THE ELECTROCARDIOGRAM IN THE ELDERLY

Diagnostic and prognostic studies

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CHAPTER 1

PREVALENCE AND PROGNOSIS OF ELECTROCARDIOGRAPHIC FINDINGS IN THE ELDERLY: A REVIEW

Introduction

In most developed countries the proportion of elderly people in the population is expected to increase in the next decades. Cardiovascular disease is a leading cause of death and disability in the elderly and it is predicted that the absolute incidence rates of cardiac disease in older adults will increase significantly in the years to come.

Since the invention of electrocardiography in 1902 by Willem Einthoven, the electrocardiogram (ECG) has gained an important position in clinical cardiology[1]. In the last decade, computer programs for ECG interpretation with good performance have become available[2], improving the applicability of ECGs in medical practice and in epidemiologic research. The ECG offers an inexpensive, noninvasive instrument to determine the presence of coronary heart disease as well as other cardiac abnormalities, such as ventricular hypertrophy and atrial fibrillation, known to be associated with the risk of future cardiovascular events. Especially in the elderly, in whom medical histories may be troubled by concomitant diseases and are not always as reliable as one would desire, the ECG could serve as a useful diagnostic and prognostic instrument.

Since the 1950s, large epidemiologic studies among young and middle-aged men and women have provided important information on the prevalence and prognosis of ECG abnormalities. Relatively few studies have been performed in the elderly. A comparison of individual studies is hampered because of differences in diagnostic criteria applied in the individual studies, although comparability has improved since the introduction in 1960 of the Minnesota Code as a standardized coding system for the ECG[3]. Recently, several studies reported that ECG indicators of autonomic balance, such as heart rate variability and QTc interval duration, may be strong predictors of cardiac and all-cause mortality, both in middle-aged and in older subjects.

Chapter 1

In this chapter, the prevalence and prognosis of ECG abnormalities in the elderly will be reviewed. The ECG abnormalities included are Minnesota Code items, myocardial infarction, left ventricular hypertrophy, repolarization disturbances, conduction defects, and atrial fibrillation. Finally, new developments concerning ECG parameters of autonomic balance will be discussed.

Methods

A thorough literature search using computerized literature databases and lateral literature references was performed. In addition, several recent reviews, concerning electrocardiography in epidemiology[4] and ECG findings in the elderly[5, 6], were scrutinized.

The review of literature on the prevalence of ECG abnormalities was limited to studies that apply the Minnesota Code. In selecting studies reporting prevalence of Minnesota Code abnormalities, we only included studies that were performed in the general population aged 60 years or older, or studies in the general adult population that presented data in age strata. Studies limited to hospitalized patients or to men only were excluded. In total, seven studies could be found in which prevalence of Minnesota Code items in the elderly population at large was reported[7-13]. In addition, we computed the prevalence of Minnesota Code items among men and women aged 60 years or older in the Rotterdam Study, a population-based study among men and women aged 55 years or older, living in the Rotterdam district of Ommoord[14].

Prevalence of ECG abnormalities according to the Minnesota Code

Selected characteristics of the eight population-based cross-sectional studies are shown in Table 1. Tables 2, 3, and 4 summarize the major findings from these studies.

Q-QS patterns

The overall prevalence of Q-QS abnormalities, suggestive of myocardial infarction, in the elderly population varies between 4.5% and 15.7% . The prevalence ratio of

minor and major infarct patterns is consistent, approximately 0.40, across all studies apart from the Rotterdam Study. Prevalence of Q-QS patterns, in particular minor Q-QS abnormalities, in the Rotterdam Study is higher than in the other studies. In all studies, Q-QS patterns are more frequent in men than in women, with prevalence clearly increasing with age in both sexes.

QRS axis deviation

Ostrander et al.[9, 15] reported a prevalence of left axis deviation of 18% in men and women 60 years or over, whereas in other studies considerably lower prevalences are found. An increase in the prevalence of axis deviation with advancing age in both sexes is demonstrated in all studies, and men are more frequently affected than women.

Ventricular hypertrophy

Major differences exist in the reported prevalence of left ventricular hypertrophy (LVH), which varies from 8.8% to 16.9%. Also, the presence of LVH with ST-T abnormalities varies considerably, from 4.2% to 8.0%. In six of the eight studies, women appear to be more often affected by LVH than men. Only Ostor et al.[8] and Casiglia et al.[13] reported a higher prevalence of LVH in men. Right ventricular hypertrophy is rarely found and more refined criteria to detect minor abnormalities of the right ventricle have been proposed[7].

ST-T abnormalities

Also the prevalence of ST-T wave abnormalities varies widely across studies. The prevalence of ST-segment items varies from 5.4% to 19.3% in men, and from 6.7% to 24.0% in women. Similarly, the prevalence of T-wave abnormalities varies from 5.5% to 33.1% in men and from 6.8% to 33.6% in women. The prevalence of ST-T abnormalities rapidly increases with age and no clear gender differences are present.

Table 1. Summary of major characteristics of eight population-based studies in the elderly

	First author (reference)							
	Ostrander (9)	Kennedy (10)	Kitchin (11)	Campbell (7)	Östör (8)	Furberg (12)	Casiglia (13)	Rotterdam Study
Subjects (n)	663	400	487	2254	4118	5150	2254	5089
Men, %	46	48	44	39	49	43	36	40
Response rate (%)	>70	NR	NR	60	72	NR	73	70
Age range (y)	≥60	≥65	62-90	≥65	≥60	≥65	≥65	60-106
Mean age (y)	70	74	NR	71	68	73	NR	72
Men	70	74	NR	71	68	74	NR	70
Women	71	75	NR	71	67	73	NR	73

NR= not reported

Table 2. Prevalence of electrocardiographic evidence of myocardial infarction (Q-QS abnormalities) in eight population-based studies in the elderly

	First author (reference)							
	Ostrander (9)	Kennedy (10)	Kitchin (11)	Campbell (7)	Östör (8)	Furberg (12)	Casiglia (13)	Rotterdam Study
Q-Qs abnormalities,								
Code 1.1-1.3	6.8	9.5	7.7	6.3	4.5	NR	NR	15.7
Men	9.1		7.9	10.0	6.3			20.0
Women	4.7		7.4	4.0	2.7			12.9
Major Q-QS abnormalities								
Code 1.1-1.2	5.0	NR	5.4	4.7	3.1	5.2	2.3	8.7
Men	6.8		5.6	7.8	4.3	7.3	3.6	11.6
Women	3.6		5.2	2.4	2.0	3.6	1.4	6.8
Minor Q-QS abnormalities								
Code 1.3	1.8	NR	2.3	1.6	1.4	NR	NR	7.0
Men	2.3		2.3	2.2	2.0			8.3
Women	1.4		2.2	1.2	0.8			6.1

NR= not reported

Table 3. Prevalence of axis deviation, ventricular hypertrophy, and ST-segment and T-wave abnormalities in eight population based studies in the elderly

	First author (reference)							
	Ostrander (9)	Kennedy (10)	Kitchin (11)	Campbell (7)	Östör (8)	Furberg (12)	Casiglia (13)	Rotterdam Study
LAD, Code 2.1	18.4	6.5	8.5	NR	7.9	NR	13.1	8.9
Men	21.0		10.2		10.2		15.9	10.9
Women	16.2		7.1		5.6		11.4	7.5
RAD, Code 2.2	0.2	NR	0.8	NR	0.7	NR	NR	0.1
Men	0.3		1.9		0.8			0.1
Women	0.0		0.0		0.5			0.1
LVH, Code 3.1-3.3	10.1	14.0	9.7*	8.8	16.9	NR	10.0	11.9
Men	8.2		3.7	6.7	20.6		11.7	12.4
Women	11.5		7.1	10.2	13.1		8.9	11.6
LVH with ST-T	NR	6.3	NR	4.6	NR	4.2	NR	8.0
Men				2.9		4.3		7.4
Women				5.6		4.1		8.4
RVH, Code 3.2	NR	0.0	2.5	0.7	NR	NR	NR	0.0
Men			3.3	1.4				0.1
Women			1.9	0.3				0.0
ST segment items, Code 4.1-4.4	10.9	NR	10.1	6.2	10.6	NR	NR	20.3
Men	7.9		13.0	5.4	11.6			19.3
Women	13.4		24.0	6.7	9.7			20.9
T-wave items, Code 5.1-5.4	32.1	10.5**	27.0	15.3	24.4	6.3	23.6*	30.9
Men	33.1		23.0	19.2	26.3	5.5	18.1	27.0
Women	31.3		30.0	12.9	22.6	6.8	27.0	33.6

NR= not reported; *Only code 3.1; ** ST-T combined Code 4.1 or 4.3 and Code 5.1 or 5.3

Table 4. Prevalence of atrioventricular and ventricular conduction defects, extrasystoles, and atrial fibrillation in eight population-based studies in the elderly

	First author (reference)							
	Ostrander (9)	Kennedy (10)	Kitchin (11)	Campbell (7)	Östör (8)	Furberg (12)	Casiglia (13)	Rotterdam Study
AV conduction defects,	NR	2.3	3.3	1.1	6.9	NR	NR	6.8
Code 6.1-6.3			3.7	1.5	8.7			8.0
Men			3.0	0.8	5.2			6.0
Women								
First degree AV block, Code 6.3	6.2	2.0	NR	0.9	6.8	5.3	3.9	6.8
Men	6.9			1.5	8.7	8.1	5.0	8.0
Women	5.6			0.6	5.0	3.2	3.2	6.0
LBBB, Code 7.1	1.7	2.5	0.6	1.4	1.6	1.7	3.9	2.9
Men	0.7		1.4	1.6	1.9	1.6	3.9	2.7
Women	2.5		0.0	1.2	1.3	1.8	3.9	3.0
RBBB, Code 7.2	2.0	3.5	2.3	1.8	2.3	4.3	7.4*	4.1
Men	3.0		2.3	2.8	3.6	6.8	10.8	6.5
Women	1.1		2.2	1.2	1.1	2.4	5.4	2.4
Incomplete RBBB, Code 7.3	2.1	2.8	1.5	1.4	1.7	NR	NR	2.8
Men	3.3		1.4	1.6	1.8			3.5
Women	1.1		1.5	1.3	1.5			2.4
Intraventricular block, Code 7.4	NR	NR	NR	0.5	0.8	2.7	NR	0.8
Men				0.8	1.2	4.7		1.2
Women				0.3	0.3	1.2		0.5
Extrasystole, Code 8.1	5.6	4.5	NR	3.1	3.1	NR	NR	3.7
Men	8.9			3.6	3.6			4.8
Women	2.8			2.5	2.5			3.0
Atrial fibrillation, Code 8.3	2.4	3.0	2.5	1.4	1.4	3.2	4.0	3.6
Men	2.6		2.3	1.3	1.3	4.0	3.8	4.0
Women	2.2		2.6	1.5	1.5	2.6	4.1	3.3

NR= not reported; * Code 7.2 and 7.3 combined

Conduction defects

First degree AV block is by far the most common atrioventricular conduction defect, ranging from 0.9% to 6.8% in older subjects.A right bundle branch block occurs more frequently than a left bundle branch block (range 1.8% to 4.3% and 0.6% to 3.9%, respectively). Right bundle branch block and intraventricular block appear to be more frequent in men than in women. Such a difference does not exist for left bundle branch block.

Arrhythmias

The prevalence of cardiac arrhythmias increases with age. Atrial fibrillation, with a reported prevalence of 1.4% to 4.0%, is the most common cardiac arrhythmia.

Comments

Reported prevalences of most ECG abnormalities according to the Minnesota Code showed considerable variation between individual studies. Although all studies reviewed were performed in non-hospitalized and unselected populations, these studies differ with regard to the number of participants, age and gender distribution, and response rate. Apart from regional differences in the occurrence of cardiovascular diseases, different selection criteria may explain at least part of the variation in prevalence of ECG abnormalities. In addition, the period in which the studies were performed, varying from the sixties to the nineties, may be a source of variation. Although coding took place according to the Minnesota Code, differences in coding procedures, by one or more observers, by hand or computer, may also account for part of the variation. Inter- and intraobserver variability in Minnesota Coding may be considerable[10, 16, 17]. The Rotterdam Study is the only study using an extensively validated computer program for ECG coding[18, 19].

Several ECG abnormalities according to the Minnesota Code, e.g., Q-QS patterns, left axis deviation, left bundle branch block, high amplitude R-waves, ST-T abnormalities, and atrial fibrillation are established risk indicators of future cardiovascular events[8, 13, 20-23]. Diagnosis and prognosis of these and other ECG abnormalities will be discussed in more detail in the next paragraphs.

Chapter 1

Diagnosis and prognosis of specific ECG abnormalities

Myocardial infarction

Myocardial infarction may occur with or without symptoms[24] and with or without lasting ECG abnormalities[25, 26]. Especially in the elderly, patients with myocardial infarction often present themselves with atypical symptoms and signs[14].

The proportion of myocardial infarctions that occur without typical symptoms, silent myocardial infarctions, ranges from 20% to 68% (Table 5). This proportion appears to be higher in women than in men. The prevalence of silent myocardial infarction (on average 4.6% in men and 3.5% in women in the Rotterdam Study) increases with age[14].

