTc 1990	410±28	418±25	429±36	414±27
QTc† 1985	403±30	406±31	407±32.5	409±37
Plasma glucose (mmol/l)				
fasting	5.6±0.5	6.0±0.6	8.1±2.1	9.9±3.7
60 min	8.5±2.2	11.1±1.7	15.4±2.8	-
120 min	5.4±1.3	9.0±1.0	13.9±3.6	-
area under curve (mmol*min/l)	839±156	1119±122	1579±305	-
Serum insulin (pmol/l)				
fasting	62.8±27.1	86.3±36.5	100.8±67.3	64.2±27.5
area under curve (pmol*min/l)	36756±16154	49785±20495	36620±23932	-
Fasting C-peptide (nmol/l)	0.68±0.26	0.88±0.43	1.03±0.65	0.63±0.22

IGT: Impaired Glucose Tolerance
NDD: Newly Diagnosed Diabetes
KD: Known Diabetes
* According to the guidelines of the WHO, men with previous myocardial infarction excluded
† QTc in the standard 12-lead resting electrocardiogram 5 years before

All indicators of carbohydrate metabolism, except the area under the insulin curve, were significantly correlated with QTc. A significant correlation was also observed between QTc on one hand and Body Mass Index, diastolic blood pressure, serum triglycerides, and subscapular skinfold thickness on the other (age-adjusted Pearson correlation coefficients (r): 0.23, 0.17, 0.13, and 0.17 respectively).

The associations of QTc with physical activity and HDL-cholesterol were somewhat weaker (r=-0.11 for both). Total serum cholesterol and smoking were not significantly associated with QTc. Adjusted for coronary heart disease risk factors, fasting C-peptide and glucose levels after the glucose load were still significant contributors to QTc length, although the estimates were somewhat lower (table 3).

Table 3. Regression coefficients of indicators of carbohydrate metabolism on QTc

independent variable	age-adjusted	model 2†	model 3‡
Glucose (mmol/l)			
fasting	3.37*	2.43	2.16
60 min	1.88*	1.55*	1.43*
120 min	1.98*	1.63*	1.46*
area under curve (mmol*min/l)	0.022*	0.018*	0.016*
Fasting insulin (pmol/l)	0.15*	0.09	0.06
Area under insulin curve (pmol*min/l)	0.00016	0.00004	-0.00001
Fasting C-peptide (nmol/l)	19.1 *	13.4*	11.3*

Men with known diabetes or previous myocardial infarction excluded.
Regression coefficients are change of QTc in msec per unit of the independent variable.
† adjusted for age, Body Mass Index, current smoking, minutes of physical activity, and subscapular skinfold
‡ adjusted for all previous variables and for diastolic blood pressure, serum triglycerides, serum total cholesterol, and HDL-cholesterol.
* significantly different from 0 (p less than 0.05)

In the most extensive models fasting C-peptide, area under the glucose curve, age, Body Mass Index, and diastolic blood pressure were the strongest predictors of QTc. When these five variables were combined in one regression model, both area under the glucose curve and fasting C-peptide remained significant independent predictors of QTc. This is illustrated in figure 1, where average QTc is shown in combined categories of fasting C-peptide and area under the glucose curve, adjusted for age, Body Mass Index, and diastolic blood pressure.

Discussion

In the present study both insulin secretion (fasting C-peptide) and glucose tolerance were independently associated with the length of the heart-rate adjusted QT (QTc) interval in the standard 12-lead electrocardiogram in men 70-89 years of age.

This study was conducted in elderly men, because insulin resistance is rather prevalent in this age group. Our study population represents relatively healthy elderly, who were able to come to the study center by their own means. Since the main

interest of the present study is in disease etiology, this selection is rather an advantage than a disadvantage.

QT prolongation has been reported in diabetic patients with autonomic neuropathy[19,20]. It is not very likely that diabetic neuropathy was already present in subjects with newly diagnosed diabetes or impaired glucose tolerance, since its development usually takes many years. The electrocardiograms made five years before, suggest that the observed difference in QTc-length developed rather recently, while QTc in men with known diabetes was similar to QTc in men with normal glucose tolerance.

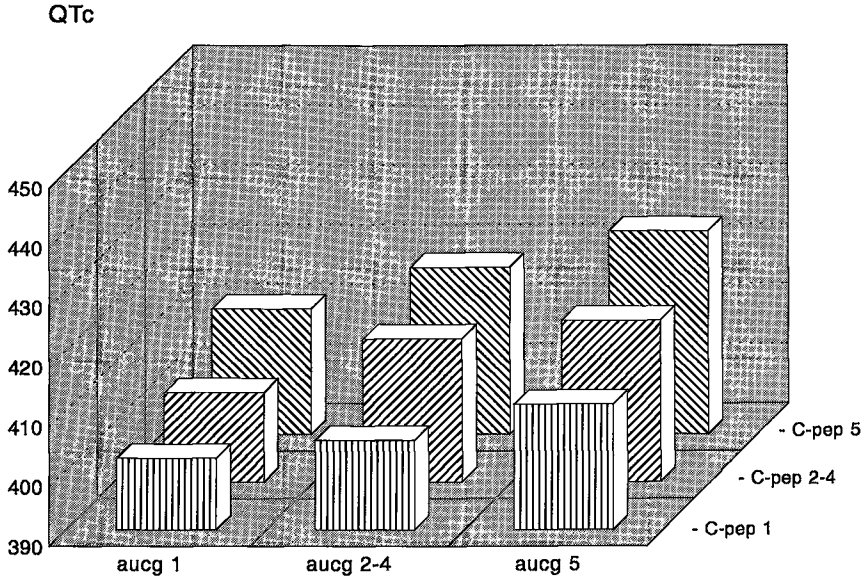

Figure 1. QTc in quintile categories of plasma C-peptide (C-pep) and Area Under the Glucose Curve (AUCG), adjusted for age, Body Mass Index, and diastolic blood pressure

In previous studies increased risk of coronary heart disease death was reported in apparently healthy persons with prolonged QTc[4,5]. This has been explained by ventricular electrical instability as a consequence of sympathetic stimulation, unopposed by vagal activity[6]. The presently observed association between QTc and fasting insulin suggests that insulin-induced sympathetic activity may be one of the precipitating factors[6,7,12]. Furthermore, an association of QTc with the insulin-resistance syndrome may also provide an explanation for the previously reported elevated

incidence of (non-fatal) myocardial infarction in men with QTc prolongation[5]. Like the unfavourable cardiovascular risk profile, QTc prolongation may also determined by insulin resistance. In the present study cardiovascular risk factors, including QTc, exhibited a tendency to cluster. Particularly Body Mass Index was observed to be an important predictor of QTc. Recently Scherrer et al. reported body fat to be a major determinant of muscle sympathetic nerve discharge, and both were positively correlated with fasting insulin levels.[21] Weight loss is reported to lead to lower sympathetic activity and blood pressure[22], which have been attributed to a fall in insulin level. In the Normative Aging Study, the association between urinary norepinephrine excretion and hyperinsulinemia was partially explained by Body Mass Index[23]. Interestingly however, in our study fasting C-peptide and the area under the glucose curve still contributed to QTc prediction after adjustment for Body Mass Index, while insulin did not. Perhaps C-peptide, as a measure of insulin secretion, is a better indicator for the effect of insulin on the sympathetic nervous system than fasting insulin level, which results from both insulin secretion and uptake by all tissues.

Besides the effect of insulin on sympathetic activity, an additional explanation for the association between QTc prolongation and indicators of carbohydrate metabolism, could be an effect of the disturbed glucose metabolism on the myocardium, possibly mediated by changes in cation (sodium and potassium) concentrations. Modan et al.[24] reported sodium and potassium abnormalities in serum and in erythrocytes of subjects with hyperinsulinemia. Such abnormalities in the myocardium may lead to de- and repolarization disturbances and ventricular electrical instability, especially in the presence of high sympathetic activity[6,25]. Animal studies have shown that glucose-insulin infusion reduces ischemia-induced extracellular potassium accumulation and improves the associated conduction delay[26]. Altered ion exchange activities may be induced by reduced myocardial glucose uptake resulting from impaired insulin binding[27]. The observed additive effects of C-peptide, indicating hyperinsulinemia, and the area under the glucose curve, indicating disturbed glucose uptake, suggest that both mechanisms may contribute to QTc prolongation.

In two recent studies among type I diabetic patients[28] and among type I diabetic identical twins[29], QTc length did not correlate with the severity of autonomic neuropathy as indicated by other cardiovascular autonomic tests. However, diabetic twins did have longer QTc than their non-diabetic co-twins, independently of

autonomic neuropathy. This is in line with the present observations, and it may contribute to our understanding of the high mortality in diabetic patients. The excess ischemic heart disease mortality in diabetics in the NHANES I epidemiologic follow-up study[30] and the Zutphen Study[31], and the bad prognosis following myocardial infarction in diabetic patients in the Framingham Study[32] could not be attributed to differences in coronary heart disease risk factors. Ventricular instability, as manifest in QTc-prolongation may add to the elevated risk.

In conclusion, the insulin-resistance syndrome seems to involve myocardial repolarization. At least two mechanisms, e.g. insulin-induced sympathetic activity and reduced glucose uptake, may be responsible for this. Further research is needed to clarify this issue.

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5. ST and T-wave characteristics as indicators of coronary heart disease risk. The Zutphen Study[4]

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Abstract

Certain ST-T-characteristics may reflect favourable autonomic cardiac control. Previously slight ST-elevation has been reported to indicate low risk of coronary heart disease mortality. The predictive value of T-wave amplitude and ST-segment level in lead I for angina pectoris, first myocardial infarction, sudden death and coronary heart disease death was studied in middle-aged and elderly men.

876 Men, born between 1900 and 1920, were followed and repeatedly examined from 1960 to 1985. In 1985 the remaining cohort was extended to 836 elderly men from the same birth cohort, and followed until 1990. Both middle-aged and elderly men with T-waves $\geq$ 0.15 mV had lower risk of myocardial infarction, coronary heart disease death and sudden death than men with T-waves 0.05-0.15 mV. The adjusted relative risk of coronary heart disease death was 0.5 (95% confidence interval 0.2 to 1.0); in men with T-waves $\leq$ 0.05 mV it was 2.0 (1.3 to 3.1). Also slight ST-elevation was associated with decreased risk: 0.5 (0.3 to 1.0) compared to isoelectric ST. In men with ST-depression it was 2.2 (1.4 to 3.4). The relationships of T-wave amplitude and ST-level were independent from each other.

Besides the elevated risk of coronary heart disease which is associated with ST-T abnormalities, we observed normal variations of repolarisation characteristics to be predictive of future heart disease.

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[4] Submitted for publication

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Introduction

Several population studies have reported on the increased risk of coronary heart disease mortality and sudden death in subjects with clear ST-depression or T-wave abnormalities[1-3]. However, the more subtle variation in normal electrocardiograms represents predictive information as well. We have previously reported on the lower risk of coronary heart disease mortality in apparently healthy middle-aged Dutch men with slight ST-elevation (0.025 mV or more) in a standard 12-lead resting electrocardiogram[4]. The most likely explanation is involvement of the autonomic nervous system. In ambulatory electrocardiographic monitoring studies among healthy subjects transient ST-deviations and T-alterations have been documented[5-7]. T-wave inversions or ST-depression mostly occurred during periods of emotional or physical stress, whereas ST-elevation occurred during sleep at low heart rates and relatively high parasympathetic activity. If ST and T characteristics in the normal resting electrocardiogram reflect cardiac autonomic control, primarily an association with future sudden cardiac death might be hypothesized, because of an influence on the propensity for arrhythmia.

In the present study we investigated the predictive value of T-wave amplitude and ST-segment level for coronary heart disease morbidity (i.e. incidence of angina pectoris and first myocardial infarction), for coronary heart disease mortality, and for sudden cardiac death. Because autonomic function changes with increasing age[8], and the prevalence of minor ST and T abnormalities is high in elderly people, a cohort of elderly men was included in the study as well.