The prognosis of silent MI with regard to the occurrence of new coronary events, such as recurrent myocardial infarction, ventricular fibrillation, and sudden cardiac death, is similar to that of symptomatic myocardial infarction[27-31]. In the elderly, the absolute risk of new coronary events is usually high. For example, Aronow et al.[28] reported that during four years of follow-up new coronary events occurred in 65% of men and women with recognized myocardial infarction and in 56% of men and women with silent myocardial infarction. As the detection of silent myocardial infarction is completely dependent of the ECG, these findings may have important implications for the use of ECGs for cardiovascular screening of elderly patients in medical practice.

Non-Q-wave myocardial infarction, defined as symptomatic myocardial infarction without matching ECG abnormalities, but confirmed by raised cardiac enzyme

Table 5. Proportion of proven electrocardiographic myocardial infarction that occurs without symptoms (silent) in the elderly.

First author (reference)	Prevalence (% (number of silent events/ total number of myocardial infarctions))
Rodstein (37)	31% (16 /52)
Aronow (38)	68% (78 / 115)
Furberg (12)	20% (147 / 744)
Nadelmann (27)	34% (25 / 72)
De Bruyne (14)	36% (127/353)

levels or autopsy, may occur in 38% to 62% of all myocardial infarctions, depending on the Minnesota Code criteria used, and is more frequent in myocardial infarctions that occurred farther in the past[26]. In the Bronx Aging Study[27], among men and women aged 75 to 85 years, 62% of the reported myocardial infarctions are non-Q-wave myocardial infarctions. In the Rotterdam Study, the prevalence of non-Q-wave myocardial infarction is 4.4% in men and 1.8% in women. Overall, 26% of all myocardial infarctions were non-Q-wave infarctions. The prognostic implications of non-Q-wave myocardial infarctions are similar those of electrocardiographic myocardial infarctions[32-36].

Left ventricular hypertrophy

Diagnosis of left ventricular hypertrophy measured by ECG has a poor sensitivity and predictive value in detecting echocardiographically determined left ventricular hypertrophy. In a report of Aronow et al.[39], the sensitivity of five different ECG criteria for left ventricular hypertrophy varies from 12% to 29%, the specificity ranges from 93% to 96%, and the positive predictive value ranges from 62% to 72%. In the Framingham Heart Study the sensitivity of ECG criteria of left ventricular hypertrophy (using R in aVL, S in V3 and QRS duration) for echocardiographic left ventricular hypertrophy is 39% in men and 51% in women, at a specificity level of 95%[40]. An even poorer sensitivity has been reported when diabetes, a common comorbidity, is present[41]. Prevalence estimates of left ventricular hypertrophy by ECG are strongly influenced by the ECG criteria used.

Prognosis of left ventricular hypertrophy in the elderly is reported to be similar to that of silent myocardial infarction[42]. Subjects with left ventricular hypertrophy are at increased risk for coronary events, atherothrombotic brain infarctions, congestive heart failure, peripheral artery disease, ventricular arrhythmias, and total mortality[32, 42-46]. Also, serial changes in electrocardiographic left ventricular hypertrophy have prognostic implications. Serial increase of left ventricular hypertrophy has a poorer prognosis and serial decrease of left ventricular hypertrophy has a better prognosis for cardiovascular disease[32, 47]. Recent studies indicate that treatment of left ventricular hypertrophy can reduce the incidence of coronary heart disease[48].

Repolarization disturbances

In previous studies, ST-T changes, either isolated or in combination with other ischemic or hypertrophic changes, have been associated with coronary heart disease and sudden cardiac death in middle-aged populations[22, 49-59], as well as in elderly populations[8, 21, 60-65]. In middle-aged populations, the association of ST-T abnormalities has often been reported to be more pronounced in men than in women, but this difference seems to be absent in the elderly. Although ST-T abnormalities often are transient, they are independently associated with future coronary heart disease. The risk associated with ST-T abnormalities is more pronounced in combination with other ECG abnormalities, such as pathologic Q-waves, left ventricular hypertrophy or intraventricular conduction defects. Repolarization disturbances on the ECG are multifactorial and may be associated with increasing age, myocardial ischemia, hypertension, ventricular hypertrophy, ventricular conduction defects, use of digitalis, autonomic dysfunction, and other pathophysiologic processes.

Conduction defects

Atrioventricular conduction time increases with age, due to changes both in the atrioventricular nodal and the His-Purkinje system[66]. In addition, atrioventricular block is associated with coronary ischemia, vagotonia and digitalis use[67]. In contrast to younger populations, in which the presence of atrioventricular block is usually considered a benign condition, not associated with an increased risk for coronary heart disease[68, 69], in older populations an association of atrioventricular blocks with coronary heart disease has been reported in several studies[70-72]. Other studies in elderly patients report no association of atrioventricular block with coronary events[73].

Left bundle branch block is uncommon in the absence of cardiovascular disease[74] and is associated with future coronary heart disease[65, 75] and all-cause mortality[22, 73] in elderly men and women. Right bundle branch block occurs more frequently than left bundle branch block. Only in 20% of subjects with right bundle branch block, clinical and necropsy findings of coronary heart disease are present[76]. Contradictory results have been published on the risk associated with right bundle branch block in the elderly. An association with mortality was observed in a study by Caird et al.[22] and an association with coronary events was present in the Framingham Study[77],

while no associations were found in several other studies[62, 73, 78, 79].

Intraventricular conduction defects, defined as a prolonged QRS duration (≥0.11 seconds) in the absence of left or right bundle branch block, has been reported to increase the incidence of total mortality[78] and cardiac events[73] in the elderly. In the Framingham Heart Study, elderly men and women with intraventricular conduction defect were at increased risk for coronary heart disease, although this was not statistically significant[65].

Arrhythmias

The prevalence of atrial fibrillation increases with age[80] and is higher in those with overt cardiovascular disease[12, 81, 82]. Many studies have reported that chronic atrial fibrillation is independently associated with thromboembolic stroke[83-86]. Recently, an association of atrial fibrillation with dementia was reported[87]. In addition, atrial fibrillation was a risk factor for all-cause mortality in the Coronary Drug Project[78] and for cardiovascular mortality in the Framingham Heart Study[80].

Premature ventricular complexes on the resting ECG were a risk factor for total mortality in the Coronary Drug Project[78] and for cardiovascular mortality in the Busselton Study[62]. In the elderly an increased risk of cardiovascular events associated with frequent ventricular premature beats on ambulatory ECGs has been reported several times[88-90]. However, no association with cardiac outcome was found between ventricular premature beats on the resting ECG in elderly in the Baltimore Longitudinal Study[91]. Using 1-minute rhythm strips, no association was found in subjects without clinical heart disease, but a strong association was present in elderly subjects with a history of clinical heart disease[92]. The latter finding suggests that ventricular premature complexes are markers of underlying ischemic heart disease.

ECG indicators of autonomic function

Prolonged QTc interval and decreased heart rate variability (HRV) have been put forward as indicators of autonomic balance[93, 94]. With increasing age, sympathetic activity increases relative to vagal activity[95]. Autonomic balance, in particular QTc interval and heart rate variability, is influenced by various physiological and patho-

physiological conditions, such as respiration[96], diabetic neuropathy[97-100], left ventricular function[101], and coronary heart disease[102-105]. Both risk indicators have been associated with a poor prognosis in patients after myocardial infarction[106-112].

Recently, some studies on the prognostic value of prolonged QTc interval were performed in the general population, producing controversial results. In the Dutch Civil Servants Study[113], men and women with prolonged heart-rate adjusted QT intervals had a twofold risk for death from coronary heart disease. Also in the Zutphen Study[114] among middle-aged and elderly men, increased risks for cardiac mortality were reported. However, no association was found between QTc interval and cardiac outcome in the Framingham Study[115] and the Bronx Aging Study[71].

Results from population-based studies concerning the risk associated with decreased HRV are more consistent. In middle-aged men and women, decreased HRV was associated with a poorer cardiac prognosis in three studies[116-118]. An increased risk for all-cause mortality associated with decreased HRV was found in elderly men and women in the Framingham Study[119] and in elderly men in the Zutphen Study[120]. However, no association of decreased HRV with both cardiac and all-cause mortality was found in the Bronx Aging Study[71].

Comments

Reports from literature show that the ECG contains a wealth of both etiologic and prognostic information. However, many studies use their own definitions of ECG diagnoses and thus results from different studies show wide variation and cannot easily be compared. In addition, characteristics of subjects included in individual studies differ. Measurement techniques of intervals and amplitudes need to be standardized, to allow results from epidemiological studies to be applicable in medical practice. Since computer programs with good performance have become available[2], they offer an efficient, inexpensive, and, in particular, a standardized way to interpret ECGs.

Conclusions

The prevalence of abnormal ECG findings is relatively high in the elderly, increases

with age and is higher in men than in women. Most ECG findings that are often markers of coronary heart disease or other disease processes, are associated with future coronary heart disease. However, diagnostic criteria show wide variation among studies, and standardization is urgently needed. Computer programs for ECG analysis may offer a solution The significance of conventional and new ECG risk indicators in elderly men and women needs to be confirmed and the predictive value of ECG findings in addition to established cardiovascular risk indicators needs to be determined. Although in younger subjects without heart disease the ECG is not considered a useful tool for screening purposes[121], the ECG may well be valuable to identify elderly subjects at risk for future coronary heart disease, because both prevalence of ECG abnormalities and incidence of cardiac disease are higher at older age.

This thesis addresses several diagnostic (chapter 2) and prognostic (chapter 3) aspects of the ECG in non hospitalized subjects. In chapter 2.1 diagnostic ECG interpretation in population-based research by computer and by trained research physicians is evaluated, using experienced cardiologists as a reference. In addition, three scenarios for ECG interpretation in large population-based studies are studied. Reproducibility of computerized ECG measurements and coding is described in chapter 2.2. Prevalence of ECG abnormalities is directly based on diagnostic criteria for ECG abnormalities. In elderly men and women, we studied the prevalence of different types of myocardial infarction and of prolonged heart-rate adjusted QT intervals, and the influence of diagnostic criteria for these ECG abnormalities on their estimated prevalence. In chapter 3, the prognostic value of several "new" ECG abnormalities, notably prolonged QTc (chapter 3.1), QTc dispersion (chapter 3.2), T axis deviation (chapter 3.3) and heart rate variability (chapter 3.4), is described. Clinical relevance of electrocardiographic risk indicators largely depends on the added value of ECG abnormalities to the cardiovascular risk profile, in indicating subjects at increased absolute risk for future heart disease. In chapter 3.5 we studied the predictive value of conventional and "new" ECG abnormalities for cardiac mortality, when used in addition to the cardiovascular risk profile, commonly available in general practice. Finally, in chapter 4 the implications of the studies presented in this thesis are discussed and recommendations for future research are provided.

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Chapter 2

DIAGNOSTIC STUDIES

2.1 Diagnostic interpretation of electrocardiograms in population-based research: computer program, research physicians, or cardiologists?

2.2 Reproducibility of computerized ECG measurements and coding in a non-hospitalized elderly population

2.3 Prevalence, determinants and misclassification of myocardial infarction in the elderly

2.4 Prolonged QT interval: a tricky diagnosis?

CHAPTER 2.1

DIAGNOSTIC INTERPRETATION OF ELECTROCARDIOGRAMS IN POPULATION-BASED RESEARCH: COMPUTER PROGRAM, RESEARCH PHYSICIANS, OR CARDIOLOGISTS?

Abstract

We assessed the performance of diagnostic ECG interpretation by the computer program MEANS and by research physicians, compared to cardiologists, in a population-based study. To establish a strategy for ECG interpretation in health surveys, we also studied the diagnostic capacity of three scenarios: use of the computer program alone (A), computer program and cardiologist (B), and computer program, research physician and cardiologist (C). A stratified random sample of 381 ECGs was drawn from ECGs collected in the Rotterdam Study (n=3057), which were interpreted both by a trained research physician using a form for structured clinical evaluation and MEANS. All ECGs were interpreted independently by two cardiologists; if they disagreed (n=175) the ECG was judged by a third cardiologist.

Five ECG diagnoses were considered: anterior and inferior myocardial infarction (MI), left and right bundle branch block (LBBB and RBBB) and left ventricular hypertrophy (LVH). Overall, sensitivities and specificities of MEANS and the research physicians were high. The sensitivity of MEANS ranged from 73.8% to 92.9% and of the research physician ranged from 71.8% to 96.9%. The specificity of MEANS ranged from 97.5% to 99.8% and of the research physician from 96.3% to 99.6%. To diagnose LVH, LBBB and RBBB, use of the computer program alone gives satisfactory results. Preferably, all positive findings of anterior and inferior MI by the program, should be verified by a cardiologist. We conclude that diagnostic ECG interpretation by computer can be very helpful in population-based research, being at least as good as ECG interpretation by a trained research physician, but much more efficient and therefore less expensive.

Introduction

The use of electrocardiograms (ECGs) in population-based studies may lead to enormous numbers of ECGs to be interpreted. Traditionally, ECG interpretation is performed by cardiologists. To reduce the workload for cardiologists, trained research physicians or computer programs for ECG interpretation can be used, with or without supervision by an experienced cardiologist. Computer programs have two major advantages compared to human readers: the intra- and interobserver variability in ECG interpretation and coding is reduced and it saves time spent by physicians, and therefore costs.

In health surveys most experience with the use of ECG computer programs has been gathered with the Minnesota Code or related coding schemes[1-3]. These schemes, however, only purport to describe ECG wave forms and not to deliver a diagnosis. If, somehow, diagnoses are appended to the descriptions, they have a rather poor sensitivity and specificity, notably for myocardial infarction (MI) and left ventricular hypertrophy (LVH)[3].

An alternative for descriptive ECG codes such as the Minnesota Code, diagnostic ECG interpretation can be used in health surveys. The performance of diagnostic ECG interpretation by computer programs or cardiologists has been studied some years ago in the study Common Standards for Quantitative Electrocardiography (CSE), sponsored by the European Community, with promising results [4-7]. However, the CSE project was based on hospitalized patients only. As severity of disease in hospitalized patients will differ from that in the population at large, the CSE results cannot be extrapolated to the general population. Little is known about the value of diagnostic ECG interpretation by computer programs or research physicians in health surveys.

The primary objective of the present study was to assess the performance of diagnostic ECG interpretation by our ECG computer program MEANS (Modular ECG Analysis System)[8,9] and by research physicians, compared to cardiologists, in population-based research. Our second objective was to establish a strategy for ECG interpretation in health surveys. We anticipated that combining ECG interpretations from computer program, research physician and cardiologist would improve sensitivity and specificity of ECG diagnoses and effectively decrease the workload for human readers. We

compared three different scenarios: one in which the ECGs were interpreted by the computer program alone, a second in which the ECGs were initially interpreted by the computer program and positive findings were checked by a cardiologist, and a third in which all ECGs were interpreted independently by a research physician and by the computer program, and only those on which they disagreed were interpreted by a cardiologist.

Methods

Data Collection

The ECGs used in this study were collected during the baseline examination of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence and risk factors of chronic diseases in the elderly. Objectives and methods of the Rotterdam Study are described in detail elsewhere[10]. Briefly, in the Rotterdam Study all men and women aged 55 years or older, living in the Rotterdam district Ommoord, were invited to participate. Of 7,983 participants (response rate 78%) baseline data, were collected from 1990 to 1993, including an ECG, information on history of cardiovascular disease, and established cardiovascular risk factors.

The first 3,436 ECGs collected in the Rotterdam Study were evaluated by research physicians, using an extensive form for structured clinical ECG evaluation. All research physicians had finished their theoretical and clinical medical training, resulting in a diploma of "medical doctor", without specialization. Training for ECG interpretation by an experienced cardiologist (DACM Kruijssen) consisted of two phases. First, in ten plenary sessions, special lectures about ECG interpretation were given and the use of the evaluation form was practiced. Second, in a teaching period, ECGs were double-coded by the research physician and the experienced cardiologist. Discrepancies between their interpretations were discussed in detail and a consensus was reached. After this training period the research physicians worked independently.

Of the first 3,436 ECGs, 3,057 were stored digitally and interpreted by the ECG computer program MEANS. The MEANS program uses complex decision trees for diagnostic classification. Signal analysis and diagnostic classification of the MEANS program have been extensively evaluated by the developers themselves[8,9,11] and in the

CSE study[5-7], in which cardiologists and clinical evidence were the reference. The ECGs used in the present study were sampled from the set of 3,057 ECGs.

Patient selection and ECG interpretation

For two reasons, we enriched the sample of ECGs with abnormal ECGs and ECGs on which the MEANS program and the research physician disagreed. First, because of low disease prevalence in the general population, we wanted to increase the number of ECG abnormalities to improve the precision of sensitivity estimates. For the purpose of selection we considered an ECG abnormality to be present if the MEANS program and the research physician agreed on the abnormality. Second, as we wanted to compare the MEANS program with human readers, we hypothesized that those cases in which the ECG interpretation of the MEANS program and the research physician differed would be most informative. Thus, we included a relatively large proportion of such ECGs in our sample.

We distinguished five main ECG diagnoses: anterior myocardial infarction (AMI), inferior myocardial infarction (IMI), left ventricular hypertrophy (LVH), left bundle branch block (LBBB) and right bundle branch block (RBBB). The MEANS program grades the diagnoses AMI, IMI and LVH using one of four levels of certainty: 'no', 'possible', 'probable' or 'definite'. For LBBB and RBBB the MEANS program provides a dichotomous classification, indicating 'no' or 'definite'. The research physicians used a dichotomous classification for all categories.

For a particular ECG diagnosis we defined a disagreement between the MEANS program and the research physician as 'minor' if the corresponding levels of certainty were adjacent (e.g., 'no' and 'possible'); if not, the disagreement was considered 'major' (e.g., 'no' or 'possible' and 'definite'). For each of the five main ECG diagnoses separately, the 3057 ECGs were categorized in four groups according to agreement or disagreement on ECG classification between computer and research physician: (A) agreement on presence of an abnormality, (B) agreement on absence of an abnormality, (C) 'major' disagreement, and (D) 'minor' disagreement. For instance, a particular ECG could be classified in group A for AMI, group B for IMI, LBBB and RBBB and group C for LVH.

We selected a stratified random sample of 400 ECGs from these four groups: (A) 50 ECGs with agreement on the presence of an abnormality, (B) 100 ECGs with agreement on the absence of an ECG abnormality, (C) 200 ECGs with 'major disagreement', and (D) 50 ECGs with 'minor disagreement'. Within these strata the five main ECG categories were represented proportionally: 50% AMI or IMI, 20% LVH, and 30% LBBB or RBBB. As ECG abnormalities are not mutually exclusive, there was some overlap in the ECGs sampled. The final data set consisted of 381 ECGs.

Reference ECG interpretation

A reference ECG interpretation was obtained by having two experienced cardiologists (JWD and MG) interpret the set of 381 ECGs, using a standardized form. The cardiologists graded ECG diagnoses using four levels of certainty. Each cardiologist was blinded for the ECG interpretation of the research physician, the MEANS program and the other cardiologist. The ECG interpretations of the cardiologists were compared similarly as described above for the comparison between the MEANS program and the research physician. When both cardiologists fully agreed on the ECG interpretation (n=206), this interpretation was taken as the reference. In case the two cardiologists had a 'minor' (n=76) or 'major' (n=99) disagreement, the ECG was interpreted by a third cardiologist (GvH) with large experience in reading ECGs, who was also blinded for prior ECG interpretations. This interpretation was then taken as a reference. There was 'major' disagreement between the third cardiologist and both other cardiologists in 20 of the 175 cases. No attempt was made to verify ECG readings of AMI, IMI, and LVH to clinical evidence.

Data Analysis

In all analyses the cardiologists' interpretation served as the reference. For each of the five main ECG diagnoses two-by-two tables were computed, both for the MEANS program and the research physician against the reference. This required the levels of certainty of the MEANS program for AMI, IMI and LVH, and of all diagnoses by the cardiologists to be dichotomized. As a standard procedure the threshold was put between 'possible' and 'probable', i.e. 'no' and 'possible' were taken as 'no abnormality' and 'probable' and 'definite' were taken as 'presence of abnormality'. Two alternative

procedures for classification of AMI, IMI and LVH by the MEANS program resulted from shifting the threshold one level of certainty up or down. These alternative procedures did not apply to the classification of LBBB and RBBB by the MEANS program and to all ECG diagnoses by the research physician, as only two levels of certainty had been used for these classifications.

To assess diagnostic performance, sensitivity and specificity were computed. Because of the enrichment, a stratified analysis had to be performed. For sensitivity the prevalence of disease in each stratum was taken as a weight, whereas for specificity the prevalence of non-diseased subjects in each stratum was taken as a weight[12]. Confidence intervals of the sensitivity and specificity were computed using the delta-method to estimate the standard error of a rate ratio, in which both numerator and denominator are estimates[13].

Strategies for ECG interpretation

To establish a strategy for ECG interpretation in population-based research we envisaged three scenarios which are logistically feasible, anticipating that combining ECG interpretations from computer program and research physician with that of a cardiologist in selected cases, may improve sensitivity and specificity of a certain ECG diagnosis. We then studied the trade-off between workload on the one hand, and diagnostic performance on the other hand. For each scenario workload (expressed as percentage of all ECGs to be interpreted by research physicians or cardiologists), prevalence estimates of ECG diagnoses, and proportions of ECGs correctly classified as abnormal or normal, were computed. The proportion correctly classified as abnormal or normal represent the positive and negative predictive values of the ECG interpretation, respectively, again with the cardiologists' interpretation as a reference.

In the first scenario, the MEANS program alone was used to interpret all ECGs. In the second scenario, all ECGs were initially interpreted by the MEANS program and only the positive findings were verified by cardiologists. In the third scenario, all ECGs were independently judged by both the research physician and the MEANS program, and those ECGs on which they disagreed were judged by cardiologists.

In all scenarios we used the standard procedure of the MEANS program for

classification of AMI, IMI and LVH and the cardiologists' interpretation in the present study was taken as the reference.

Results

General characteristics of the Rotterdam Study participants (n=3057) and the study sample (n=381), and the prevalence of ECG abnormalities according to the MEANS program are presented in Table 1. Due to the enrichment procedure, history of MI and major ECG abnormalities are more prevalent in the study sample. The other characteristics of the participants included in the study sample and the Rotterdam Study population are comparable, except for current smoking which is less prevalent in the study sample.

Sensitivity and specificity for the ECG interpretations of the MEANS program, using the standard procedure for dichotomization, and of the research physician, are presented in Table 2. Overall, sensitivity and specificity of the MEANS program and the research physician were high. Sensitivity of the MEANS program ranged from 73.8% (95%CI: 58.9-88.7) to 92.9% (95%CI: 85.9-99.8), whereas sensitivity of the research physician ranged from 71.8 % (95%CI: 56.8-86.7) to 96.9% (95%CI: 93.0-100). Both the MEANS program and the research physician had the lowest sensitivity for the diagnosis

Table 1. General characteristics and prevalence of ECG abnormalities according to MEANS in the sample and study population of the Rotterdam Study. Values are means (with standard deviations) and percentages (with standard errors).

	Sample (n=381)	Study population (n=3057)
Men (%)	49.0	39.0
Age (years)	72.7 (9.6)	70.1 (8.9)
Body mass index (kg/m^2)	26.0 (3.8)	26.3 (3.7)
Systolic BP (mmHg)	143.4 (22.6)	140.2 (22.8)
Diastolic BP (mmHg)	74.6 (13.0)	73.7 (11.7)
Cholesterol (mmol/l)	6.6 (1.3)	6.6 (1.2)
Current smoking (%)	27.4 (2.3)	40.3 (0.9)
History of MI (%)	17.3 (1.9)	9.3 (0.5)
MI on the ECG (%)	14.7 (1.8)	4.4 (0.4)
LVH on the ECG (%)	9.4 (1.5)	4.8 (0.4)
Left bundle branch block (%)	5.0 (1.1)	2.2 (0.3)
Right bundle branch block (%)	6.0 (1.2)	3.2 (0.3)

Abbreviations: BP, blood pressure; MI, myocardial infarction; LVH, left ventricular hypertrophy

Table 2. Sensitivity and specificity of the ECG interpretation of the research physician and of the MEANS program, using the standard dichotomization procedure, as compared to the reference ECG interpretation of cardiologists.

	Research physician		MEANS program	
	Sens (95%CI)	Spec (95%CI)	Sens (95%CI)	Spec (95%CI)
Anterior MI	71.8 (56.8-86.7)	97.7 (97.0-98.4)	73.8 (58.9-88.7)	97.5 (96.8-98.2)
Inferior MI	72.7 (59.9-85.4)	98.4 (97.7-99.2)	90.1 (77.5-100)	97.6 (96.8-98.4)
LVH	78.2 (66.0-90.5)	96.3 (95.8-96.8)	88.9 (77.5-100)	99.1 (98.7-99.5)
LBBB	95.2 (89.2-100)	99.3 (98.9-99.6)	92.9 (85.9-99.8)	99.8 (99.5-100)
RBBB	96.9 (93.0-100)	99.6 (99.2-100)	88.7 (81.7-93.6)	99.6 (99.2-100)

Abbreviations: Sens, sensitivity; Spec, specificity; CI, confidence interval; MI, myocardial infraction; LVH, left ventricular hypertrophy; LBBB, left bundle branch block; RBBB, right bundle branch block.

AMI. Compared to the research physician, the MEANS program had a higher sensitivity for AMI, IMI and LVH and a lower sensitivity for LBBB and RBBB, but confidence intervals are wide. Specificity of the MEANS program ranged from 97.5% (95%CI: 96.8-98.2) to 99.8% (95%CI: 99.5-100) and specificity of the research physician ranged from 96.3% (95%CI: 95.8-96.8) to 99.6% (95%CI: 99.2-100). Specificity of MEANS was higher than that of the research physician for the diagnosis LVH and LBBB, equal for RBBB, and slightly lower for AMI and IMI.

Effects of changing the threshold for dichotomization of the classification of AMI, IMI and LVH of the MEANS program on sensitivity and specificity for the program are presented in Table 3. As expected, shifting the threshold for presence of an ECG abnormality one level down, i.e. taking 'possible' abnormalities as 'presence of abnormality', improved sensitivity, while specificity decreased. The reverse occurred when the threshold for presence of an ECG abnormality was shifted one level up, i.e. taking 'probable' abnormalities as 'absence of abnormality'; specificity improved and sensitivity decreased.