Methods

Study population

From 1960 on the Zutphen Study, a prospective study on coronary heart disease, has been carried out in the frame of the Seven Countries Study[9]. In 1960 a random sample of 1088 men, residents of the town of Zutphen, the Netherlands, and born between 1900 and 1920, were invited for a medical examination and a dietary survey. Thirty two men refused to participate, while 178 only took part in the dietary survey

or were examined later than 1960. In 877 of the remaining 878 participants a 12-lead electrocardiogram was recorded. Because in one ST-segment level could not be determined, the 1960 study population consists of 876 middle-aged men. During follow-up examinations in 1965 and 1970, 718 and 625 men took part respectively. In 1985 the 555 survivors and an additional sample of 711 men, drawn from the same birth cohort (then aged 65-85) were invited to take part in the elderly study. Of these, 156 did not volunteer and 171 did not participate for various reasons (illness or death, could not be traced, etc.). In 54 men no electrocardiogram was made, and 49 recordings were lost during follow up, leaving 836 men in the 1985 study population.

Data Collection

Standard resting 12-lead electrocardiographic recording and assessment of cardiovascular risk factors were performed according to the protocol of the Seven Countries Study[9] in 1960, 1965, 1970, 1985 and 1990. The electrocardiograms were classified and coded according to the Minnesota Code[10]. In 1992 the levels of the ST segment in leads I and AVL were determined 80 msec past J point relative to the baseline level. Deviations were classified in 0.25 mm steps (corresponding to 0.025 mV). T-wave amplitudes in leads I and AVL were measured in mm (corresponding to 0.1 mV) using a digitizing tablet (Calcomp) and a personal computer. The observers were blinded for baseline information and survival.

Supine systolic and diastolic blood pressures at all examinations were measured twice at the end of the physical examination in the right arm. Between 1960 and 1970 only the last value was recorded. For 1985 and 1990 the mean of duplicate readings was calculated. Serum total cholesterol was determined in a standardized laboratory by the Abell-Kendall[11] method in 1960 and 1965, by the method of Zlatkis[12] in 1970, and by the enzymatic method of Siedel et al.[13] and Stahler et al.[14] in 1985. All methods produced Abell-Kendall equivalents. The Body Mass Index was calculated from height and weight (height was measured in 1960 and 1985 only). Before 1985 smoking was assessed by the Seven Countries Study questionnaire on smoking habits. From 1985 on a newly developed questionnaire[15] was used.

Mortality was registered weekly by means of the municipal registry of the town of Zutphen. Causes of death were obtained from the death certificates, the hospital

and/or the general practitioner. Information on cardiovascular disease was collected during the medical examinations. Between 1960 and 1973 medical examinations were performed annually, and after that period in 1977/1978, 1985 and 1990. In addition, questionnaires on health status were filled in in 1980 and 1982. The information on morbidity provided was verified by contacting the general practitioner. For the period 1985 to 1990, hospital discharge data of the members of the cohort who were hospitalized in Zutphen were made available as well. The follow-up of both the middle-aged and the elderly cohort is 100%.
Coding of causes of death was performed according to the International Classification of Diseases[16] (8th revision in the period of 1960 to 1985, 9th from 1985 to 1990). Coronary heart disease mortality was defined as ICD-8 codes 410, 411.9-413.9 and as ICD-9 codes 410-414.

Angina pectoris was coded only in men without prior myocardial infarction, when the subject had complaints of chest pain during physical effort, relieved within 10 minutes after stopping the effort. Myocardial infarction was coded when 2 of the following 3 criteria were present: 1. a specific medical history, e.g. severe chest pain lasting for more than 20 minutes and not disappearing during rest; 2. electrocardiographic changes corresponding to Minnesota Codes 1.1 (major Q waves) code 1.2 accompanied by 5.1 or 5.2 (smaller Q waves and major T-wave abnormalities); or 3. specific enzyme level elevations. Only first occurrence of myocardial infarction (fatal or non fatal) was recorded. Sudden cardiac death was not coded until recently by one of the authors (JD). Because of the limitations of the available information, sudden cardiac death in this study was coded in two situations: 1. when it was documented that death occurred within two hours after onset of typical symptoms, and no other causes of death were known; or 2. in subjects with a history of heart disease: when "mors subita" was notified by the physician or death occurred unwitnessed (within 12 hours after men had been observed to be well).

Data analysis

The predictive value of T-wave amplitude and ST-level for the incidence of angina pectoris, first myocardial infarction, coronary heart disease mortality, and sudden death was analyzed using Cox proportional hazards models. Subjects were categorized in three groups according to T-wave amplitude in lead I: small or inverted

T-wave: < 0.05 mV, the reference category: T wave 0.05-0.15 mV, or T-wave ≥ 0.15 mV. According to lead AVL these categories were: < -0.05 mV, -0.05 to +0.05 mV, and ≥ 0.05 mV respectively. Categories of ST-segment level were ST-depression (≥ 0.025 mV), the reference category (isoelectric ST), and slight ST-elevation (≥ 0.025 mV). To evaluate the stability of the associations, rate ratios for three, partly overlapping, 15-year periods were estimated using 1960, 1965, and 1970 as baseline respectively. In order to have full profit of the repeated measurements, a time-dependent Cox model was fitted. The resulting coefficients represent in fact short-term (5-year) rate ratios, estimated from the full dataset of repeated measurements[17,18].

In all regression analyses age was included to adjust for confounding. Other possible confounders (systolic blood pressure, serum total cholesterol, Body Mass Index, and the product of number of cigarettes and years of smoking) were included simultaneously in multivariate models. Proportional hazards assumptions were verified by inspection of log-log-survival curves. All data analyses were performed on a VAX-computer with SAS software[19]. Because the associations in categories of ST or T in lead I were similar to associations in categories based on measurements in lead AVL, only the results for ST and T in lead I are presented.

Results

The percentage of men with small or inverted T-wave or ST depression increased from 5% in middle-aged men in 1960 to 20% in the elderly men in 1985. Almost half of the middle-aged cohort had slight ST elevation and more than half had T-waves with amplitude ≥ 0.15 mV, whereas in the elderly only 14% had ST elevation and one third had firm T-waves. In table 1 population characteristics are presented according to T-amplitude in 1960 and 1985.

At all repeated measurements, mean age and systolic blood pressure were highest in the category with T-wave < 0.05 mV, and lowest in men with T-wave ≥ 0.15 mV. The percentage of men with ST-elevation was increasing with increasing T-amplitude. In the categories of ST-segment, age and systolic blood pressure were highest in men with depression, and lowest in men with elevation.

Table 1. Population characteristics in categories of T-wave amplitude. The Zutphen Study

	T < 0.05 mV	T 0.05-0.15 mV	T ≥ 0.15 mV
Middle Aged			
N	39	375	462
age (years)	52.4 ± 5.2	50.5 ± 5.4	49.5 ± 5.6*
systolic blood pressure (mm Hg)	153 ± 32	144 ± 21	142 ± 18*
serum total cholesterol (mmol/l)	6.12 ± 1.29	6.10 ± 1.22	6.07 ± 1.16
Body Mass Index (kg/m^2)	24.2 ± 3.0	23.6 ± 2.8	24.5 ± 2.6*
cigarettes * years smoked	287 ± 274	409 ± 278	352 ± 281*
% ST-depression	28	4	3†
% ST-elevation	3	32	58†
Elderly			
N	166	391	279
age (years)	72.7 ± 5.7	71.8 ± 5.1	71.7 ± 5.0
systolic blood pressure (mm Hg)	154 ± 23	150 ± 21	150 ± 21
serum total cholesterol (mmol/l)	6.08 ± 1.03	6.11 ± 1.14	6.07 ± 1.01
Body Mass Index (kg/m^2)	25.3 ± 3.5	25.4 ± 3.1	25.7 ± 3.0
cigarettes * years smoked	552 ± 552	510 ± 470	502 ± 545
% ST-depression	43	18	9†
% ST-elevation	4	9	26†

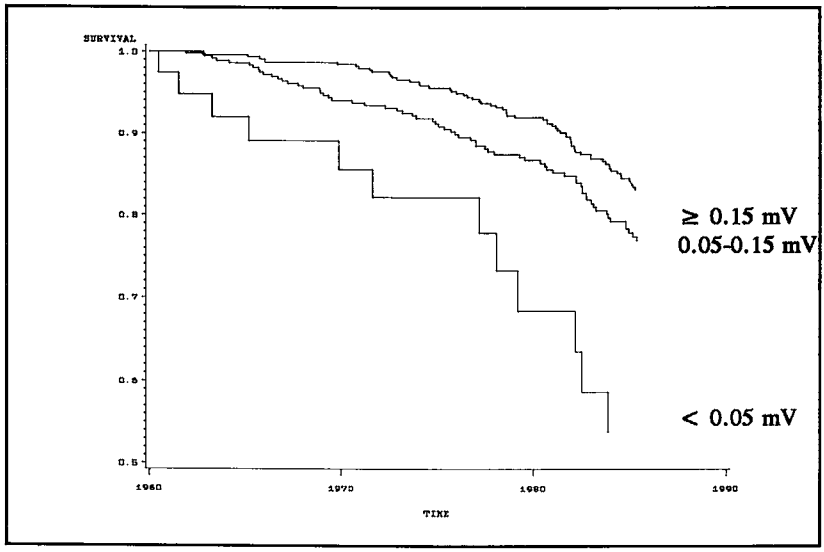
Values are mean ± sd

* Significant differences between categories ($p<0.05$), Scheffé Test for multiple comparisons

† Significantly different proportions ($p<0.05$), Chi square test

Figure 1 shows coronary heart disease survival in categories of T-wave amplitude and ST-segment in 1960 in the middle-aged men. A gradient of coronary heart disease mortality rate according to T-wave and ST is apparent. The survival curves in elderly men are similar. In tables 2 and 3 the results of risk analysis in middle-aged and elderly men respectively are shown. In both age groups, risk of all end points was increased among men with T-wave < 0.05 mV compared to men with T-wave of 0.05-0.15 mV. ST-depression was associated with elevated risk of sudden death only in the middle aged, with both coronary heart disease death and sudden death in the elderly.