Table 4 shows estimates of prevalence, proportions correctly diagnosed cases and controls, and the workload for research physicians and cardiologists, for the three scenarios of ECG interpretation in health surveys that we examined. Scenario A, using the MEANS program only, performs satisfactorily in diagnosing LVH, LBBB and RBBB. However, the prevalences of AMI and IMI are overestimated, 4.3% versus 2.5% for AMI and 5.1% versus 3.1% for IMI, and cases of AMI and IMI are

Table 3. The standard procedure and two alternative procedures for the classification of anterior and inferior MI and LVH by the MEANS program. The MEANS program uses four levels of certainty ('no', 'possible', 'probable', 'definite') to classify ECG abnormalities, which are dichotomized to estimate sensitivity and specificity. The procedures differ in the threshold to dichotomize the classification of ECG abnormalities:

Standard procedure: threshold for presence of an abnormality between 'possible' and 'probable';
Procedure A: threshold for presence of an abnormality between 'no' and 'possible';
Procedure B: threshold for presence of an abnormality between 'probable' and 'definite'.

	Standard procedure		Procedure A		Procedure B	
	Sens	Spec	Sens	Spec	Sens	Spec
Anterior MI	73.8	97.5	82.3	97.0	69.4	97.9
Inferior MI	90.1	97.6	90.1	95.8	81.0	98.9
LVH	88.9	99.1	94.3	94.0	77.4	99.8

Abbreviations: Sens, sensitivity; Spec, specificity; MI, myocardial infarction; LVH, left ventricular hypertrophy.

correctly diagnosed in only 43% and 54% of the cases respectively. On the other hand, there is no workload for research physician and cardiologists.

Scenario B, in which all positive diagnoses of the MEANS program are verified by a cardiologist, is the best procedure for all ECG diagnoses to identify cases with an ECG abnormality, but underestimates the prevalence of ECG abnormalities, for instance 1.9% instead of 2.5% for AMI. The workload is much less than that of scenario C, but following this scenario would require that, depending on the specific ECG abnormality, 2 to 5 percent of all ECGs have to be interpreted by cardiologists. Overall, scenario C, in which all ECGs are judged independently by a research physician and the MEANS program, and only those ECGs on which they disagree are judged by a cardiologist, provides the best estimates of prevalence and the highest proportions correctly classified as normal, but also has by far the highest workload: 100 percent of all ECGs should be interpreted by research physicians and, depending on the specific ECG diagnosis, 1 to 9 percent by cardiologists.

Discussion

The results of our study indicate that in population-based research the sensitivity and specificity of the diagnostic ECG interpretation by the MEANS computer

Table 4. Three different scenarios for interpreting ECGs in population-based studies. Estimated prevalence in the Rotterdam Study (n=7,983), proportion of ECGs correctly classified as abnormal or normal, and workload for human readers are presented. Workload is expressed as the percentage of all ECGs in the study to be interpreted by research physician or cardiologist.

Scenario A: all ECGs are interpreted by the MEANS program only;

Scenario B: all positive findings of the MEANS program are checked by a cardiologist;

Scenario C: independent interpretation by the research physician and the MEANS program and only those ECGs on which they disagree are interpreted by a cardiologist.

	Reference prevalence[1]	Scenario	Estimated prevalence	Correctly classified as abnormal	Correctly classified as normal	Workload research physician	Workload cardiologist
	n (%)		n (%)	(%)	(%)	(%)	(%)
AMI	201 (2.5)	A	343 (4.3)	43.1	99.3	0	0
		B	148 (1.9)	100	99.3	0	4.3
		C	242 (3.0)	75.1	99.8	100	5.3
IMI	245 (3.1)	A	409 (5.1)	54.0	99.7	0	0
		B	221 (2.8)	100	99.7	0	5.1
		C	232 (2.9)	95.3	99.7	100	8.1
LVH	268 (3.4)	A	306 (3.8)	78.1	99.6	0	0
		B	238 (3.0)	100	99.6	0	3.8
		C	253 (3.2)	100	99.8	100	9.4
LBBB	183 (2.3)	A	184 (2.3)	91.8	99.8	0	0
		B	169 (2.1)	100	99.8	0	2.3
		C	193 (2.4)	94.4	100	100	0.9
RBBB	258 (3.2)	A	256 (3.2)	88.5	99.6	0	0
		B	226 (2.8)	100	99.6	0	3.2
		C	272 (3.4)	95.0	100	100	0.9

[1] according to cardiologists;

Abbreviations: RP, research physician; AMI, anterior myocardial infarction; IMI, inferior myocardial infarction; LVH, left ventricular hypertrophy; LBBB, left bundle branch block; RBBB, right bundle branch block.

program, taking cardiologists as a reference, is high. The performance is at least as good as that of a research physician using an extensive form for structured clinical ECG evaluation.

In population-based research an attractive approach is to use the MEANS program, without human readers, to diagnose LVH, LBBB and RBBB (Scenario A), while having all positive findings of AMI and IMI by the MEANS program verified by a cardiologist (Scenario B). This will result in reasonable estimates of prevalence of ECG abnormalities and classification of normal and abnormal ECG findings, while the workload for human readers is kept to a minimum.

The results of this study may also be applied in a primary care setting. A physician with little experience in interpreting ECGs can use the computer program to interpret ECGs and have positive computer findings checked by a cardiologist. A more experienced physician may use the ECG interpretation by the computer program and take his own independent judgment as a second opinion. If he agrees with the computer, the ECG interpretation is probably right. If he disagrees with the computer it is worthwhile to have the ECG judged by a cardiologist.

Nowadays, with physicians becoming less experienced in interpreting ECGs, the use of a computer program for ECG interpretation may improve the quality of ECG interpretation in health care.

In the CSE study sensitivity of the MEANS program with cardiologists as a reference was 89.4% for AMI, 81.1% for IMI and 83.1% for LVH[14]. These values lie within the confidence intervals of the sensitivity estimates of the MEANS program in the present population-based study, except for AMI, which is just outside. Due to methodological differences specificity cannot be compared.

In this study the cardiologists' interpretation served as a reference. By definition, the performance of the MEANS program and the research physician can never be better than this reference[15]. This may be a problem if the reference is of poor quality. In this study three experienced cardiologists formed the reference and we consider the quality of their interpretation high. The confidence intervals of sensitivity estimates are wide, due to a relatively low frequency of ECG abnormalities, even after enrichment.

We conclude that diagnostic ECG interpretation by a computer can be very useful in population-based research. To detect cases of LVH, LBBB and RBBB, use of our computer program alone gives satisfactorily results. Cases of AMI or IMI, according

to our computer program, should preferably be interpreted also by a cardiologist. Interpretation of the MEANS computer program is at least as good as ECG interpretation by trained research physicians using a form for structured clinical evaluation, but much more efficient and therefore less expensive.

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CHAPTER 2.2

REPRODUCIBILITY OF COMPUTERIZED ECG MEASUREMENTS AND CODING IN A NON-HOSPITALIZED ELDERLY POPULATION

Abstract

The standard 12-lead ECG is used in many epidemiological studies to diagnose and predict cardiovascular disease. In view of this, knowledge about the reproducibility of ECG measurements and coding is essential. We assessed minute-to-minute, day-to-day, and year-to-year variability of ECG measurements, composite scores, and Minnesota Code classification, using a computer program, in 101 non-hospitalized elderly men and women.

ECG interval measurements were more reproducible than amplitude measurements. The best reproducibility was found for overall QTc interval (coefficient of variation: 3.1%, 4.0%, and 5.2% for the minute-to-minute, day-to-day, and year-to-year group, respectively) and the poorest for the Cardiac Infarction Injury Score (coefficient of variation 67.1%, 78.5%, and 94.3%).

Minnesota Code discrepancies occurred in 16%, 19% and 22% of the ECGs in the minute-to-minute, day-to-day and year-to-year group, respectively. Reproducibility within specific code categories was much better. Overall, variability tended to increase with time. In the routine setting, electrode positioning had relatively little effect on the total variability.

Chapter 2.2

Introduction

Measurements obtained from the standard 12-lead electrocardiogram (ECG) and classification of the ECG according to the Minnesota Code[1, 2] are used in many epidemiological studies to diagnose and predict cardiovascular disease. In addition, serial changes in ECG characteristics are being studied for their value as determinants of future events. In clinical practice, the relevance of a diagnostic or prognostic factor heavily depends on its reproducibility in the individual. In view of this, knowledge about the reproducibility of ECG measurements and coding is essential.

Variability of ECG measurements and coding originates from multiple sources. One important source is intra- and inter-observer variability among physicians interpreting ECGs[3-5], which does not apply to computer programs for ECG analysis. Differences in recording technique, especially electrode placement, are another source. The magnitude of the variation induced by changes in electrode positions can be estimated by comparing minute-to-minute variation with marked electrode positions, to day-to-day variation without marked electrode positions. Other sources of variation that cannot easily be disentangled are: (1) random physiological fluctuations, for example, respiration movements, fluctuations in autonomic balance, and changes in body position; (2) signal-analysis errors of the computer program, and (3) true clinical and subclinical changes in health status. An impression of the contribution of changes in health status to the variability of the ECG can be obtained by comparing year-to-year with day-to-day variability.

Published reports on the variability of ECG measurements and coding are scarce. Most studies on the reproducibility of measurements were performed many years ago on manual ECG measurements[3, 6], or on measurements obtained from computer-processed vectorcardiograms[7, 8]. Reports on the reproducibility of ECG measurements and coding by computer are limited to year-to-year variation in wave measurements[9] and indices of left ventricular hypertrophy (LVH) [10, 11], and to day-to-day variation of Minnesota Code categories 1 and 3[12]. Reproducibility of QT dispersion[13] and QT interval[14] have been studied in manual measurements only.

No information is available on minute-to-minute and day-to-day variability of com-

puterized ECG measurements and of most Minnesota Codes in population-based studies. Furthermore, reproducibility data are lacking for some relatively new ECG characteristics of which a predictive value for future heart disease has been reported, notably the Cardiac Infarction Injury Score (CIIS)[15, 16], the QTc interval[17-22], and left ventricular mass index (LVMI)[23]. To our knowledge, minute-to-minute, day-to-day, and year-to-year variability have not been studied together in the same population. These issues are addressed in the present study, using computerized ECG measurement and coding, in a non-hospitalized elderly population.

Methods

Study population and ECG recordings

A random sample of 101 subjects participating in the population-based Rotterdam Study was invited for the present research. Objectives, methods and data collection of the Rotterdam Study have been described elsewhere[24]. Briefly, all men and women aged 55 years or older, living in the Ommoord district of the city of Rotterdam, were invited to participate. Of 7,983 participants (response rate 78%) baseline data were collected from 1990 to 1993, including medical history and established cardiovascular risk factors, as well as a 12-lead resting ECG.

During the second round of the Rotterdam Study, one to two years later, a second ECG was recorded. Year-to-year variability was studied by comparing the baseline ECG with the second ECG. As part of the protocol of the present study, two to three weeks later a third ECG was recorded. Day-to-day variability was assessed by comparing the second and the third ECG. A fourth ECG was recorded 15 to 30 minutes after the third, with marked electrode positions, and the latter two ECGs were used to compute minute-to-minute variability. All ECGs were recorded with an ACTA electrocardiograph (ESAOTE, Florence, Italy) at a sampling rate of 500 Hz.

Four ECGs that could not be processed due to excessive noise or signal clipping were excluded. Thus, minute-to-minute and day-to-day variability were assessed in 97 paired ECGs. In the year-to-year comparison, 12 tracings were not available, mainly due to temporary technical problems with the ECG recorder during the baseline visit, resulting in 85 paired ECGs in the year-to-year comparison. None of

the subjects reported signs or symptoms of intercurrent heart disease to the research physician, the general practitioner, or the cardiologist in the period between the first and last ECG. Thus, no clinical changes in health status occurred.

ECG analysis

Each ECG was analyzed by the Modular ECG Analysis System (MEANS)[25]. Both the measurement and the classification section of MEANS have extensively been evaluated by the researchers themselves and by others[25-28].

Measurements are derived from the representative complex that results from selective averaging of dominant beats. The QT interval is determined commonly over all 12 leads. To adjust the QT interval for heart rate Bazett's formula is used[29].

To measure QT dispersion, the program takes the location of the overall end of the T wave as a starting point and searches each lead forward and backward to establish the lead-specific end of the T wave. QT dispersion was defined as the difference between the maximum and minimum QT interval in the 6 precordial leads, the shortest extremity lead and the median of the 5 other extremity leads. As measures of LVH, the Sokolow index (S in V1 + maximum R in V5 or V6) and the left ventricular mass index (LVMI)[23] were studied.

To determine a classification according to the Minnesota Code, MEANS was adapted to comply with the measurement and coding rules as specified in the Minnesota Code standard[30]. The only difference is that MEANS operates on averaged beats whereas the standard prescribes the analysis of individual beats and then applies a majority rule to arrive at the final code. The Minnesota coding of MEANS showed excellent performance in a recent evaluation study[31]. Every code from categories 1 to 7 was analyzed. For categories 8 and 9, only codes 8-3-1 (Atrial fibrillation) and 9-2 (ST-segment elevation) were taken into account.