T-amplitude



ST-level

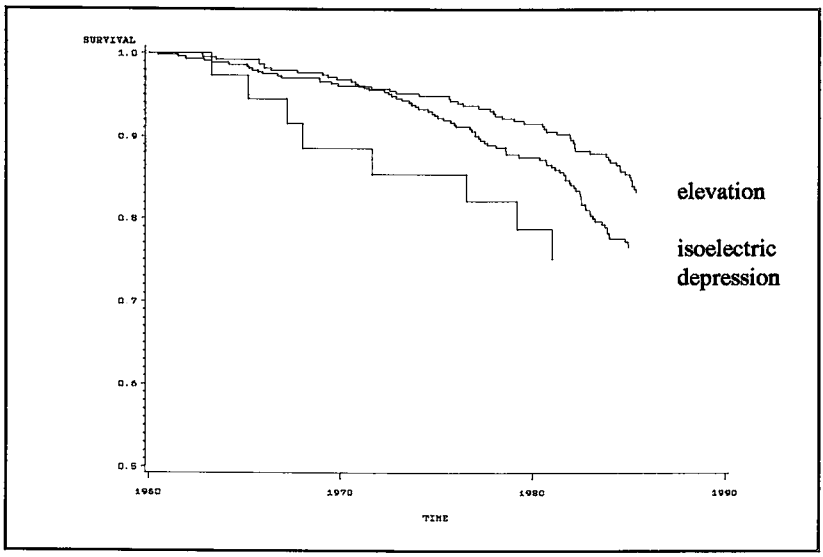


Figure 1. Kaplan Meier Curves of coronary heart disease mortality during the period 1960-1985, in categories of T-wave amplitude and ST-segment level in 1960

Table 2. The predictive value of T amplitude and ST level in lead I for 15-year coronary heart disease in middle-aged men. The Zutphen Study, 1960

	N	AP n=99*	MI n=101	CHD death n=62	sudden death n=62
T-wave amplitude					
< 0.05 mV	39	1.8 (0.7-4.1)†	1.3 (0.5-3.3)	1.9 (0.8-4.6)	4.1 (2.0-8.5)
		1.8 (0.8-4.4)‡	1.3 (0.5-3.3)	1.8 (0.7-4.6)	3.3 (1.5-7.4)
0.05-0.15 mV	375	1	1	1	1
≥ 0.15 mV	462	1.1 (0.7-1.6)	0.8 (0.5-1.2)	0.5 (0.3-0.9)	0.6 (0.3-1.0)
		1.1 (0.7-1.7)	0.7 (0.5-1.1)	0.5 (0.3-0.8)	0.6 (0.3-1.0)
ST-segment level					
depression	39	1.1 (0.4-2.9)†	1.1 (0.4-2.7)	1.4 (0.5-3.5)	2.2 (1.0-5.1)
		1.2 (0.5-3.1)‡	0.9 (0.3-2.3)	0.8 (0.3-2.50	1.5 (0.6-4.1)
isoelectric	447	1	1	1	1
elevation	390	0.9 (0.6-1.3)	0.7 (0.5-1.1)	0.6 (0.3-1.0)	0.7 (0.4-1.1)
		0.9 (0.6-1.4)	0.7 (0.5-1.1)	0.6 (0.3-1.0)	0.7 (0.4-1.3)

AP: angina pectoris
MI: myocardial infarction
CHD: coronary heart disease
* Number of cases
† Age adjusted hazard ratio (95% confidence interval)
‡ Hazard ratio adjusted for age, Body Mass Index, systolic blood pressure, serum total cholesterol, and smoking

Men with T-wave ≥ 0.15 mV or slight ST elevation had lower risk of myocardial infarction, coronary heart disease death and sudden death. The risk of angina pectoris was not clearly associated with ST and T characteristics. When analyses were repeated, using the electrocardiograms from 1965 or 1970 for ST-T classification, relative risks in the subsequent 15-year periods were similar.

Table 3. The predictive value of T amplitude and ST level in lead I for 5-year coronary heart disease in elderly men. The Zutphen Study, 1985

	N	AP n=36*	MI n=39	CHD death n=52	sudden death n=42
T-wave amplitude					
< 0.05 mV	166	1.3 (0.6-2.7)	0.9 (0.4-2.0)	2.1 (1.2-3.7)	1.3 (0.7-2.6)
		1.1 (0.5-2.8)	0.8 (0.3-1.9)	2.0 (1.1-3.6)	1.2 (0.6-2.4)
0.05-0.15 mV	391	1	1	1	1
≥ 0.15 mV	279	0.8 (0.4-1.7)	0.7 (0.4-1.0)	0.3 (0.1-0.7)	0.3 (0.1-0.8)
		0.8 (0.4-1.8)	0.5 (0.2-1.0)	0.3 (0.1-0.7)	0.3 (0.1-0.8)
ST-segment level					
depression	164	1.2 (0.5-2.9)	1.2 (0.5-2.6)	2.6 (1.4-4.5)	2.0 (1.1-3.9)
		1.2 (0.5-2.9)	1.0 (0.5-2.4)	2.3 (1.3-4.2)	1.7 (0.9-3.3)
isoelectric	557	1	1	1	1
elevation	115	1.1 (0.4-2.9)	0.7 (0.2-2.0)	0.7 (0.2-2.0)	0.6 (0.2-2.0)
		1.0 (0.4-2.6)	0.7 (0.2-2.0)	0.7 (0.2-2.0)	0.7 (0.2-2.4)

AP: angina pectoris
MI: myocardial infarction
CHD: coronary heart disease
* Number of cases
† Age adjusted hazard ratio (95% confidence interval)
‡ Hazard ratio adjusted for age, Body Mass Index, systolic blood pressure, serum total cholesterol, and smoking

The short-term predictive value of ST-level and T-wave amplitude, shown in table 4, was only slightly different from the results of the long-term analyses.

Adjustment for traditional risk factors or exclusion of subjects with electrocardiographic signs of possible prevalent heart disease decreased the relative risks of T-wave < 0.05 mV or ST depression, but did not affect the estimates of risk in men with higher T-waves or ST elevation. When both characteristics were combined in one model, both ST level and T amplitude remained independently predictive of coronary heart disease and sudden death. The estimated relative risks remained virtually the same, but the level of significance was somewhat lower.

Table 4. The predictive value of T amplitude and ST level in lead I for 5-year incidence* of coronary heart disease in middle-aged and elderly men. The Zutphen Study

	AP n=134†	MI n=133	CHD death n=113	sudden death n=140
T-wave amplitude				
< 0.05 mV	1.5 (0.9-2.6)‡	1.0 (0.6-1.8)	2.1 (1.4-3.2)	2.2 (1.4-3.4)
	1.5 (0.9-2.6)§	1.0 (0.5-1.7)	2.0 (1.3-3.1)	1.9 (0.2-3.1)
0.05-0.15 mV	1	1	1	1
≥ 0.15 mV	0.9 (0.6-1.40	0.6 (0.4-0.9)	0.3 (0.2-0.5)	0.4 (0.3-0.6)
	1.0 (0.7-1.4)	0.6 (0.4-0.9)	0.5 (0.2-1.0)	0.4 (0.3-0.7)
ST-segment level				
depression	1.6 (0.9-2.7)	1.4 (0.9-2.4)	2.5 (1.7-3.9)	2.3 (1.5-3.6)
	1.5 (0.9-2.6)	1.2 (0.7-2.1)	2.2 (1.4-3.4)	1.8 (1.1-2.9)
isoelectric	1	1	1	1
elevation	1.0 (0.6-1.6)	0.7 (0.4-1.1)	0.5 (0.3-1.0)	1.5 (0.3-0.8)
	1.0 (0.6-1.6)	0.7 (0.4-1.1)	0.5 (0.3-1.0)	0.6 (0.3-0.9)

AP: angina pectoris
MI: myocardial infarction
CHD: coronary heart disease
* Taking measurements 1960, 1965, 1970, and 1985 and subsequent 5-years of follow up as 1 observation, stratified for period
† Number of cases
‡ Age adjusted hazard ratio (95% confidence interval)
§ Hazard ratio adjusted for age, Body Mass Index, systolic blood pressure, serum total cholesterol, and smoking

Discussion

In the present study among middle-aged and elderly men, the expected increased risk of coronary heart disease among men with small or inverted T-waves and ST-depression was observed. Furthermore, T-wave of ≥ 0.15 mV or slight ST-segment elevation (≥ 0.025 mV) was accompanied by lower risk of myocardial infarction, coronary heart disease death and sudden death. These results confirm our previous finding of lower risk of coronary heart disease in men with a nicely upsloping ST segment[4].

Methodological considerations

Age, systolic blood pressure, serum cholesterol, smoking habits and Body Mass Index were considered as possible confounding factors. In the categories of flat or inverted T-wave or ST-depression these risk factors had slightly elevated levels. However, only age appeared to be a confounder of importance.

To evaluate a possible medication effect, elderly men using anti-arrhythmic, ß-blocking or diuretic agents, which may affect repolarization, were excluded from the analysis. This did not change the associations. Unfortunately information about use of drugs was not available before 1985. However, it is known that very few men were on medication in the sixties. Therefore a substantial drug effect is not likely.

Misclassification is another possible source of bias. The original aim of the Seven Countries Study was to study risk factors for coronary disease. Consequently, these end points were well defined and much emphasis was given to their definite ascertainment. Because sudden death originally was not an item of interest in the Zutphen Study, detailed information on time between the first occurrence of symptoms and death was not systematically obtained. However, it is not likely that slight ST deviations or T-wave differences affected the ascertainment of end points. Also, the end points or baseline information were not known to the coders of the electrocardiograms. Thus differential misclassification of either end points or exposure can virtually be ruled out. Non-differential misclassification of the electrocardiographic variables may have occurred, because the electrocardiograms were paper recordings and had to be coded visually. A random sample of 50 electrocardiograms was repeatedly measured by all observers. The correlation between duplicate measurements of T-wave amplitude was very high: 0.9. The percentage of ST-deviation classified in the same category on average was 75%, indicating that there might be considerable misclassification of ST level.

Interpretation

T-wave amplitudes of $\geq$ 0.15 mV and a nicely curved upwards sloping ST-segment should be distinguished from taller T-waves and ST elevation of $\geq$ 0.1 mV combined with J-point elevation, which indicate myocardial ischemia. This type of high T-waves or ST-elevation did not occur in our study population at all.

In clinical practice an electrocardiogram with a firm T-wave and upsloping ST-segment is preferred to one with small T-waves and a stretched isoelectric ST-segment, although evidence for this preference until recently has been lacking in the literature. It may be questioned whether the observed associations result from higher prevalence of coronary atherosclerosis without apparent symptoms in men with the small T-waves and a stretched isoelectric ST-segment. In that case, the age-related increased risk of coronary atherosclerosis may contribute to the reduced proportion of elderly men with T-wave $\geq$ 0.15 mV or slight ST-elevation. However, whereas after exclusion of men with any sign of heart disease according to the Minnesota Code, only few subjects with ST-depression or small T-waves remained and the relative risks were no longer significant, the relative risks of T-wave $\geq$ 0.15 mV and slight ST elevation remained identical. This suggests prevalent heart disease is not the explanation.

We hypothesized that the underlying mechanism may be autonomic nervous system function. Age-related changes of autonomic function, with higher level of circulating catecholamines in elderly subjects[20,8], may contribute to the reduced number of men with T-waves $\geq$ 0.15 mV and ST-elevation. Experimental blocking of parasympathetic activity, by administration of atropine, in healthy volunteers results in a decrease of T-wave amplitude[21]. ST-elevation and high T-waves occur in healthy people during periods of low sympathetic and relatively high parasympathetic activity[5-7]. Such a pattern of autonomic activity is reported to increase ventricular electrical stability[22], while among patients with the reverse pattern high risk of sudden death is observed[23,24]. However, the relationship of ST-T-characteristics with coronary heart disease mortality could not completely be attributed to sudden death, and an association with first myocardial infarction was present too. This may indicate that other mechanisms are operative as well.

A possibility may be the level of physical fitness. A comparison of the electrocardiograms of athletic students and sedentary controls showed higher ST-elevation and higher T-wave amplitude in the athletes[25]. Regular physical exercise has numerous favourable effects on the cardiovascular system, including effects on autonomic cardiac control. In the present study detailed information on physical activity was available for elderly men only. Indeed men with high T-waves did tend to spend more time on physical activities, but the differences did not reach statistical signifi-

cance and did not explain the observed association. Between categories of ST-segment no differences in physical activity were observed.

Further study of the determinants of T-wave amplitude and ST-segment level is warranted to explain their predictive value.

In conclusion, this longitudinal study using repeated electrocardiographic measurements confirms previous findings of lower risk of coronary heart disease in men with slight ST-elevation, and shows reduced risk in men with T-wave $\geq$ 0.15 mV. Besides the increased risk of coronary heart disease which is associated with clear ST-T abnormalities, we have shown that normal variations are predictive as well in both middle-aged and elderly men.

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6. Heart rate variability predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study[5]

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Abstract

Low heart rate variability is accompanied with high risk of sudden death in patient populations. In the present study the predictive value of heart rate variability for mortality from several causes was determined in a follow-up study of middle-aged and elderly men. From 1960 to 1985, 760 middle-aged men, born between 1900 and 1920, were followed and repeatedly examined. Subjects with frequent premature beats or second or third degree atrio-ventricular blocks were excluded. In 1985 the remaining cohort was extended to 612 elderly men with the same criteria, and followed until 1990. Heart rate variability was determined from a 20-second resting 12-lead electrocardiogram (standard deviation of duration of all normal RR-intervals).

The 5-year age-adjusted relative rate of total mortality of men with heart rate variability less than 20 msec compared to men with heart rate variability 20 to 40 msec was 1.9 (95% confidence interval 1.3 to 2.7) in the middle-aged, and 1.4 (0.9 to 2.2) in the elderly. Death from non-coronary causes, specially cancer, contributed significantly to this elevated risk. The association of low heart rate variability with sudden death or coronary heart disease mortality was inconsistent.

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[5] Submitted for publication

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In both middle-aged and elderly men low heart rate variability was predictive of mortality from all causes. This suggests that low heart rate variability is an indicator of compromised health.

Introduction

Decreased heart rate variability is accompanied by high risk of sudden death in myocardial infarction patients[1-3] and subjects referred for Holter monitoring[4]. Also patients with heart failure[5], hypertensive hypertrophy[6], and atherosclerosis[7] have been reported to have less variability of heart rate than healthy controls. This has been explained by a shift of autonomic cardiac control towards sympathetic dominance[1-8]. An increase of sympathetic activity, usually with concomitant lowering of parasym-pathetic activity, leads to reduction of total heart rate variability, primarily in the breathing-related component[8]. Experimental studies have pointed out that respiratory sinusarrhythmia is parasympathetically mediated[8]. Because sympathetic dominance lowers the ventricular fibrillation threshold[9], it may be an important factor underlying the observed high risk of sudden death in patients with low heart rate variability.

Even short electrocardiographic recordings, reflecting respiratory sinusarrhythmia only, may suffice to characterize a person with respect to cardiac autonomic function. In the Men born in 1913 Study[10], heart rate variability was defined as the length of a line that was drawn from a beat-to-beat plot of only 10 intervals. In this population of healthy middle-aged men, mortality of ischemic heart disease was higher among men with low heart rate variability. Surprisingly, however, since this study in 1975 no further studies have been performed in healthy subjects. In the Zutphen Study, the Dutch contribution to the Seven Countries Study, a cohort of middle-aged men has been followed for over 30 years, and has been repeatedly examined. We used the electrocardiograms from this study, to investigate the predictive value of heart rate variability for mortality from several causes. Because in elderly subjects heart rate variability is lower[11], a cohort of elderly men was included as well.

Subjects and methods

Subjects

From 1960 on the Zutphen Study, a prospective study on coronary heart disease, has been carried out in the frame of the Seven Countries Study[12]. In 1960 a random sample of 1088 men, residents of the town of Zutphen, the Netherlands, and born between 1900 and 1920, were invited for a medical examination and a dietary survey. Thirty two men refused to participate, while 178 only took part in the dietary survey or were examined later than 1960. In 877 of the remaining 878 participants a 12-lead electrocardiogram was recorded. During follow-up examinations in 1965 and 1970, 717 and 625 men took part respectively. In 1985 the 555 survivors and an additional sample of 711 men, drawn from the same birth cohort (then aged 65-85) were invited to take part in the elderly study. Of these, 156 did not volunteer and 171 did not participate for various reasons (illness or death, could not be traced, etc.). In 54 men no electrocardiogram was made, and 49 recordings were lost during follow up, resulting in a cohort of 836 men.

Men with more than one abnormal interval in the electrocardiogram, second- or third-degree atrio-ventricular block, pacemaker, or with less than 10 normal intervals available were excluded. The study population of middle-aged men finally comprises 760 men in 1960, 665 in 1965, and 567 in 1970. The elderly cohort consists of 612 men in 1985.

Data collection

ELECTROCARDIOGRAMS

Standard resting 12-lead electrocardiographic recording and assessment of cardiovascular risk factors were performed according to the protocol of the Seven Countries Study[12] in 1960, 1965, 1970, and 1985. The duration of recording ranged from 15 to 30 seconds. Of the 1960-electrocardiograms, from 202 subjects only clippings with a few intervals from each lead were kept. Recently the intervals between all normal sinus beats were measured, using a digitizing tablet (Calcomp) and a personal computer. The resolution of the tablet is 100 lines/mm and the reproducibility is 0.25 mm (corresponding to 10 msec). Non-sinus beats were marked. All intervals

were measured by observers who were blinded for other baseline information and survival.

OTHER VARIABLES

At all examinations systolic and diastolic blood pressure were measured twice at the end of the physical examination on the right arm in supine position. Before 1985 only the last value was recorded. From the duplicate recordings in 1985, the mean was calculated. Serum total cholesterol was determined in a standardized laboratory by the Abell-Kendall[13] method in 1960 and 1965, by the method of Zlatkis[14] in 1970, and by the enzymatic method of Siedel et al.[15] and Stahler et al.[16] in 1985. All methods produced Abell-Kendall equivalents. The Body Mass Index was calculated from height and weight (height was measured in 1960 and 1985 only). Before 1985 smoking was assessed by the Seven Countries Study questionnaire on smoking habits. In 1985 a newly developed questionnaire[17] was used.

ENDPOINTS

Mortality was registered weekly by means of the municipal registry of the town of Zutphen. Causes of death were obtained from the death certificates, the hospital and/or the general practitioner. Information on cardiovascular disease was collected during regular medical examinations. In addition, questionnaires on health status were answered in 1980 and 1982. The information on morbidity provided was verified by contacting the general practitioner. For the period 1985-1990, hospital discharge data of the members of the cohort who were hospitalized in Zutphen were made available as well. Follow-up of both the middle-aged and the elderly cohort was 100%.

Coding of causes of death was performed according to the International Classification of Diseases[18] (8th revision in the period of 1960 to 1985, 9th from 1985 to 1990). Coronary heart disease mortality was defined as ICD-8 codes 410, 411.9-413.9 and as ICD-9 codes 410-414. Sudden cardiac death was not coded until recently by one of the authors (JD). Because of the limitations of the available information, sudden cardiac death in this study was coded in two situations: 1. when it was documented that death occurred within two hours after onset of typical symptoms, and no other causes of death were known; or 2. in subjects with a history of heart

disease: when "mors subita" was notified by the physician or death occurred unwitnessed (within 12 hours after a man had been observed to be alive and well).

Data analysis

Heart rate variability was defined as the standard deviation of the duration of all normal RR-intervals. Intervals which differed more than 20% from the preceding interval were considered abnormal. The two intervals following abnormal beats were excluded as well. Subjects were categorized into three groups of heart rate variability: low ($<$ 20 msec), intermediate (20-40 msec) and high ($\geq$ 40 msec). These cut-off points separate the lowest and the highest approximate 25%, based on the distribution of the combined observations of 1960, 1965, and 1970.
The predictive value of heart rate variability for coronary heart disease death, sudden death, non-coronary heart disease death, and death from all causes was analyzed using Cox proportional hazards models. In order to have full profit of the repeated measurements, in the middle-aged population a time-dependent Cox model was fitted. The resulting coefficients can be interpreted as short-term (5-year) rate ratios[19,20]. All risk-analyses were performed twice: 1. adjusted for age only, and 2. for age and other possible confounders (systolic blood pressure, serum total cholesterol, Body Mass Index, and the product of number of cigarettes and years of smoking). Proportional hazards assumptions were verified by inspection of log-log-survival curves. Data analysis was performed with SAS software[21].

Results

Mean heart rate variability was 32 msec in the middle-aged men in 1960, gradually decreasing to 24 msec in elderly men in 1985. With increasing age, the proportion of men with low heart rate variability increased from 25% to 47%, and the proportion of men with high variability decreased from 26 to 10%. In table 1 population characteristics are presented according to categories of heart rate variability.

Table 1. Population characteristics* and mortality in categories of Heart Rate Variability in middle-aged and elderly men. The Zutphen Study

	HRV < 20	HRV 20-40	HRV ≥ 40
Middle-aged N	187 (25%)	378 (50%)	195 (26%)
age (years)	51.6 ± 5.5	49.7 ± 5.4	49.3 ± 5.4†
systolic blood pressure (mm Hg)	146.4 ± 18.7†	139.9 ± 17.6	142.7 ± 20.9†
serum cholesterol (mmol/l)	6.23 ± 1.30	6.06 ± 1.15	6.00 ± 1.07
Body Mass Index (kg/m^2)	24.2 ± 2.8	23.9 ± 2.6	24.2 ± 2.8
heart rate (beats/min)	82.7 ± 10.9†	74.7 ± 10.9	68.3 ± 9.4†
product of cigarettes and years smoking	413 ± 337	368 ± 258	360 ± 260
15 year CHD mortality (%)	9	6	5
15 year sudden death (%)	10	6	5
15 year non-CHD death (%)	21‡	11	14
15 year total mortality (%)	30‡	17	19
Elderly N	290 (47%)	260 (43%)	62 (10%)
age (years)	72.0 ± 5.2	71.0 ± 4.9	72.5 ± 5.8
systolic blood pressure (mm Hg)	150.8 ± 21.9	149.8 ± 21.3	150.7 ± 22.4
serum cholesterol (mmol/l)	6.09 ± 1.02	6.11 ± 1.28	6.15 ± 1.20
Body Mass Index (kg/m^2)	25.7 ± 3.1	25.5 ± 3.0	25.5 ± 2.8
product of cigarettes and years smoking	546 ± 529	494 ± 504	533 ± 403
heart rate (beats/min)	77.3 ± 11.8†	70.7 ± 10.0	67.4 ± 7.9
5 year CHD mortality (%)	5	4	7
5 year sudden death (%)	3	4	6
5 year non-CHD mortality (%)	15‡	10	16
5 year total mortality (%)	20‡	14	23

CHD: coronary heart disease
HRV: heart rate variability (msec); values are mean ± sd, unless otherwise indicated
* Individual parameters have missing data
† Significant F-test ($p < 0.05$) over the HRV categories; indicated value significantly different from category HRV 20-40 msec (Scheffé test, $p < 0.05$)
‡ Significantly different from category HRV 20-40 msec (Chi-square test for different proportions $p < 0.05$)

Age, systolic blood pressure, and heart rate were significantly higher in the category with low heart rate variability in middle-aged men; in the elderly men only heart rate. In both age groups the proportion of men who died from non-coronary

causes and from all causes was significantly higher in the low-heart rate variability category. In figure 1 survival curves of total mortality according to heart rate variability are shown.

When the time to the event and possible confounding factors were taken into account in multivariate hazards analyses (table 2), the 15-year total mortality rate ratio in middle-aged men in the low heart rate variability-category was 1.5 (95% confidence interval, CI, 1.1 to 2.2) compared to the intermediate category. This could partly be accounted for by the elevated risk of sudden death in the low heart rate variability category, although this association was not significant any more after adjustment for other coronary heart disease risk factors. Also death form non-coronary causes was significantly higher in the low-heart rate variability category. Because 50% of non-coronary deaths were due to cancer of all sites, we studied the association between cancer mortality and heart rate variability. The age-adjusted relative risk of cancer death in the 1960 low-heart rate variability category was 1.7 (CI 0.9 to 3.1).