Data analysis

Variability of ECG measurements was expressed by the standard deviation (SD) of the difference between paired measurements and by the coefficient of variation, taken as the SD of the difference between paired measurements divided by the mean

Table 1. General characteristics of the study sample and the Rotterdam Study population. Values are means (standard deviations) or percentages.

Characteristics	Study sample n=97	Rotterdam Study n=6,202
Gender (% men)	45	40
Age (y)	65 (7)	69 (9)
Systolic blood pressure (mmHg)	132.5 (23.8)	139.4 (22.4)
Diastolic blood pressure (mmHg)	72.1 (10.2)	73.5 (11.6)
Cholesterol (mmol/l)	6.8 (1.2)	6.6 (1.2)
History of myocardial infarction (%)	5.3	6.9
Angina pectoris (%)	7.4	6.8

of the pooled measurements[32].

If no P wave was detected in either ECG in the comparison, the subject was excluded from the analysis of PR-interval durations and P-wave amplitudes. Similarly, a subject was excluded from the analysis of Q-wave amplitudes if no Q wave was present in both ECGs in the comparison. Relabeling of Q waves, which occurs for example when a small initial R wave that is present in one ECG disappears in the other ECG, can result in large differences in Q-wave amplitudes. When relabeling occurred, Q-wave measurements were excluded from the analysis (n=3 in the minute-to-minute group, n=2 in the day-to-day group, and n=3 in the year-to-year group). In the comparison of the Cardiac Infarction Injury Score, subjects were excluded if relabeling of the Q wave in lead III or aVL occurred.

Minnesota Code items were compared for each coding category separately. If a case did not qualify for any code from the category under consideration, a zero code was assigned. Thus, for each category separately, all ECGs were given a code. For categories 1, 4,and 5, where coding (partly) follows a graded scale[31], we considered the codes of paired ECGs to be in agreement if the difference was not more than one grade. All other changes were considered discrepancies.

With the help of an experienced cardiologist, the reasons for discrepancies in the Minnesota coding were analyzed and classified as: (1) wave-detection or waveform-recognition errors of the computer program, or (2) random fluctuations caused by physiological variations, electrode-position variations or signal disturbances.

Table 2. Variability of paired ECG measurements (amplitudes in μV and durations in ms)

	Mean	Minute-to-minute			Day-to-day			Year-to-year		
	n=97	n=97			n=97			n=85		
		n	SD*	Coef. Var† (%)	n	SD	Coef Var (%)	n	SD	Coef Var (%)
PR interval	172.5 (22.5)	91	7.6	4.4	92	8.3	4.8	81	11.8	6.8
QRS interval	99.6 (19.0)	97	6.5	6.5	97	6.4	6.4	85	9.5	9.4
QTc interval	423.8 (23.0)	97	12.9	3.1	97	16.9	4.0	85	22.0	5.2
QT dispersion	50.0 (22.6)	97	32.5	66.2	96	32.9	62.2	84	33.1	65.8
P amplitude II	110.3 (37.2)	91	20.0	18.5	92	26.7	24.6	81	29.8	27.2
Sokolow	2110.8 (587.4)	97	257.9	12.2	97	317.4	14.9	85	394.7	17.8
LVMI	110.8 (23.6)	97	10.9	9.8	96	15.3	13.7	84	15.9	13.8
T amplitude aVF	140.4 (96.0)	97	37.8	27.5	97	40.2	29.0	85	53.3	42.1
Q amplitude aVF	-76.5 (51.3)	45	24.9	32.5	44	31.9	35.5	42	62.2	61.8
Q amplitude V6	-62.0 (58.3)	66	15.1	24.4	67	30.0	48.3	60	31.3	47.1
CIIS	7.2 (9.5)	92	4.9	67.1	90	5.6	78.5	74	6.6	94.3

*SD=standard deviation of the difference; † Coef Var= coefficient of variation.

Results

General characteristics

The baseline characteristics of the participants in the study sample and of the Rotterdam Study population were very similar (Table 1). Characteristics of the subjects included in the year-to-year comparison (n=85) did not substantially differ from those in the minute-to-minute and day-to day comparison (n=97).

Variability of paired ECG measurements is shown in Table 2. Overall, variability tended to increase with time. Interval measurements tended to be more reproducible than amplitude measurements. Best reproducibility was found for QTc interval (coefficient of variation 3.1%, 4.0%, and 5.2% for the minute-to-minute, day-to-day, and year-to-year group, respectively) and PR interval (coefficient of variation 4.4%, 4.8%, and 6.8%). Reproducibility was poorest for QT dispersion (coefficient of variation 66.2%, 62.2%, and 65.8%) and the Cardiac Infarction Injury Score (coefficient of variation 67.1%, 78.5%, and 94.3%). Findings in men and women were similar. Exclusion of cases with definite ECG abnormalities according to MEANS, or of cases with a history of myocardial infarction did not substantially influence the results.

Table 3 shows that the prevalence of Minnesota Code items, determined in the third ECG (n=97) of the present study, was relatively low as can be expected in a non-hospitalized population. The total number of discrepancies increased with time: 15 in the minute-to-minute group, 18 in the day-to-day group, 24 in the year-to-year group. Reproducibility within code categories was much better. No changes occurred for code 2 (QRS axis deviation) and code 6 (Atrioventricular conduction defects) in any of the comparison groups. Variability was highest for code 4 (ST-segment depression), varying from 4.1% in the minute-to-minute group to 7.1% in the year-to-year group. Since a single pair of ECGs may have more than one discrepancy in Minnesota Code items, we also assessed the total number of ECGs in at least one discrepancy occurred: 15 (16%) in the minute-to-minute group, 18 (19%) in the day-to-day group, and 19 (22%) in the year-to-year group.

All 15 code discrepancies in the minute-to-minute group were due to random

fluctuations. In the day-to-day group, 17 (95%) of the discrepancies were due to random fluctuations and 1 (5%) was due to a P-wave detection error, giving a discrepancy for code 8-3-1. In the year-to-year group, 22 (92%) discrepancies were due to random fluctuations, and 2 (8%) were due to P-wave detection errors.

Discussion

This study in a non-hospitalized elderly population demonstrates that minute-to-minute variability comprises a major part of total variability of computerized ECG measurements and coding. As the time span increases and therewith the number of sources of variation, the variability of the ECG measurements and coding increases as well. In a routine setting, electrode positioning has relatively little effect on the total variability of ECG measurements and coding, as day-to-day variability is only slightly larger than minute-to-minute variability. Although clinical cardiovascular events did not occur during one to two years of follow-up in this 'healthy' population, subclinical changes in health status may have given rise to changes in ECG measurements. However, the difference between day-to-day and year-to-year variation is small compared to the total variation.

Minnesota Code discrepancies occurred frequently, in 16%, 19% and 22% of the ECGs in the minute-to-minute, day-to-day and year-to-year group, respectively. Within code categories variability was much smaller. As the prevalence of Minne-

Table 3. Variability in Minnesota Code items.

Minnesota Code category	Prevalence n=97 n (%)	Minute-to-minute n=97 n (%)	Day-to-day n=97 n (%)	Year-to-year n=85 n (%)
1 Q and QS patterns	10 (10.3)	4 (4.1)	3 (3.1)	2 (2.4)
2 QRS axis deviation	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
3 High-amplitude R waves	3 (3.1)	1 (1.0)	2 (2.1)	5 (5.9)
4 ST-segment depression	5 (5.2)	4 (4.1)	5 (5.2)	6 (7.1)
5 T-wave items	19 (19.6)	0 (0.0)	2 (2.1)	3 (3.5)
6 Atrioventricular conduction defects	6 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)
7 Ventricular conduction defects	16 (16.5)	2 (2.1)	2 (2.1)	4 (4.7)
8-3-1 Atrial fibrillation	1 (1.0)	0 (0.0)	1 (1.0)	2 (2.4)
9-2 ST-segment elevation	2 (2.1)	4 (4.1)	3 (3.1)	2 (2.4)

sota Codes was rather small in our sample, no reliable reproducibility estimates for specific codes can be obtained from our data. However, our findings do show what overall variability of Minnesota Codes is to be expected in population-based studies. Part of this variability may be explained by the all-or-none fashion in which most codes are decided, using a single threshold. For borderline measurements, a few microvolts or milliseconds difference may clinch the coding. Minor measurement differences may thus result in major coding differences.

Since our study sample was representative for the complete population of the Rotterdam Study, we believe our findings are generalizable to other populations of non-hospitalized older adults. However, our findings may not be applicable to hospital settings, as prevalence and severity of disease in hospitalized subjects differ considerably from the general population.

Comparison with prior studies

Two early studies were performed on reproducibility of manual ECG measurements[3,6]. The day-to-day variability of PR duration, QRS duration, P amplitude in lead II and T-wave amplitude in aVF of our computerized measurements were found to be within the 'permissible' range, as defined in one of these studies[6]. Year-to-year variation in computerized ECG measurements in non-hospitalized adult men and women has been reported by Michaelis[9]. The year-to-year variability in QRS duration and T-wave amplitude in lead aVF was very similar to our findings. The variation in Q-wave amplitudes as reported by Michaelis was smaller than our observation. This may be explained by the fact that we, in contrast to Michaelis, excluded paired ECGs that had no Q wave in both ECGs.

In two studies on variability of LVH criteria smaller minute-to-minute variability of the Sokolow index was found than in the present study [10,11]. This can be explained by the fact that in these studies minute-to-minute variability was assessed by two ECGs measured 1 to 2 minutes apart with an unchanged position of the patient, whereas in our study, although electrode positions were marked, participants were allowed to move in the 30 minutes between the two ECG recordings. Our day-to-day variability of the Sokolow index is similar to the findings in these studies.

Chapter 2.2

Day-to-day variability of QT dispersion has been reported in a small group of men and women [13, 14]. In these studies, like in the present study, the reproducibility of QT dispersion is poor. In view of this, the relatively large differences in QT dispersion between cardiovascular cases and control subjects that have been reported in many clinical studies are remarkable. Due to poor measurement precision, the reported association between QT dispersion and morbidity or mortality will be strongly diluted.

Day-to-day variation of computerized Minnesota coding of category 1 (Q waves) and category 3 (high- amplitude R waves) has been assessed in 104 paired ECGs in the MRFIT study[12]. In this study, 17.3% discrepancies in category 1 and 9.6% discrepancies in category 3 were reported. However, in this study Minnesota Codes were grouped differently, and these numbers are difficult to compare with our results. In another study in manually coded ECGs, 7% discrepancies occurred in the minute-to-minute group and 17% in the day-to-day group for category 3[10]. A comparison with our results is hampered because codes 3-1 and 3-3 were combined in one category and population characteristics differ.

Clinical implications

In the present study, reproducibility was better for interval measurements than for amplitude measurements. Reproducibility of the CIIS and QT dispersion was very poor. Also, Minnesota coding was fairly unstable.

One way to deal with the problem of poor reproducibility is the use of repeated measurements to establish a measurement value. This procedure is best known from the measurement of blood pressure. As far as Minnesota Codes are concerned, reproducibility may be improved by including additional codes that allow gradual transition, instead of using a dichotomous classification based on a single threshold.

The results of this study can also be applied for serial ECG analysis. Usually, twice the standard deviation of the serial difference in measurements is used as the 'normal' variation. Although this choice is rather arbitrary, for out-clinic patients two times the standard deviation of the day-to-day variability may be used as the normal variation in ECGs. Changes within these 'normal limits' may be due to random error and not necessarily reflect a change in health status. For continuous

ECG monitoring, our results for minute-to-minute variability may be used to determine confidence limits of 'normal' variation.

Availability

The dataset is available from the authors for further investigations by other researchers.

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CHAPTER 2.3

PREVALENCE, DETERMINANTS AND MISCLASSIFICATION OFMYOCARDIAL INFARCTION IN THE ELDERLY

Abstract

We evaluated the prevalence, determinants and misclassification of different types of myocardial infarction (MI) in 3272 men and women age 55 years or older. We defined self-reported MI with electrocardiographic (ECG) evidence as *"typical MI"*. We defined self-reported MI without ECG evidence, but verified with additional clinical information, as *"non-Q-wave MI"*. Finally, we defined MI detected by ECG that was not self-reported as *"silent MI"*, after verification of absence of symptoms. Overall, the prevalence of "typical MI" was 4.1% (95%CI 3.5-4.9), of "non-Q-wave MI" 2.8% (95%CI 2.2-3.4) and of "silent MI" 3.9% (95%CI 3.2-4.5). "Silent MI" was more prevalent in women, in hypertensives, cigarette smokers, and in those with higher post-load blood glucose. Self-reported MI without ECG characteristics could be verified as MI by means of additional clinical information in 56% of the cases.

We conclude that MIs occur frequently in the elderly without typical symptoms or ECG changes. As all these manifestations of MI convey an increased risk of symptomatic heart disease or death, they require further attention. Misclassification due to limited sources of information can be considerable and should be taken into account in the design and interpretation of epidemiologic studies.

Chapter 2.3

Introduction

Myocardial infarction (MI) accounts for a considerable proportion of deaths and is an important risk indicator for future cardiac events in both men and women[1,2]. There are different manifestations of MI, notably with or without symptoms of cardiac distress and with or without lasting electrocardiographic characteristics. To assess the occurrence of these different types of MI, multiple sources of information, such as a patient interview, an electrocardiogram (ECG), and additional clinical information from a general practitioner or a cardiologist, are necessary.