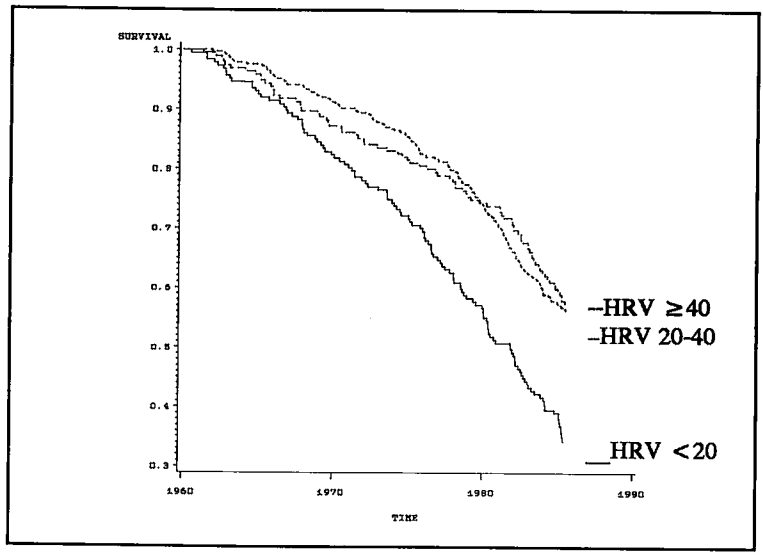
An elevated risk of non-coronary mortality was observed in the high heart rate variability-category, although not significant. This increased mortality could not be attributed to any particular cause.

In order to assess the stability of the observed associations, analyses were repeated using the heart rate variability measurement of 1965 or 1970 as baseline. The relative mortality rates in the 1965-low heart rate variability category during 1965 to 1980 were lower and non-significant, whereas 15-year mortality ratios of all endpoints (including cancer) following measurements in 1970 were higher and highly significant (data not shown).

The short-term predictive value of heart rate variability for total and non-coronary mortality, determined by the 5-year rates from the measurements in 1960, 1965, and 1970 among the middle-aged men was similar to the long-term predictive value (table 2). Short-term risk of coronary heart disease mortality in the low heart rate variability was elevated as well.

Also in the elderly men 5-year total and non-coronary heart disease mortality were increased in the low heart rate variability category. There was no significant association of heart rate variability with sudden death, coronary heart disease mortality or cancer mortality.

Middle-aged men



Elderly men

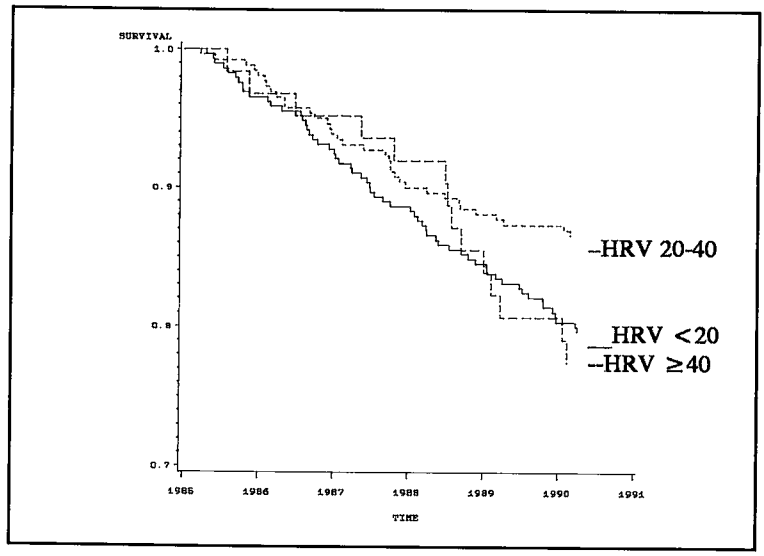


Figure 1. Kaplan-Meier survival curves of total mortality in categories of Heart Rate Variability in middle-aged and elderly men

Table 2. The predictive value of Heart Rate Variability for coronary heart disease and mortality. The Zutphen Study

	%	CHD death	sudden death	non-CHD death	all causes
Middle-aged men					
1960-1975		n=51*	n=52	n=110	n=161
HRV < 20	25	1.3 (0.7-2.4)†	1.9 (1.0-3.4)	1.9 (1.2-2.9)	1.7 (1.2-2.4)
		1.0 (0.5-1.9)‡	1.7 (0.9-3.1)	1.9 (1.2-3.0)	1.5 (1.1-2.2)
HRV ≥ 40	26	0.9 (0.4-1.9)	0.8 (0.4-1.7)	1.4 (0.9-2.3)	1.2 (0.8-1.8)
		0.8 (0.4-1.8)	0.7 (0.3-1.6)	1.5 (0.9-2.4)	1.2 (0.8-1.9)
5-year mortality§		n=51	n=83	n=104	n=155
HRV < 20	30	1.8 (1.0-3.4)	1.6 (1.0-2.6)	1.9 (1.2-3.0)	1.9 (1.3-2.7)
		1.7 (0.9-3.1)	1.3 (0.8-2.2)	2.2 (1.4-3.5)	2.0 (1.4-2.9)
HRV ≥ 40	23	0.9 (0.4-2.0)	0.8 (0.5-1.5)	1.4 (0.8-2.5)	1.2 (0.8-1.9)
		0.9 (0.4-2.2)	0.8 (0.4-1.5)	1.7 (1.0-3.0)	1.4 (0.9-2.2)
Elderly men					
1985-1990		n=29		n=25	n=79n=108
HRV < 20	47	1.3 (0.6-2.9)	0.8 (0.3-1.8)	1.5 (0.9-2.4)	1.4 (0.9-2.2)
		1.3 (0.6-2.9)	0.8 (0.3-1.9)	1.6 (1.0-2.6)	1.5 (1.0-2.3)
HRV ≥ 40	10	1.5 (0.5-4.9)	1.3 (0.4-4.2)	1.5 (0.7-3.2)	1.5 (0.8-2.3)
		1.5 (0.5-4.8)	1.2 (0.4-3.8)	1.6 (0.8-3.4)	1.6 (0.8-2.9)

HRV: heart rate variability (msec)
CHD: coronary heart disease
* Number of cases
† age adjusted hazard ratio (95% confidence interval), reference category: HRV 20-40 msec
‡ hazard ratio adjusted for age, Body Mass Index, systolic blood pressure, serum total cholesterol, and smoking, reference category: HRV 20-40 msec
§ Taking measurements in 1960, 1965, and 1970 and subsequent 5 years of follow-up as separate observations, stratified for period.

Discussion

In this follow-up study of middle-aged and elderly men, low heart rate variability in the resting 12-lead electrocardiogram, was accompanied by elevated risk of death. This association was not specifically due to cardiac causes.

Methodological issues

In epidemiology, large cohort studies like the Zutphen Study are viewed as the most reliable way to study determinants of disease. Because exposure is measured when the outcome is still unknown, selection and recall bias, which may affect the validity in other study designs are unlikely. Furthermore, because the present hypothesis was not raised at the time the endpoints were determined, and measurements of RR-intervals were performed by technicians, unaware of the medical history of the subjects or the present hypothesis, differential misclassification is not expected. Still, some nondifferential misclassification cannot be excluded, particularly because a short recording may not be sufficient to measure heart rate variability of an individual with precision. The original aim of the electrocardiogram was not heart rate variability but the diagnosis of prevalent heart disease. Before 1985, the applied electrocardiographs had only three or six simultaneous channels. Thus, in order to get a 12-lead electrocardiogram, more than one recording had to be made. This resulted in an approximately 15 to 30 seconds recording, with interruptions for lead switching. In 1985, 30-seconds recordings were made. If nondifferential misclassification between categories of heart rate variability did occur, this will probably have diluted the true association.

In 1960 from 202 electrocardiograms only clippings with a few intervals from each lead were available, and the estimated heart rate variability may thus be less precise. These 202 men were a selection from the total cohort with a higher risk of coronary heart disease: 75% of them had an electrocardiographic abnormality according to the Minnesota Code. Furthermore mean age, blood pressure and serum cholesterol were higher, and heart rate variability was lower. To exclude the possibility that the association in the 1960-data might have resulted from this selection, we repeated the analyses after exclusion of these subjects. The relative rates of all endpoints in the low compared to the intermediate heart rate variability category were higher than observed in the full 1960-cohort. (age-adjusted relative risk of coronary heart disease mortality: 1.9, CI, 0.9 to 4.1). The associations with high heart rate variability did not change.

Misclassification of heart rate variability because of use of medication that affects heart rate may be a concern in this study. In the middle-aged men these drugs were not frequently prescribed, but in the elderly population a substantial

part used medication. Exclusion of men using anti-arrhythmics or ß-blocking agents did not markedly change the results. Other medication may also be of influence, however, further exclusion of men using any drugs, resulted in insufficient numbers for analysis. Thus, an obscuring effect of medication cannot be excluded for the elderly population.

Age, systolic blood pressure, Body Mass Index, smoking, and serum cholesterol were considered as possible confounding factors. Including them in the multivariate analyses lowered the estimates of coronary heart disease mortality and sudden death, but not of mortality form other causes. Also heart frequency may be considered as a confounding factor. In a number of large studies[22-23], high heart rate was associated with increased mortality or coronary heart disease. When we adjusted heart rate variability for heart rate by dividing heart rate variability by mean interval[24], the lowest quartile still had the highest risk of all endpoints, indicating heart rate was not responsible for the observed associations with heart rate variability.

To determine autonomic contributions to heart rate variability, spectral analysis would have been the preferable method. However, because of the limited duration of the electrocardiographic recording, this was impossible. Therefore the standard deviation had to be used as measure of heart rate variability. Hayano et al. observed a high correlation between standard deviation, and the high frequency spectral component in an experimental study[25].

Elderly

In the present study almost 50% of men in the age of 65 to 85 had low heart rate variability. Also in previous studies reduced heart rate variability in elderly subjects has been reported[11,26]. In contrast to the middle-aged, elderly men with high heart rate variability often had many electrocardiographic abnormalities. In these men, the variability was irregular. Possibly the standard deviation in a short electrocardiographic recording in elderly subjects is not a good measure of autonomic cardiac control. In this age category, spectral analysis of longer recordings, in which the contribution of regular fluctuations of heart rate can be studied[8], may provide more relevant information.

Mechanism

Heart rate variability represents adaptive responses of the autonomic nervous system to challenges to the circulation, like respiration. The sum of sympathetic and parasympathetic effects mainly determines the total amount of variability. Therefore heart rate variability to a certain extent reflects sympatho-vagal balance[8]. Because sympathetic dominance has been reported to lower the ventricular fibrillation threshold[9], the strongest relationship was expected between heart rate variability and sudden death or coronary heart disease mortality. This was not confirmed in the present study. Possibly the baroreceptor reflex rather than heart rate variability may be a more important risk determinant. A comparison of baroreflex sensitivity, determined as the change of heart rate to a drug-induced blood pressure change, and measures of heart rate variability in myocardial infarction patients showed that these are not exchangeable[27]. Farell et al. found baroreflex sensitivity to be the strongest predictor of arrhythmic events in myocardial infarction patients, but heart rate variability independently provided additional predictive information[28].

Besides baroreflex sensitivity, a number of other characteristics may affect heart rate variability, including participation in sport activities[29], frequency and depth of breathing[30], smoking[31] or depression[32]. These other determinants may partially account for the predictive value of heart rate variability for non-cardiac death in the middle-aged men.

The unexpected association with cancer merits further attention. We initially believed that subjects with subclinical cancer may have increased sympathetic activity, resulting in lower heart rate variability. However, when we excluded the first 5 years of follow-up the relationship persisted. Furthermore when the period of follow-up was prolonged from 15 to 20 or 25 years, we found even higher relative risks. The elevated risk was not confined to a specific site of cancer. Therefore, it may be hypothesized that autonomic nervous system function is associated with a general risk factor like immune function. A number of studies report direct effects of sympathetic activity on function, number and subset distribution of circulating lymphocytes[33,34]. Also, in a large British cohort study high heart rate and low level of physical activity, both associated with autonomic nervous system function, were independent predictors of long-term cancer mortality[35].

We observed a consistent U-shaped relationship with mortality from non-coronary causes. Also in the Men born in 1913 Study[10] death from causes, other than ischemic heart disease, was higher in the highest heart rate variability-category. We do not have an explanation for this finding.

In conclusion, low heart rate variability is associated with risk of death from all causes in both middle-aged and elderly men. The association does not exclusively result from coronary heart disease mortality. This suggests low heart rate variability may be an indicator of poor general health.

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7. General Discussion

In population studies of cardiovascular disease the electrocardiogram is primarily used for the diagnosis of heart disease. However, there is more to the electrocardiogram, than (early) signs of ischemia or infarction injury. We studied a number of electrocardiographic characteristics which are manifestations of cardiac control and may indicate electrical vulnerability of the ventricle. Length of the heart-rate adjusted QT interval, heart rate variability, ST-segment level and T-wave amplitude, all within normal ranges, were predictive of future coronary heart disease morbidity and mortality (table 1). These associations were observed in both middle-aged and elderly men. Further study of determinants of QTc duration provided evidence that the carbohydrate metabolism may play a not yet fully understood role.

The electrocardiographic characteristics which were studied in this thesis: the CIIS, QTc, ST-level, T-amplitude, and heart rate variability were correlated to each other. The correlations were between 0.25 to 0.4, and significant in all years (1960, 1965, 1970, and 1985). The predictive value of all these characteristics combined was evaluated by simultaneous inclusion in one proportional hazards model. Analysis was repeated for each year of measurement. For all years, parameters which are known to indicate the presence of a myocardial infarction or ischemia (CIIS $\geq$ 20, T-wave inversion and ST-depression) had the highest regression estimates. This finding was consistent for both coronary morbidity and mortality, for each repeated measurement. Low heart rate variability was a consistent predictor of total mortality only. The predictive values of a firm T-wave (T $\geq$ 0.15 mV), slight ST-elevation, and QTc-prolongation in the combined models were less consistent. Depending on period and endpoint the pattern of associations differed. This may be because these characteristics all reflect the same underlying determinant, e.g. autonomic cardiac control.

In the following, first, the validity of the study will be evaluated, with special attention to the measurements of the electrocardiographic variables. Then the analysis of repeated measurements, which was only briefly mentioned in the previous chapters, will be commented on in more detail. Finally, some considerations on the mechanisms underlying the observed associations, and the implications for future research will be discussed.

Table 1. Summary of results

Characteristic	AP	MI	CHD	SD	TM
CIIS (reference: < 5)					
5-10	0	0	+/0		
10-19	+/0	+	+		
≥ 20	+	+	+		
QTc (reference: < 385 msec)					
385-420 msec		0	+	+	
≥ 420 msec		+	+	+	
T-wave amplitude (reference: 0.05-0.15 mV)					
< 0.05 mV	+/0	0	+	+	
≥ 0.15 mV	0	-	-	-	
ST-segment level (reference: isoelectric)					
depression	0	0	+	+	
elevation	0	-	-	-	
Heart rate variability (reference: 20-40 msec)					
< 20 msec			+/0	+	+
≥ 40 msec			0	0	0

AP: angina pectoris
MI: myocardial infarction
CHD: coronary heart disease death
SD: sudden death
TM: total mortality

CIIS: cardiac infarction injury score
0: no consistent association
-: lower risk
+: elevated risk

Validity

Possible sources of bias

In epidemiology, large cohort studies like the Zutphen Study, are viewed as the most reliable observational design to study determinants of disease[1]. Because exposure is measured when the outcome did not yet occur, selection and recall bias, which may affect the validity in other study designs, are unlikely. Loss to follow up could hamper validity in cohort studies, especially when it is differential. Therefore a country town with little mobility was selected, and much attention was given to the follow-up procedures. In this way loss to follow up was completely avoided.

Information bias may still be a problem in our study. If the determination of the endpoints would depend on knowledge of the exposure status, spurious associations could arise. But at the time the coding of morbidity and mortality of the Zutphen Study took place, the present hypotheses were not raised yet. If the endpoint was known to the coders of the electrocardiograms, it may influence their judgement. Particularly, if the coders had been cardiologists, recognition of certain electrocardiographic abnormalities could have possibly affected their measurements[2]. By hiring technicians who were blinded for the outcome, we tried to prevent this kind of bias. Misclassification which is not related to exposure or disease, or non-differential error, in general reduces the power to detect existing relationships[1]. Dosemeci et al. showed some hypothetical examples of consequences of misclassification in the case of multiple levels of exposure. A high level of non-differential misclassification between nonadjacent categories only (40% in the example) can actually reverse effect estimates[3]. However, Birkett showed that in more realistic and limited models of non-differential misclassification, which are expected in the present study, in general the bias is towards the null value[4].

It should be questioned whether the traditional risk factors for heart disease should be considered as possible confounders in this study. A real confounder is *independently* related to both the exposure and the outcome. As an important additional requirement a confounder should not be involved in the causal pathway[1]. It is common practice in epidemiologic studies to adjust for possible confounders, and to assume that the estimate of effect of the determinant under study represents the association which is independent from these possible confounders. However, very often the concepts of 'independently related to exposure and outcome' and 'not involved in the causal pathway' of such a possible confounder are neglected. If these two presumptions are not valid, then the interpretation of the 'adjusted' effect estimate is unclear. Robins and Greenland have shown that it is impossible to differentiate between a 'direct' effect of the exposure, or an 'indirect' effect through an intermediate variable[5]. Furthermore, Weinberg has shown examples of bias arising from adjustment for a factor, which is a manifestation of the same underlying determinant as the exposure under study[6]. In cardiovascular epidemiology, established risk factors of coronary heart disease like blood pressure, serum cholesterol, body mass index, and smoking are usually considered as possible confounding factors. Because all

of these affect or are affected by autonomic function, it is doubtful whether these factors can and should be adjusted for in a study of indicators of autonomic cardiac control. If alleged possible confounders were included anyhow in multivariate models in our study, the observed relationships remained similar, which may suggest an indepent pathway.

As discussed above, non-differential misclassification can reduce the power of a study. Therefore, in order to improve the accuracy, and to facilitate the measurement, a method was developed for semi-automated measurement of intervals on electrocardiographic paper recordings.

Measurement of electrocardiographic characteristics

To measure intervals, the electrocardiogram was spread out on a digitizing tablet. The beginning and the endpoint of intervals were marked, using an electronic pointing device. The coordinates of these markings were read by a personal computer, and from the difference the length of the interval was calculated. Instructions and questions were provided to the coder by a computer program.

Two main sources of measurement error should be considered. The first is the limitation of the digitizing tablet. In this study a Calcomp drawing board was used. The specification of the manufacturer indicates an accuracy of 0.25 mm, corresponding to 10 msec. The second source of error is the coder. The magnitude of this error, examined by repeated measurements of the same interval by several coders, was only 0.125 mm or 5 msec.

When successive intervals are measured (like in a series of intervals between R-waves), using each point as the end of the preceding and as the beginning of the following interval, these intervals are necessarily correlated. Therefore series of successive intervals were measured twice, and the mean of the two values of each interval was recorded. The validity of this method was studied by comparing results on 50 electrocardiograms, recorded digitally on a Marquette MAC-12 electrocardiograph (sampling frequency of 250/s) and printed on paper. The correlation between 455 RR intervals on paper, measured by the semi-automated method and from the digital information was 0.9991. This indicates that this method provides reliable measurements.

Certain electrocardiographic intervals are clearly defined and clearly distinguishable on the electrocardiogram. Others may be very difficult to discern, and the measurements may vary considerably between coders[7]. The determination of the end of the QT interval is an example of the latter. Systematic differences between coders in tendency to mark points somewhat to the outside or to the inside of a blurred line can be a serious problem. During our study, coder differences were monitored by duplicate measurements in 30 electrocardiograms. A clear coder difference was observed in the QT-measurements, making it necessary to remeasure QT in part of the electrocardiograms. The reproducibility within one coder was high (correlation coefficient of 0.9). Therefore, preferably all QT intervals in a study should be measured by a single coder. If this is not possible, much attention should be given to training and standardization of the measurement.

Another problem is the use of different electrocardiographs over time. Murray et al. showed that differences in paper speed and electrocardiogram gain can affect manual measurement of QT length[7]. In the Zutphen Study the electrocardiograms fortunately were all taken at 25 mm/sec, and with 1 V/cm. Furthermore, all amplitude measurements were adjusted for deviations of the calibration pulses. Still, there may be differences which could systematically affect certain measurements, and introduce a systematic difference between the repeated measurements. This may have affected the comparison of changes over time in the present study. Because within a year in which the periodical medical examinations were carried out, the same electrocardiograph was used, this did not hamper the classification within the years.

In conclusion, the possibility of bias in this study seem to be limited, and the semi-automated method of measuring electrocardiograms provides a useful and accurate method to reduce measurement error. Therefore we think the observed associations in this study are valid.

Analysis of repeated measurements

In longitudinal studies like the Zutphen Study, the population is usually characterized by the baseline measurement. Methods of analysis of the predictive value of one baseline classification, like logistic regression and Cox proportional hazards analysis, are well known and reliable. However, after very long follow-up periods the predictive value of risk factor level at baseline decreases. A good example is the association between systolic blood pressure at baseline in 1960 and coronary heart disease mortality in the Zutphen Study. When a 25-year follow-up period is considered, the age adjusted hazard ratio of the highest relative to the lowest tertile is 3.0. When the analysis is limited to the first 15 years, the hazard ratio is 6.0. The main reason for this finding probably is, that the single measurement of exposure (systolic blood pressure) is less representative of the true level if the follow-up period increases. For this reason in many longitudinal studies repeated measurements are made. The cohort is examined regularly to determine change of risk factor level.

When repeated measurements are available, the study hypothesis must be considered: is the emphasis on the predictive value of certain levels of the risk factor or on change? When change is subject of study, is a correction for baseline level appropriate[8]? A problem, which especially complicates the analysis of change, is measurement error and the associated problem of regression to the mean[8,9]. Most literature on these topics is on linear regression analysis. When the dependent variable is a binary outcome, the problem is even more complicated. Cain et al. showed how spurious associations between change over time in a risk factor and the outcome may result from measurement error[10]. In chapter 2 this problem was encountered in the analyses of the predictive value of change of the CIIS. There was regression to the mean, because change of the CIIS over a period and its initial value were correlated. A decrease was even associated with elevated risk of coronary heart disease mortality in the following five years. Stratification by initial value made it clear that this increased risk was entirely due to the category with a high initial CIIS. Thus stratification improved insight in the effect of regression to the mean. However, it was not possible to discern between true changes, changes due to measurement error or possible differences resulting from the use of different

electrocardiographs. The effect of using different electrocardiographs could not be evaluated anymore, because historical material was used. To reduce measurement error, duplicate measurement might have been considered. In the present study this was not feasible. Therefore the use of anyway change was limited.

The analysis of the predictive value of a number of covariates for a binary outcome, using repeated measurements is complicated. Very limited information is available in the epidemiologic literature. Only during the last few years there has been interest of biostatisticians in this field. An extension of Cox model has been proposed, a so-called time-dependent model, in which the covariates are allowed to change over time. However, the interpretation of the resulting coefficients is difficult. An example was encountered in the analysis of systolic blood pressure in the Zutphen Study. The relative risk of coronary heart disease mortality in the following 15 years of men in the category 170 mm Hg or more compared to men in the category less than 150 mm Hg in 1960 was 3.3 (1.1-9.7). When time-dependent analysis was carried out, allowing systolic blood pressure to change, the resulting relative risk was 1.8 (1.0-3.3). This may be explained by the age-related shift in the population distribution to a higher blood pressure. A considerable part of surviving subjects moved to a higher category during follow-up.