The ECG characteristics of MI are due to changes in electrical properties of ischemic or necrotic areas of the heart. Depending on the size or location of the injured region of the heart, however, typical ECG characteristics may or may not appear[3]. Moreover, typical ECG characteristics may disappear with time[4]. Another reason for absence of ECG abnormalities may be that some patients reporting MI in reality did not suffer from MI, but, for instance, had a severe attack of chest pain or underwent coronary artery bypass surgery[5].

Subjects with electrocardiographic MI who do not report MI may either have forgotten their MI or never have noticed the MI because there were no serious symptoms. The mechanisms that underlie silent ischemia are not fully understood, but it is an accepted phenomenon that occurs frequently and has an unfavorable prognosis[6,7].

All MIs, with or without symptoms or ECG characteristics, are associated with an increased risk of future cardiac events[2, 6-14], but little is known about their frequency in the population at large or about their determinants. The aim of this study was to assess the prevalence and determinants of different manifestations of MI in older men and women, and to study the degree of misclassification of MI resulting from the different methods by which MI can be assessed.

Methods

Study design

The Rotterdam Study is a population-based cohort study in which chronic diseases in the elderly are studied. Objectives, methods and data collection of the Rotterdam

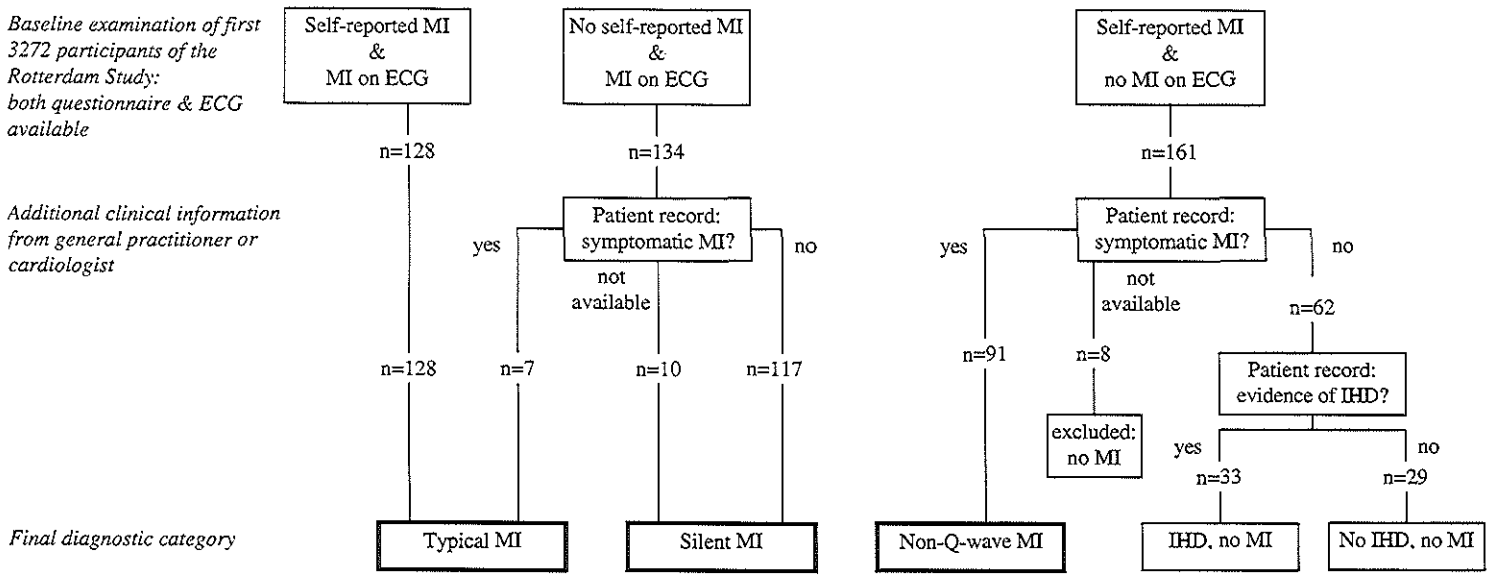

Figure 1. Classification of myocardial infarction based on questionnaire, ECG recording and additional clinical information from general practitioner or cardiologist. MI = myocardial infarction; ECG = electrocardiogram; IHD = ischemic heart disease

Study have been described in detail elsewhere[15]. Briefly, all men and women age 55 years or older, living in the district Ommoord of Rotterdam, were invited to participate. Of 7983 participants (response rate 78%) baseline data were collected, including medical history, presence of angina pectoris, smoking habits, body-mass index, blood pressure, serum cholesterol, use of medications and results of the Mini Mental State Examination as a measure of cognitive function[16].

We calculated body mass index as weight/length^2 in kg/m^2. We calculated blood pressure as the average of two consecutive measurements with a random zero sphygmomanometer. A 12-lead ECG was recorded with an ACTA cardiograph (Esaote, Florence) with a sampling frequency of 500 Hz and stored digitally. Questions on history of MI included the following: "Did you ever have a heart attack?" and, if so, "At what age?", "Who made the diagnosis?" and "Were you admitted to a hospital?".

The present study is restricted to the first 3272 participants of the Rotterdam Study. The ECGs of these participants were evaluated by research physicians, blinded for other clinical information, using a protocol for standardized clinical ECG evaluation. All ECGs with possible or definite MI according to the research physicians were checked by an experienced cardiologist who determined the final diagnosis. In addition, all ECGs of subjects with self-reported MI without ECG evidence were analyzed by the Modular ECG Analysis System (MEANS)[17,18] to detect cases of electrocardiographic MI that had been missed by the research physician. The final diagnosis for these cases was made by another cardiologist, who specialized in reading ECGs. This review led to reclassification of 29 cases of self-reported MI without ECG characteristics to self-reported MI with ECG characteristics.

Of subjects with self-reported MI without ECG evidence and subjects with no self-report of MI but with ECG evidence, additional information was collected from the general practitioner or cardiologist (Figure 1). In addition, of a sample of 29 cases of self-reported MI with ECG evidence additional clinical information from the general practitioner or cardiologist was obtained. Since all these 29 cases were verified as having symptomatic MI with matching ECG evidence or elevated cardiac enzymes in the acute phase, we classified all other subjects with self-reported MI

with ECG evidence as such.

Definitions

By using all available information we distinguished three main categories of MI (Figure 1).

1. Typical MI: Self-reported MI with matching ECG characteristics, e.g., pathological Q-waves or a significant loss of R-wave potential in the precordial leads of a single ECG. In addition, we classified a MI based on ECG without a self-report but where additional information from the general practitioner or cardiologist revealed that the MI had been symptomatic, as "typical MI".

2. Silent MI: MI based on the ECG of subjects who reported never to have suffered from MI and for which the absence of symptoms of MI was confirmed by general practitioner or cardiologist.

3. Non-Q-wave MI: Self-reported MI without matching ECG characteristics, while additional clinical information from general practitioner or cardiologist confirmed the diagnosis of MI based on elevated cardiac enzymes or prior ECG abnormalities. This group includes subjects in which a prior pathologic Q-wave disappeared.

In addition, two secondary diagnostic categories arose when a self-reported MI without ECG evidence could not be verified as MI by means of additional information from the general practitioner or cardiologist (Figure 1):

4a. Ischemic heart disease, no MI: Self-reported MI, without ECG evidence, in which additional clinical information from general practitioner or cardiologist showed evidence of angina pectoris, coronary bypass grafting or percutaneous transluminal coronary angioplasty, but no MI.

4b. No ischemic heart disease, no MI: Self-reported MI, without ECG evidence, in which additional clinical information from the general practitioner or cardiologist could not confirm MI or other ischemic heart disease.

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Data analysis

We calculated prevalence of different types of MI among the 3272 men and women and used multivariate logistic regression analysis to identify determinants of "non-Q-wave MI" and "silent MI" in comparison with "typical MI", adjusting for age and gender. In a second analysis we studied determinants of unconfirmed self-reports of MI without ECG evidence (categories 3 and 4). Within the group of patients with self-reported MI without ECG characteristics were compared patient characteristics of those in whom MI could be confirmed as non-Q-wave MI with those in whom MI could not be verified as such, by using additional clinical information from the general practitioner or cardiologist.

Table 1. Prevalence of categories of myocardial infarction (MI) of the first 3272 participants aged 55 years or older in the Rotterdam Study (Figure 1).

	Prevalence (%)	95%CI* (%)	Number (n)
"Typical MI"	4.1	3.5-4.9	135
men	7.3	5.9-8.9	93
women	2.1	1.5-2.8	42
"Non-Q-wave MI"	2.8	2.2-3.4	91
men	4.4	3.3-5.5	56
women	1.8	1.2 -2.4	35
"Silent MI"	3.9	3.2-4.5	127
men	4.6	3.5-5.8	58
women	3.5	2.7-4.3	69
Total MI	10.8	9.7-11.9	353
men	16.3	14.3-18.4	207
women	7.3	6.2-8.5	146
Self-reported MI:			
Ischemic heart disease, no MI			
men	1.0	0.7-1.4	33
women	0.9	0.4-1.5	11
	1.1	0.7-1.7	22
Self-reported MI:			
No ischemic heart disease, no MI			
men	0.9	0.6-1.3	29
women	1.1	0.6-1.8	14
	0.8	0.4-1.2	15

* CI = confidence interval; † MI = myocardial infarction

Results

Among 3272 men and women in our study, 289 (8.8%, 95% CI 7.9 - 9.9) reported having suffered from MI, 262 (8.0%, 95% CI 7.1 - 8.9) had ECG characteristics of MI and 128 (3.9%, 95% CI 3.3 - 4.6) had both a self-report of MI and MI by ECG. Overall, 353 (10.8%, 95% CI 9.7 - 11.9) of the participants had suffered from MI. The prevalence of the different diagnostic categories of MI as defined above are presented in Table 1. In men, "typical MI" (7.3%, 95% CI 5.9 - 8.9) was more frequent than "non-Q-wave MI" (4.4%, 95% CI 3.3 - 5.5) and "silent MI" (4.6%, 95% CI 3.5 - 5.8). In women, "silent MI" (3.5%, 95% CI 2.7 - 4.3) was most frequent, followed by "typical MI" (2.1%, 95% CI 1.5 - 2.8) and "non-Q-wave MI" (1.8%, 95% CI 1.2 - 2.4). Of the 91 cases of "non-Q-wave MI", in 58 cases (64%) a Q-wave had never occurred, in 17 cases (18%) a prior pathologic Q-wave had decreased or had disappeared and in 16 cases (18%) no information on prior ECG characteristics was available.

In men, the prevalence of all manifestations of MI increased from the age of 55 years until the age of 75 years (Table 2). After age 75, the prevalence of "non-Q-wave MI" and "typical MI" decreased and the prevalence of "silent MI" slightly increased. In women, the prevalence of all types of MI increased with age, except for "typical MI", which was less common in the very old.

We present general characteristics and cardiovascular risk factors of the different manifestations of MI in Table 3. There was no difference in both general characteristics and cardiovascular risk factors between those with "typical MI" and "non-Q-wave MI", although "non-Q-wave MI" occurred somewhat more often in those with a higher body mass index (age and gender adjusted OR 1.08 per kg/m^2, 95% CI 0.99 - 1.18). "Silent MI", as compared with "typical MI", was more frequent in women than in men (adjusted OR 2.45, 95% CI 1.46-4.10), in those with hypertension (adjusted OR 2.59, 95% CI 1.37 - 4.94), in those with higher post load blood glucose levels (adjusted OR 1.10, 95% CI 1.00 - 1.22), and in cigarette smokers (adjusted OR 1.93, 95% CI 1.06 - 3.53). A history of angina pectoris was associated with a lower frequency of "silent MI" (adjusted OR 0.23, 95% CI 0.10 - 0.57).

Table 2. Age and sex specific prevalence of "typical myocardial infarction (MI)", "silent MI", "non-Q-wave MI", and of unconfirmed self-reported MI classified as "ischemic heart disease (IHD), no MI" and "no IHD, no MI".

		55-64 (years)	65-74 (years)	75-84 (years)	>85 (years)
Typical MI*	Men	4.6	8.9	8.8	7.5
	Women	1.1	2.2	3.6	1.2
Silent MI	Men	2.6	5.0	6.5	7.5
	Women	2.0	2.5	4.7	9.8
Non-Q-wave MI	Men	3.3	5.4	5.0	0
	Women	0.6	1.8	2.6	3.7
IHD†, no MI	Men	0.2	1.2	1.5	0
	Women	0.2	1.5	1.3	2.5
no IHD, no MI	Men	0.2	1.7	0.8	5.0
	Women	0.2	0.8	1.3	1.2

* MI = myocardial infarction; † IHD = ischemic heart disease;

Self-reports of MI without ECG evidence that could not be confirmed as MI with additional clinical information from the general practitioner or cardiologist were classified as "ischemic heart disease, no MI" in 33 cases (53%) and "no ischemic heart disease, no MI" in 29 cases (47%). Probable reasons for self-reported MI in the category "no ischemic heart disease, no MI" were sterno-costal pain (n=3), gastric pain (n=3), pulmonary disease (n=2), cholecystitis (n=1), nervousness (n=1), and hospital admissions for other reasons (n=6). In 13 subjects no apparent reason for a self-report of MI could be found.