Therefore we followed the line of the discrete time proportional hazards model[10,11]. In this analysis the dataset is made up of one observation for each participant at risk, at each new measurement, using the exposure, and the outcome during the 5-year interval until the next measurement, and an indicator variable representing the time interval. These pooled repeated measurements data were analyzed using the proportional hazards model. The resulting coefficients can be interpreted as the short-term relative risk. In a relatively small cohort of middle-aged men the 5-year incidence of coronary heart disease will be low. But when the 5-year incidences following each repeated measurement are used, this is somewhat comparable to extending the population with each repeated measurement[11], that way enlarging the power. An illustration of a difference in the long- and short-term predictive value was observed in the study of QTc and coronary heart disease mortality. The 15-year hazard ratio in men with QTc of 385-420 msec compared to men with QTc < 385 msec was about twofold. The 5-year relative hazards following measurements in 1960, 1965, and 1970 were all higher, but not significant when analyzed separately,

because of the limited number of cases in the reference category. When taken together the resulting hazard ratio of more than 3 was significant.

Repeated measurements can also be used as a method to study the reproducibility of an observed association, and to check the possibility of chance findings. This was done by separately studying the 15-year incidences following the measurements in 1960, 1965 and 1970. This can be recommended, because it also improves insight in the effects of a shifting exposure distribution and increasing event rates on the significance level of an observed relative risk.

Etiology and biological mechanism

The results presented in this thesis indicate that electrocardiographic characteristics predict future heart disease in middle-aged and elderly men. Next, possible explanations of the observed associations will be discussed.

Subclinical heart disease?

In the general population, subjects with diagnosed heart disease have elevated risk of death[12-14]. Also in this study men who had symptoms of angina pectoris or had a previous myocardial infarction had high risk. The presence of atherosclerosis in the coronary arteries or of myocardial lesions largely increases the risk for future coronary events. In subjects who do not present clinical symptoms, electrocardiographic abnormalities, which are indicative of ischemia or infarction injury, are associated with elevated risk of coronary heart disease morbidity and mortality as well. This was confirmed in our study, using both the Minnesota Code and the CIIS.

In all previous chapters, the associations were studied after the exclusion of men with angina pectoris or electrocardiographic signs of prevalent heart disease. None of the observed associations disappeared after this exclusion. Though it cannot be completely ruled out that the observed associations are still a consequence of the presence of subclinical heart disease, we think effects of autonomic cardiac control mainly explain the observed associations.

Indicators of autonomic cardiac control?

The autonomic nervous system affects the electrophysiologic properties of the heart. In general the sympathetic nervous system stimulates conduction velocities, and increases stroke force and volume, whereas vagal activity slows the pacemaker rates and conduction. The balance between sympathetic and parasympathetic activity is involved in the electrical stability of the heart, with sympathetic dominance lowering the ventricular fibrillation threshold[15].

QTc Prolongation of QTc after a myocardial infarction can be due to ischemic myocardial damage. Cardiac innervation may not be balanced anymore because the nerve terminal and/or the receiving tissue may be damaged. Therefore the myocardium will not be stimulated evenly, and conduction velocities may differ between adjacent areas. Especially in the presence of non-conducting scar tissue de- and repolarization waves will be deorganized leading to dispersion of repolarization. In that way an already repolarized area can be stimulated by a near depolarization front (reentry).

In patients with the long QT syndrome, who have a very high risk to die suddenly during periods of physical or emotional stress, left sympathetic activity may be dominant over right. These differences also affect local conduction velocities and cause dispersion of repolarization[16]. In certain families of long QT patients, a genetic marker has been identified, suggestive of an abnormality in cardiac membrane conductance. Such abnormalities may lead to afterdepolarizations (oscillations of the membrane potential that attend or follow the action potential). When the amplitude reaches a certain threshold, it may induce a spontaneous depolarization: triggered activity[17]. Sympathetic activity increases the amplitude of afterdepolarizations, and thus the possibility of one reaching the threshold. Recently Antelevitsch[18] stressed the possible role of M cells in triggered activity. These cells in the deep endocardial structures have typically slower electrophysiologic characteristics. The prolonged action potential of these cells may be manifest as an afterdepolarization-like deflection, and may also lead to QT-prolongation, or U-waves. The M-cells are very sensitive to sympathetic or catecholamine action to induce triggered activity. A common characteristic of all proposed mechanisms, is that high sympathetic activity is hazardous, and parasympathetic activity may be protective.

Most of the mentioned research was conducted in patients. Therefore, the underlying mechanism of our observations of elevated risk in apparently healthy subjects with QTc-prolongation remains somewhat speculative. Each of the three mechanisms could contribute to a high risk of arrhythmia and sudden death. However, QTc also turned out to be predictive of a first myocardial infarction, either fatal or non-fatal. This suggests the involvement of yet other mechanisms. The observation reported in this thesis, of a possible involvement of QTc-prolongation in the so called insulin resistance syndrome, might provide an explanation for an association between QTc and myocardial infarction incidence. Elevated levels of C-peptide and lower glucose tolerance were observed in elderly men with QTc-prolongation. Insulin is known to stimulate sympathetic activity[19], thus possibly reducing electrical stability. Additional explanations could be effects of the disturbed glucose metabolism on the myocardial cells. This could be mediated by changes in cation (sodium and potassium) transport and concentrations[20] which are capable of inducing afterdepolarizations. Such changes may result from reduced myocardial glucose uptake.

Some observations on the association between nutritional habits and QTc also seem to point at the importance of (cardiac) cell metabolism for electrical stability. Poor thiamin status (vitamin B1, involved in decarboxylation) was associated with prolonged QTc interval among refugees at high risk of sudden death in Thailand[21]. Carbohydrate intake, and vitamin B6 (involved in decarboxylation and transamination) consumption were shown to affect QTc in women[22].

ST segment level and T-wave amplitude Very little information is present on the mechanism underlying the low risk of men with large T-amplitudes or slight ST-elevation. Athletic students have higher ST-elevation and higher T-wave amplitude than sedentary subjects[23], suggesting physical fitness may be an explanation. Indeed in our study, time spent on different activities was weakly correlated with T-amplitude, but this did not explain the reduced risk. The most likely explanation may be an association with autonomic nervous system function. In ambulatory electrocardiographic monitoring studies among healthy subjects transient ST-deviations and T-alterations were observed[24-26]. T-wave inversions or ST-depression mostly occurred during periods of emotional or physical stress, whereas ST-elevation occurred during sleep at low heart rates and relatively high parasympathetic activity. This is in line

with results of experimental blocking of parasympathetic activity by atropine, in which the T-wave flattened[27]. More research is needed to clarify the exact mechanism.

Heart rate variability Because respiratory arrhythmia is indicative of parasympathetic activity[28], and therefore of sympatho-vagal balance, it was hypothesized that the standard deviation of RR-intervals on a 10 second electrocardiographic recording may be predictive of coronary morbidity and mortality. We did indeed observe a rather weak association, in middle-aged men only. However, to our surprise, in both age groups a strong association was observed of low heart rate variability with total and non-coronary mortality, specially cancer. This may be because a number of factors, associated with an unfavourable prognosis, can lower heart rate variability, including low baroreceptor sensitivity[29], lack of physical activity[30], fast and shallow breathing[31], smoking[32], and depression[33]. Furthermore, sympatho-vagal balance may effect the function of several organs, including immune function[34,35]. Low heart rate variability therefore may be an indicator of an unfavourable general condition. Half of the elderly men had very low heart rate variability, while in this age-category a high heart rate variability was often due to irregular variability instead of breathing related cyclic variations. Our results suggest that in elderly men the standard deviation of a short electrocardiographic recording cannot be used as a reliable measure of vagal activity.

Conclusions and implications for future research

Normal variations in the electrocardiogram have been shown to predict coronary heart disease risk in a population of middle-aged and elderly men. It should be evaluated whether the reported findings also apply to other populations. Although men and women are similar in many aspects, their hearts may function somewhat differently[36]. Previous studies have indicated gender differences in the predictive value of QTc and ST-segment level in Dutch Civil Servants[37,38]. Therefore, the predictive value of electrocardiographic indicators of autonomic function should be investigated in women and in other populations as well.

The findings, which are presented in this thesis may have implications with respect to our understanding of processes contributing to coronary heart disease incidence and mortality. Many questions remain to be answered, however, before conclusions on public health implications can be drawn.

In the Zutphen Study, which was initiated already a long time ago, many methods, which are commonly used at present, were not yet available. For instance, modern techniques can provide insight in the level of atherosclerosis (like ultrasound examination of carotid artery). This way the possibility that electrocardiographic indicators of cardiac control are affected by preclinical heart disease could be studied with more certainty. Furthermore, many factors may affect cardiac regulation. Regular physical activity seems to improve parasympathetic responsiveness[39-41], whereas smoking[42], and hyperinsulinemia[19] increase sympathetic activity. Also the fatty acid composition of the diet may modulate cardiac autonomic reflexes[43,44]. The relationship of these determinants of cardiac control with electrocardiographic characteristics warrant further attention. Especially it should be evaluated whether the electrocardiographic characteristics can be improved by interventions in the determinants, and whether this is associated with a better prognosis. If so, the electrocardiogram could be used to monitor the effect of preventive actions in particulary vulnerable subjects.

If our findings are confirmed in other populations, this may be of consequence for preventive strategies. Subjects exhibiting the investigated characteristics in combination with other risk factors may be viewed as a high risk category and receive special attention. If our hypotheses on the underlying mechanism, the balance between sympathetic and parasympathetic activity, are confirmed by other studies, this implies that certain interventions, like stimulation of sports activities and cessation of smoking, could be of special benefit to these categories of the population.

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Summary

Electrocardiography is an elegant non-invasive technique to study heart function. Although it is mainly used for diagnostic purposes, certain electrocardiographic characteristics may provide predictive information for future heart disease. Especially characteristics, which reflect autonomic cardiac control may be associated with coronary heart disease risk, because the autonomic nervous system has a crucial function in cardiac control and ventricular electrical stability. In order to verify this, their predictive value for coronary heart disease morbidity and mortality was studied.

In the Zutphen Study, a prospective study on cardiovascular disease in the general population, physical examinations (including electrocardiography) were repeatedly carried out from 1960 to 1985, among 878 men, born between 1900 and 1920. In 1985 additional recruitment from the same birth cohort in Zutphen was performed. A cohort of 939 men, then aged 65 to 84, participated. These cohorts have been followed with respect to morbidity, vital status, and causes of death (chapter 1).

The predictive value of a measure of cardiac injury was studied. The Cardiac Infarction Injury Score (CIIS) was developed as an electrocardiographic measure to determine the presence of myocardial infarction. In men with high CIIS the prevalence of (silent) previous myocardial infarction and the occurrence of ST-T abnormalities were higher. Five-year relative risks of both middle-aged and elderly men with a CIIS of 20 or more relative to men with a CIIS of less than 5 were 2.2 (95% confidence interval: 1.2-4.1) for angina pectoris, 2.4 (1.4-4.0) for myocardial infarction and 5.8 (3.4-9.9) for coronary heart disease death. Thus, the CIIS predicts coronary events in apparently healthy middle-aged as well as elderly men (chapter 2).

Prolongation of the heart rate adjusted QT-interval (QTc) can result from imbalance of autonomic innervation or from myocardial cell membrane defects. Both conditions may contribute to ventricular electrical instability in the presence of high sympathetic activity. Men with prolonged QTc (420 msec or more) were observed to have higher risk of myocardial infarction and coronary heart disease death relative to men with QTc less than 385 msec. Age adjusted coronary heart disease mortality rate ratios were 4.3 (1.3-13.8) in middle aged, and 3.3 (1.0-11.6) in elderly men.

These associations could not be attributed to prevalent heart disease, and were independent of other cardiovascular risk factors. These results indicate that within the normal range of QTc in the general population, men with long QTc are at higher risk of coronary heart disease (chapter 3).

We hypothesised that the elevated risk of non-fatal myocardial infarction in men with prolonged QTc may result from sympathetic dominance. Because high sympathetic activity may be part of the insulin resistance syndrome, the relationship between QTc and parameters of carbohydrate metabolism was studied in the elderly men. Fasting C-peptide, a measure of insulin secretion, and glucose levels following an oral glucose load, were independent, additive predictors of QTc-duration. The difference of QTc between men in the extreme quintiles of both variables was 22 msec. The associations may be explained by effects of insulin-induced increased sympathetic activity, impaired glucose utilization or both on membrane activity of myocardial cells (chapter 4).

Previous studies indicate that slight ST elevation and firm T-waves may reflect high parasympathetic activity. In this study, both middle-aged and elderly men with T-waves 0.15 mV or more had lower risk of myocardial infarction, coronary heart disease death and sudden death than men with T-waves 0.05-0.15 mV. The adjusted relative risk of coronary heart disease death was 0.5 (0.2-1.0); in men with T-waves less than 0.05 mV it was 2.0 (1.3-3.1). Also slight ST-elevation was associated with decreased risk: 0.5 (0.3-1.0) compared to isoelectric ST. In men with ST-depression it was 2.2 (1.4-3.4). The relationships of T-wave amplitude and ST-level with coronary heart disease death and sudden death were independent from each other (chapter 5).

Respiratory sinus arrhythmia is mediated by parasympathetic activity. Therefore heart rate variability, defined as the standard deviation of duration of all normal RR-intervals from the 20-second resting 12-lead electrocardiogram was studied. The 5-year age-adjusted relative rate of total mortality of men with heart rate variability less than 20 msec compared to men with heart rate variability 20 to 40 msec was 1.9 (1.3-2.7) in the middle-aged, and 1.4 (0.9-2.2) in the elderly. Death from non-coronary causes, especially cancer, contributed significantly to this elevated risk. The association of low heart rate variability with sudden death or coronary heart disease mortality was inconsistent. This suggests that low heart rate variability

is an indicator of compromised health in general. In addition, in elderly subjects the standard deviation as a measure of heart rate variability was a less reliable indicator of vagal activity (chapter 6).

In the general discussion (chapter 7) the possible limitations of the measurement methods and the analyses of repeated measurements are discussed in more detail. It is concluded that the results, described in chapters 3, 5, and 6 provide evidence that electrocardiographic characteristics do predict the occurrence of future heart disease. Furthermore, there are indications that besides autonomic cardiac control, other factors, like glucose tolerance (chapter 4), physical activity, certain nutritional factors, and smoking, may affect ventricular electrical stability as well.

If our findings are confirmed in other populations, this may be of consequence for preventive strategies. Subjects exhibiting the investigated characteristics in combination with other risk factors may be viewed as a high risk category and receive special attention. If our hypotheses on the underlying mechanism, the balance between sympathetic and parasympathetic activity, are confirmed by other studies, this implies that certain interventions, like stimulation of sports activities and cessation of smoking, could be of special benefit to these categories of the population.

Samenvatting

Met behulp van een elektrocardiogram kan men op een gemakkelijke, niet-invasieve wijze een goede indruk van de hartfunctie krijgen. In de medische praktijk wordt het elektrocardiogram vooral gebruikt bij de diagnostiek van hartaandoeningen. Het elektrocardiogram van (nog) gezonde mensen kan echter eveneens predictieve waarde hebben voor het optreden van hartziekten in de toekomst. Hierbij kan met name gedacht worden aan elektrocardiografische karakteristieken die de autonome activiteit weerspiegelen, omdat het autonome zenuwstelsel een cruciale rol speelt bij de regulatie van het hart en onder meer de elektrische stabiliteit van de ventrikel beïnvloedt. De voorspellende waarde van deze karakteristieken is onderzocht in de Zutphen Studie, een prospectief onderzoek naar hart-en vaatziekten. Vanaf 1960 is bij 878 mannen, die tussen 1900 en 1920 geboren waren, regelmatig lichamelijk onderzoek uitgevoerd, waarbij onder meer een elektrocardiogram werd gemaakt. In 1985 is het cohort uitgebreid met een nieuwe steekproef uit hetzelfde geboortecohort in Zutphen. In totaal namen 939 mannen, toen 65 tot 84 jaar oud, deel aan het ouderenonderzoek. Bij alle deelnemers van deze cohortonderzoeken is de ziektegeschiedenis vastgelegd en zijn de doodsoorzaken geregistreerd (hoofdstuk 1).

Eerst is de voorspellende waarde van een maat voor reeds aanwezige schade aan het hart onderzocht: de Cardiac Infarction Injury Score (CIIS). Deze score is ontwikkeld om op basis van het elektrocardiogram een mogelijk infarct vast te stellen. Zowel bij mannen van middelbare leeftijd, als bij oudere mannen met een hoge CIIS bleek de prevalentie van mannen met een oud (stil) myocardinfarct en ST-T-afwijkingen verhoogd te zijn. Mannen met een CIIS van 20 of meer hadden vergeleken met mannen met een CIIS van minder dan 5 een relatief risico van 2,2 (95% betrouwbaarheidsinterval: 1,2-4,1) op angina pectoris, 2,4 (1,4-4,0) op een myocardinfarct en 5,8 (3,4-9,9) op sterfte aan coronaire hartziekten gedurende de volgende 5 jaar. De CIIS heeft dus voorspellende waarde voor coronaire hartziekte bij voor zover bekend gezonde mannen op middelbare leeftijd en bij ouderen (hoofdstuk 2).

Als gevolg van onbalans van autonome innervatie van het hart, of defecten van het myocardmembraan kan het voor hartfrequentie gecorrigeerde QT-interval (QTc) langer zijn. Dit kan leiden tot elektrische instabiliteit van de ventrikel in situaties waarin sympathische stimulatie optreedt. Mannen met een verlengd QTc

(420 msec of meer) hadden een hoger risico op een myocardinfarct en sterfte aan coronaire hartziekte dan mannen met een QTc van minder dan 385 msec. Het voor leeftijd gecorrigeerde relatieve risico voor van coronaire hartziekten was 4,3 (1,3-13,8) bij mannen van middelbare leeftijd en 3,3 (1,0-11,6) bij ouderen. Deze associaties konden niet worden toegeschreven aan prevalente hartziekte en waren onafhankelijk van andere risicofactoren voor hart- en vaatziekten. Deze resultaten geven aan dat mannen met een lang, maar binnen de normale verdeling vallend QTc, een hoger risico op coronaire hartziekten hebben (hoofdstuk 3).

We veronderstelden dat het verhoogde risico op niet-fatale myocardinfarcten bij mannen met een verlengd QTc onder meer het gevolg was van sympatisch overwicht. Omdat hoge sympatische activiteit mogelijk deel uitmaakt van het insuline-resistentie-syndroom, werd de relatie tussen QTc en parameters van het koolhydraat-metabolisme bestudeerd bij de oudere mannen. Nuchter C-peptide, een maat voor de insuline-secretie, en de glucosetolerantie (oppervlakte onder de glucosecurve na een glucosebelasting) bleken onafhankelijk van elkaar met QTc geassocieerd te zijn. Het verschil in QTc tussen mannen in de laagste en hoogste quintielen van beide variabelen was 22 msec. Deze associaties kunnen mogelijk verklaard worden door de effecten van verhoogde sympatische activiteit a.g.v. hoge insulinespiegels en/of gestoorde glucoseopname op de membraanactiviteit van de myocardcellen (hoofdstuk 4).

Eerder onderzoek suggereert dat geringe ST-elevatie en hoge T-golven wellicht hoge parasymptische activiteit weerspiegelen. In dit onderzoek hadden zowel mannen van middelbare leeftijd, als oudere mannen met T-golven van 0,15 mV of meer een lager risico op een myocardinfarct, sterfte aan coronaire hartziekte en plotse dood dan mannen met T-golven van 0,05-0,15 mV. Het voor leeftijd gecorrigeerde relatieve risico op sterfte aan coronaire hartziekte was 0,5 (0,2-1,0); bij mannen met T-golven van minder dan 0,05 was het 2,0 (1,3-3,1). Ook geringe ST-elevatie was geassocieerd met een lager risico: 0,5 (0,3-1,0) vergeleken met iso-elektrisch ST. Bij mannen met ST-depressie bedroeg het relatieve risico 2,2 (1,4-3,4). De relaties van T-golf amplitude en ST-niveau met sterfte aan coronaire hartziekte waren onafhankelijk van elkaar (hoofdstuk 5).

Respiratoire sinus-aritmie wordt voornamelijk bepaald door parasymptische activiteit. Daarom werd de hartritmevariabiliteit, gedefinieerd als de standaard deviatie van de duur van alle normale RR-intervallen in een 12-afleidingen-elektrocardiogram

van ca. 20 seconden, in rust, onderzocht. Het voor leeftijd gecorrigeerde relatieve risico op totale sterfte gedurende de volgende 5 jaar bij mannen met een hartritmevariabiliteit van minder dan 20 msec vergeleken met mannen met hartritmevariabiliteit van 20-40 msec was 1,9 (1,3-2,7) op middelbare leeftijd, en 1,4 (0,9-2,2) bij ouderen. Sterfte aan niet-coronaire oorzaken, en vooral aan kanker, leverde een belangrijke bijdrage aan dit verhoogde risico. De associatie van geringe hartritmevariabiliteit met plotse dood of sterfte aan coronaire hartziekte was inconsistent. Dit suggereert dat geringe hartritmevariabiliteit meer een indicator is voor een minder gunstige gezondheid in het algemeen. Voorts bleek de gebruikte maat van hartritmevariabiliteit, de standaard deviatie, bij oudere mannen minder geschikt als indicator voor parasympatische activiteit (hoofdstuk 6).

In de algemene discussie (hoofdstuk 7) worden de mogelijke beperkingen van de meetmethoden en de analyse van herhaalde waarnemingen besproken. De conclusie is dat de resultaten, die in de hoofdstukken 3, 5 en 6 zijn beschreven, aanwijzingen leveren dat niet-diagnostische elektrocardiografische kenmerken inderdaad het optreden van toekomstige hartziekte voorspellen. Dat betekent dat mensen met deze kenmerken als een categorie met hoog risico beschouwd kunnen worden, en wellicht extra aandacht behoeven. Er zijn aanwijzingen dat behalve autonome regulatie van het hart ook andere factoren, zoals de glucosetolerantie (hoofdstuk 4), sporten, voedingsfactoren, en roken de elektrische stabiliteit beïnvloeden. Deze factoren verdienen in de toekomst nader onderzoek. Hierbij kan men denken aan onderzoek naar de vraag of verbetering in het elektrocardiogram als gevolg van interventie in deze determinanten gepaard gaat met een betere prognose.

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Curriculum Vitae

Jacqueline Dekker werd geboren op 11 oktober 1963 in Schoondijke (Z-Vl). In 1982 behaalde zij het VWO-diploma aan de Rijksscholengemeenschap Koningin Wilhelmina in Oostburg. Vervolgens studeerde zij van 1982 tot 1988 'Voeding van de Mens' aan de Landbouwuniversiteit Wageningen. Zij deed doctoraalonderzoeken bij de vakgroepen Experimentele Diermorfologie en Celbiologie, Biochemie, Humane Voeding en Gezondheidsleer. In 1988 was zij tijdelijk pro-deo epidemioloog bij de Basisgezondheidsdienst Oost-Veluwe, voor het opzetten van onderzoek naar sportblessures. Tegelijkertijd kwam zij als toegevoegd onderzoeker bij de vakgroep Gezondheidsleer (inmiddels Humane Epidemiologie en Gezondheidsleer) aan de Landbouwuniversiteit. Van 1988 tot 1991 werkte ze mee aan het project 'Determinanten van oorzaakspecifieke sterfte in een 30-jarige follow-up periode'. Daarna vervolgde zij met 'Electrocardiografische indicatoren van autonome regulatie en het risico op cardiovasculaire morbiditeit en mortaliteit', waarvan de resultaten in dit proefschrift zijn weergegeven. Vanaf juli 1994 zet zij het onderzoek op dit gebied voort in een post-doctorale aanstelling bij de vakgroep Humane Epidemiologie en Gezondheidsleer.