We compared subjects with unconfirmed self-reported MI without ECG evidence with those with self-reported MI without ECG evidence that could be confirmed as a MI. Unconfirmed self-reports were more frequent in women (OR 2.2; 95% CI 1.1 - 4.3), when the MI had occurred farther in the past (OR 1.08 per year; 95% CI 1.02-1.15) and in those who were not hospitalized for their MI (OR 0.16; 95% CI 0.06 - 0.42). In a multivariate logistic model the difference in the frequency of unconfirmed self-reports between men and women was partly explained by the fact that women were less often admitted to hospital.

Table 3. General characteristics and cardiovascular risk factors of subjects with a "typical myocardial infarction (MI)", "non-Q-wave MI" and "silent MI", and of subjects with unconfirmed self-reported MI classified as "ischemic heart disease (IHD), no MI" or "no IHD, no MI". Values are means or proportions (%).

	"typical MI"*	"silent MI"	"non-Q-wave MI"	"IHD, no MI"†	"no IHD, no MI"
Total number (n)	135	127	91	33	29
Women (%)	31.1	54.3	38.5	67	55
Age (y)	72.0	74.2	72.1	75.2	74.4
Reported time since MI (y)	8.0	_	8.1	9.5	12.4
Age at last MI (y)	63.8	_	63.7	65.3	60.8
Hospital admission (%)	89	_	92	70	55
MMSE (0-30) ‡	27.0	26.3	26.7	26.7	27.0
Body mass index (kg/m^2)	26.2	26.4	27.1	27.4	27.5
Systolic BP (mmHg) §	137.0	146.2	135.1	145.2	135.6
Diastolic BP (mmHg)	71.2	75.2	70.3	72.3	73.2
Hypertension (%)¦	15.6	31.4	16.5	33.3	10.3
Cholesterol (mmol/l)	6.5	6.4	6.7	6.4	6.6
Smoking (ever) (%)	83.7	63.8	79.1	54.5	65.5
Angina pectoris (%)	20.0	5.5	21.9	36.4	13.7
Diabetes mellitus (%)¶	24.1	27.0	24.7	37.5	31.0
Stroke (%)	7.5	6.3	6.7	6.1	7.4

* MI = myocardial infarction; † IHD = ischemic heart disease; § BP = blood pressure
‡ MMSE = Mini Mental State Examination;
¦ Hypertension = systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 95
¶ Diabetes Mellitus = non-fasting blood glucose > 11.1 mmol/l or antidiabetic medication

Discussion

The results of our study indicate that among older subjects MI frequently occurs without symptoms or ECG characteristics. Overall, the prevalence of "typical MI" (4.1%) is only slightly higher than the prevalence of "silent MI" (3.9%) and "non-Q-wave MI" (2.8%). Patient characteristics, notably the cardiovascular risk profile, of those with "non-Q-wave MI" were similar to those with "typical MI". "Silent MI" as compared with "typical MI" was more frequent in women, in those with impaired glucose tolerance, in those with hypertension, among cigarette smokers and among subjects without angina pectoris. Self-reports of MI without ECG characteristics could be confirmed with additional clinical information in 56% of the cases. Self-reported MI was more likely to be confirmed in men, in those who were hospitalized, and in more recent MI.

Studies on the prevalence of different manifestations of MI in the population at large are scarce[19-22]. Uusitopa et al. studied 1194 patients who had an ECG recorded shortly before death and who had an autopsy[20]. They found that depending on the Minnesota Code criteria used, MI had occurred without a Q-wave in 38% to 62% of all cases. In MIs that occurred longer ago a Q-wave was coded less frequently than in recent MIs; in 29% and 51% respectively in men, and in 32% and 50% respectively in women. These results are in accordance with our findings. In the Bronx Aging Study among 390 men and women aged 75 to 85 years, 62% of the reported MI were "non-Q-wave MI", which also accords with our findings[19]. In the same study MI occurred silently in 60% of the cases. The Cardiovascular Health Study reported that in men 45% and in women 69% of MIs were silent, again similar to our estimates[22]. Findings on the absolute prevalence of MI across these studies cannot easily be compared, owing to differences in population characteristics and methods to diagnose MI.

Little is known about determinants of "silent MI". Most studies were performed in men only. Both the Framingham Heart Study and the Cardiovascular Heart Study confirm our finding that "silent MI" occurs relatively more often in women[5, 22]. This finding may result from differences in presentation of symptoms of ischemic heart disease between sexes or from differences in the health care sought by, or given to, women with symptoms suggestive of ischemic heart disease [23, 24]. Classical ECG characteristics of MI are largely based on studies in men and not may be accurate for women[25]. On the other hand, denial of symptoms may play a part, as well as a delay in performance of adequate diagnostic procedures or referral. Special attention for women with atypical or incomplete symptoms of ischemic heart disease seems justified. The association between "silent MI" and glucose metabolism is still unclear. Although diabetic neuropathy might predispose to "silent MI" owing to decreased pain perception[30], studies have shown contradictory results[9, 26-30].

Several studies have validated self-reported MI in the general population, but little is known about the reliability of self-reported MI in the elderly. Rosamond et al. checked self-reported MI in a study of 3703 patients aged 25 years or older admitted to a coronary care unit with suspicion of acute MI. A previous MI could be substantiated in 60%[5]. False-positive reporting was related to previous cardiac

hospitalizations in 40% of the cases. Although this study was performed in a different setting, the results are similar to ours.

In many epidemiologic studies, a history of MI is defined as a self-report of MI with hospital admission. We found, however, that a substantial part (43%) of all self-reported MI without hospital admission could still be confirmed as an MI by additional clinical information. From our data we can estimate misclassification of MI depending on the sources of information used to assess MI in epidemiological research. If only an interview is used, "silent MI" will be completely missed, accounting for 28% and 33% of all MIs in older men and women, respectively. Moreover, 22% of self-reported MI are not confirmed as MI by additional clinical information. If only an ECG is used, all "non-Q-wave MIs" will be missed, accounting for 27% and 24% of all MIs in older men and women respectively. Finally, verification with additional clinical information from the general practitioner and cardiologist will reduce the prevalence of "non-Q-wave MI" by 40% and of "silent MI" by 5%, while the prevalence of "typical MI" will increase by 5% (Figure 1).

Depending on the purpose of the assessment of MI, misclassification will have different consequences. For the selection of cases of MI in a case-control study, complete assessment of MI is not as important as a correct diagnosis. Therefore, it is important to use a combination of sources of information, notably self-report and ECG with, preferably, additional clinical information from the patient record. In cohort studies the consequences of misclassification of MI are similar to those in case control studies.

Our strategy to assess the occurrence of MI was to be highly sensitive at the start with the question "Did you ever have a heart attack" and to refine diagnostic categories with additional clinical information. This strategy also applied to ECG diagnosis of MI: selecting all cases of possible or definite MI according to the research physicians or the MEANS computer program, and refining this diagnosis with the judgment of a experienced cardiologist. In general, this can be an efficient approach to assess MI in large studies.

Our results are based on a single 12-lead ECG recording. Serial ECG analysis may improve the diagnosis of MI on the ECG.

Chapter 2.3

In this study we benefited from the unique situation in the Dutch health care system, in which the general practitioner plays a pivotal role. In principal, patients are referred to hospital only through their general practitioner and information of each hospital stay is reported in discharge letters to the general practitioner and kept in the primary care patient record. Without this reporting system it would have been difficult to conduct a study like this. In other respects, care for patients with symptoms suggestive of MI is similar in the Netherlands to that in other industrialized countries.

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CHAPTER 2.4

PROLONGED QT INTERVAL: A TRICKY DIAGNOSIS?

Abstract

Prolonged heart-rate adjusted QT intervals on the electrocardiogram (ECG) are associated with an increased risk for coronary heart disease and sudden death. However, the diagnosis of prolonged QT interval in practice is hampered by a lack of standards. We studied variation in the prevalence of prolonged QT, based on different prevailing definitions, in a large non-hospitalized population, and compared our results with other studies applying the same definitions. The study population consisted of 2200 male and 3366 female participants of the Rotterdam Study, age 55 years or older. The QT interval was computed by the Modular ECG Analysis System (MEANS). Three different formulas to adjust QT for heart rate were used: Bazett's formula (QT_c), a linear regression equation (QT_{lr}), and the QT-index (QTI). Prolonged QT occurred frequently both in men and women, and its prevalence increased with age. Women had longer heart-rate adjusted QT intervals than men (mean QT_c 433 ms versus 422 ms), and mean values for QT_{lr} were lower than for QT_c (mean QT_{lr} 422 ms in women and 412 ms in men). Prevalence was highest for prolonged QT_{lr} (31% in men and 26% in women) and lowest for prolonged QTI (6% in men and 9% in women). Comparison with other studies applying the same correction formulas showed large discrepancies in prevalence estimates of prolonged QT_c and QT_{lr}, and to a lesser degree of prolonged QTI, probably largely attributable to differences in measurement techniques. Future research is needed, relating QT interval to prognosis, to obtain measurement technique specific reference values of heart-rate adjusted QT measurements and age- and sex-specific threshold values for prolonged QT. Such data is needed to use the QT interval in practice with confidence.

Introduction

The QT interval is of potential use in cardiovascular risk profiling[1-6], but the diagnosis of patients with prolonged QT intervals in practice may be hampered by the lack of consensus regarding measurement techniques[7], formulas to adjust QT for heart rate[8-11], and criteria to define prolonged QT[12]. Little is known about the influence of these formulas and cut-off criteria on the prevalence of prolonged QT. Furthermore, comparison of the few studies that were published was limited by the application of different formulas to adjust QT for heart rate[6,9,13]. In the present study we examined the distribution of QT interval length and the prevalence of prolonged QT, adjusted for heart rate, in a large non-hospitalized population of men and women aged 55 years or older. Three different formulas to adjust the QT interval for heart rate were used in order to establish differences between formulas and to compare our findings with published data from other population-based studies.

Methods

Study population and data collection

This study is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence and risk factors of chronic diseases in the elderly. Objectives and methods of the Rotterdam Study are described in detail elsewhere[14]. Briefly, in the Rotterdam Study all men and women aged 55 years or older, living in the Rotterdam district Ommoord, were invited to participate. Of 7,129 participants (response rate 69%) baseline data, collected from 1990 to 1993, included an ECG, information on history of cardiovascular disease, established cardiovascular risk factors and use of medications. A digitally stored ECG was available in 6,160 (86%) participants. Fourteen percent was missing mainly due to temporary technical problems with the ECG recorder. Participants with arrhythmias (n=290) and those with complete left or right bundle branch block (n=304) were excluded, leaving 2,200 men and 3,366 women in the present study.

QT measurement and correction for heart rate

A 12-lead resting ECG was recorded with an ESAOTE-ACTA cardiograph with a sampling frequency of 500 Hz, and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS)[15,16] to obtain ECG measurements and diagnostic interpretations. The QT interval was determined over all leads in one representative complex that resulted from selective averaging of dominant beats[15]. To adjust QT for heart rate three different methods were used. First, we calculated QT_c according to Bazett's formula: $QT_c = QT/\sqrt{RR}$, where RR is the RR interval in seconds[17]. Second, we used a linear regression equation that was also applied in the Framingham Study: $QT_{lr} = QT + \beta*(1-RR)$[9]. Both QT_c and QT_{lr} can be interpreted as the QT interval at a heart rate of 60 beats per minute. Third, we computed the QT-index as used in the Cardiovascular Health Study: $QTI=QT/QT_p$, where QT_p is the predicted interval and equals: $QT_{max}/(1 + 0.01*\text{heart rate})$, with $QT_{max}=656$ ms[18]. For example, a QTI of 110 denotes a QT interval that is 10 percent longer than the predicted QT interval. Based on the literature, four definitions of prolonged heart-rate adjusted QT interval were used: QT_c longer than 440 ms[6] and 460 ms[19], QT_{lr} longer than 420 ms in men and longer than 432 ms in women[9], and QTI greater than 110[13].

Data Analysis

The mean values of QT, RR, QT_c, QT_{lr}, and QTI, and the prevalence of prolonged heart-rate adjusted QT, defined in four different ways, were assessed in men and women separately and in different age groups. In addition, we studied whether QT_c, QT_{lr}, and QTI were still associated with RR interval using a linear regression model. If this is the case this would indicate that the correction for heart rate with the formula is not complete. Prevalences from published reports were compared with adjusted results from our study, using the same exclusion rules and, if necessary, adjusting for age using linear regression analysis. All analyses were performed for men and women separately, using BMDP statistical software (version 7, 1990).

Table 1. General characteristics of the study population. Values are means (with standard deviations) or proportions.

	All (n=5,566)	Men (n=2,200)	Women (n=3,366)
Age (years)	68.6 (8.8)	67.4 (8.0)	69.3 (9.2)
Body mass index (kg/m^2)	26.3 (3.7)	25.7 (3.0)	26.8 (4.1)
Systolic blood pressure (mmHg)	139.0 (22.2)	138.5 (21.8)	139.3 (22.5)
Diastolic blood pressure (mmHg)	73.6 (11.5)	74.6 (11.5)	73.0 (11.4)
Serum total cholesterol (mmol/l)	6.7 (1.2)	6.3 (1.1)	6.9 (1.2)
Serum total potassium (mmol/l)	4.1 (0.3)	4.1 (0.3)	4.1 (0.3)
Current cigarette smoking (%)	23.3	29.5	18.9
Systemic hypertension* (%)	18.4	17.1	19.3
Antihypertensive medication use (%)	30.4	27.4	32.3
Diabetes mellitus† (%)	11.6	11.5	11.6
History of MI‡ (%)	12.5	17.8	9.1
Left ventricular hypertrophy by ECG (%)	4.7	5.6	4.1
Negative T-wave§ (%)	7.7	8.4	7.3
Mean heart rate (beats per minute)	70 (12)	68 (12)	71 (11)

*: Hypertension: systolic blood pressure >160 mmHg or diastolic blood pressure > 95 mmHg;
†: Diabetes mellitus: non-fasting blood glucose > 11.1 mmol/l or antidiabetic medication;
‡: History of MI: myocardial infarction by interview or by ECG
§: Negative T-wave: at least 1.0 mm deflection in any of leads I-III, aVL, aVF, V2-V6.

Results

General characteristics of the 2,200 men and 3,366 women are presented in Table I. Women were slightly older, had higher cholesterol levels, smoked less, and had a lower prevalence of myocardial infarction than men.

QT interval and heart rate

The relation between QT and RR using linear regression formulas in our study was QT_{lr}=QT+0.140*(1-RR) in men and QT_{lr}=QT+0.163*(1-RR) in women. In the Framingham Study, application of the linear regression equation had very similar results: QT_{lr}=QT+0.147*(1-RR) in men and QT_{lr}=QT+0.167*(1-RR) in women[9]. Examination of the linear relation between QT_c, QT_{lr}, and QTI with RR showed a negative association of QT_c (regression coefficient r=-0.08, p<0.001) and QTI (r=-0.01,

$p<0.001$) with RR. Consequently, QT_c and QTI do not completely correct QT for heart rate. As expected, there was no significant linear association of QT_{lr} with RR.

Distribution of heart rate adjusted QT-intervals

In Table IIa and IIb the mean values of QT, RR, QT_c, QT_{lr}, and QTI are presented for different age groups. On average, the unadjusted QT interval was similar in both sexes. Women had shorter RR intervals and consequently longer heart-rate adjusted QT intervals than men. In men, mean QT_c increased from 415 ms in those aged 55 to 59 years to 430 ms in those over 80 years. In women, the corresponding values were 429 ms and 437 ms. Overall, QT_c ranged from 345 to 628 ms in men and from 329 to 538 ms in women. In both men and women, mean QT_{lr} was about 10 ms shorter than mean QT_c in all age groups. Mean QTI increased from 100.0 to 103.4 in men and from 102.9 to 104.7 in women, from the youngest to the oldest age group.

Table 2a. Mean values of heart-rate adjusted QT by age in men.

		QT (ms)	RR (ms)	QT_c* (ms)	QT_{lr} (ms)†	QTI‡
55-59	(n=434)	396	921	415	407	100.0
60-64	(n=520)	397	905	420	410	101.1
65-69	(n=495)	399	896	424	414	102.1
70-74	(n=350)	399	893	424	414	102.3
75-79	(n=231)	402	894	428	417	103.1
>80	(n=170)	400	876	430	417	103.4
All	(n=2200)	398	901	422	412	101.8

*: $QT_c=QT/\sqrt{RR}$; †: $QT_{lr}=QT+0.140*(1-RR)$; ‡: QTI=QT/(656/(1+0.01*heart rate)).

Table 2b. Mean values of heart-rate adjusted QT by age in women.

		QT (ms)	RR (ms)	QT_c* (ms)	QT_{lr} (ms)†	QTI‡
55-59	(n=606)	398	868	429	419	102.9
60-64	(n=678)	397	854	431	421	103.4
65-69	(n=604)	399	857	432	422	103.7
70-74	(n=566)	398	847	434	423	103.9
75-79	(n=431)	400	854	434	423	104.1
>80	(n=481)	400	843	437	426	104.7
All	(n=3366)	398	854	433	422	103.7

*: $QT_c=QT/\sqrt{RR}$; †: $QT_{lr}=QT+0.163*(1-RR)$; ‡: QTI=QT/(656/(1+0.01*heart rate)).

Chapter 2.4

Prevalence of prolonged heart-rate adjusted QT interval

The prevalence of prolonged heart-rate adjusted QT, using the four different definitions, is shown in Figures 1a and 1b. The presence of prolonged QT_c, defined as QT_c>440 ms ranged from 13.8% in men and 29.7% in women aged 55 to 59, to 34.7% in men and 44.3% in women older than 80 years, and was similar to the prevalence of prolonged QT_{lr} , but much more prevalent than prolonged QTI intervals. The prevalence of prolonged QT_c , defined as QT_c>460 ms, was similar to the prevalence of QTI, ranging from 2.5% in men and 6.4% in women aged 55 to 59, to 11.8% in men and 17.5% in women in the oldest age group.

Comparison with other studies

Prevalences reported by three other studies and the adjusted prevalence in the Rotterdam Study, applying the same exclusion criteria and adjusting for age, are presented in Table III. Mean QT_c in men aged 65 to 84 was 411(SD 27) ms in the Zutphen Study, about 10 ms shorter than the adjusted mean QT_c in the Rotterdam Study, which was 425 (SD 22) ms. Mean QT_{lr} was about 375 ms in men and 388 ms in women participating in the Framingham Study, whereas the adjusted mean values of QT_{lr} were 401 (SD 19) ms in men and 416 (SD 18) ms in women in the Rotterdam Study. Prevalences of prolonged QT_c and prolonged QT_{lr} were markedly higher in the Rotterdam Study than in published reports using the same formulas. Prevalence of prolonged QTI was lower in women in the Rotterdam Study compared to women in the Cardiovascular Health Study, except for the highest age group, but estimates for men were similar.

Discussion

The results of this study show that a prolonged heart-rate adjusted QT interval is more frequent in women than in men and that the prevalence in both sexes increases markedly with age. Mean values of heart-rate adjusted QT interval and prevalence of prolonged heart-rate adjusted QT vary substantially according to the correction formulas and threshold values used.

Figure 1a. Prevalence of prolonged QT interval adjusted for heart rate, using four different definitions, in men (%).

QTc=QT/√RR; QTIr=QT+0.140*(1000-RR); QTI=QT/(656/(1+0.01*heart rate))

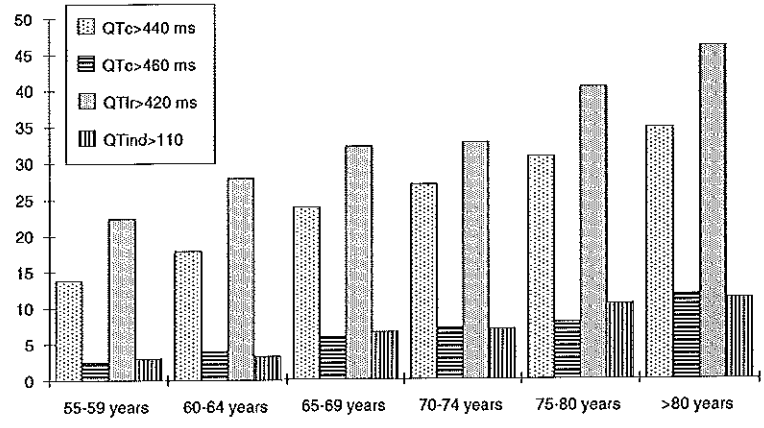

Figure 1b. Prevalence of prolonged QT interval adjusted for heart rate, using four different definitions, in women (%).

QTc=QT/√RR; QTIr=QT+0.163*(1000-RR); QTI=QT/(656/(1+0.01*heart rate))

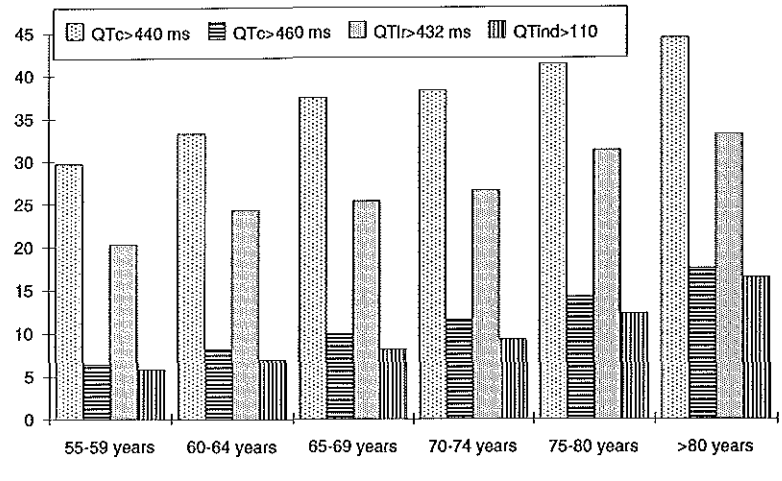

Table 3. Prevalence of prolonged QT in the Rotterdam Study compared to three population-based studies.

	Definition prolonged QT	N	Prevalence (95%CI)	Adj. prevalence[§] Rotterdam Study (95%CI)
Zutphen Study[6]	QT_c*>420 ms			
men, age 65-84		720	34.9 (31.4-38.5)	57.3 (54.4-60.2)
Framingham Study[9]				
men, age 29-62	QT_{lr}†>420 ms	2239	2.5 (1.9-3.2)	14.7 (13.1-16.4)
women, age 28 - 62	QT_{lr}†>432 ms	2779	2.5 (1.9-3.1)	17.1 (15.7-18.5)
Cardiovascular Health Study[13]	QTI‡>110			
men,				
age 65-69		625	6.7 (4.9-9.0)	6.5 (4.5-9.0)
age 70-74		626	8.0 (6.0-10.4)	6.9 (4.4-10.0)
age 75-79		381	12.3 (9.2-16.1)	10.4 (6.8-15.1)
age 80-84		201	12.4 (8.2-17.8)	11.1 (5.9-18.6)
age >85		73	19.2 (10.9-30.1)	11.3 (4.7-21.9)
women,				
age 65-69		1097	13.4 (11.4-15.6)	8.1 (6.1-10.6)
age 70-74		836	16.4 (13.9-19.1)	9.2 (6.9-11.9)
age 75-79		541	16.3 (13.3-19.6)	12.3 (9.3-15.8)
age 80-84		229	20.1 (15.1-25.9)	13.7 (9.8-18.5)
age >85		76	22.4 (13.6-33.4)	19.7 (14.7-25.6)

*: $QT_c=QT/\sqrt{RR}$;

†: $QT_{lr}=QT+0.140*(1-RR)$ in men and $QT_{lr}=QT+0.163*(1-RR)$ in women;

‡: QTI=QT/(656/(1+0.01*heart rate)).

§: Adj. prevalence = adjusted prevalence after applying the same exclusion criteria as in the comparison study and adjusting for age using linear regression if necesary. Numbers of participants in different age groups in the Rotterdam Study are presented in Table II.

Comparison of our findings with data presented from other studies showed that even if the same formulas to adjust QT for heart rate are used, large differences in estimates of prevalence of prolonged QT can be observed.

As QT_{lr} was the only formula without a residual linear association with RR interval, this formula may be preferable to QT_c and QTI when linear associations of QT with cardiovascular determinants are examined. The linear regression coefficients estimated from the Framingham Study were very similar to our estimates. Thus, in studies with a relatively small number of participants, regression coefficients need not be derived, but coefficients from the Framingham Study or from the present study

can be used.

Comparison to previous studies showed that marked differences in prevalence estimated of prolonged QT were present between studies using the same correction formulas. These discrepancies may at least partly be explained by differences in measurement techniques. In the Rotterdam Study the QT interval was measured by computer over all leads. Largest differences were found between the Rotterdam Study and two studies using manual measurements. In the Zutphen Study, ECG intervals were measured manually with a digitizing tablet taking the longest QT interval from leads I, II, III, V2 or V6, and in the Framingham Study measurements were performed manually in all 12 leads. Our findings were more similar to those of the Cardiovascular Health Study in which a computer program was used in combination with an interactive graphics procedure for correcting computer measurement errors. This computer program applies another method to detect the end of the T wave than our MEANS program. This is important in view of the large variability reported between different human observers, different computer programs, and between human observers and computer programs, in measurements of the end of the T wave[7]. Another explanation for part of the discrepancies in prevalence estimates between populations may be differences in prevalences of cardiovascular risk indicators, such as body mass index, medication use, or coronary heart disease.

Which measurement technique should be preferred to diagnose prolonged QT is unclear. Even though QT intervals have been found to differ systematically, the association of prolonged QT intervals, established with different measurement techniques, with future cardiovascular disease has been shown in many studies. However, it seems clear that computerized QT measurements using a single program, and excluding the problem of intra- and inter-observer variability among different physicians measuring ECGs, are preferable to manual measurements.

The definition of prolonged heart-rate adjusted QT, depending on the threshold value used to distinguish between normal and prolonged QT, can be based on prognostic implications for clinical endpoints. Depending on the purpose of diagnosing prolonged QT, higher or lower thresholds and associated risk levels may be considered relevant, which also influences the number of subjects detected with pro-

longed QT. Instead of dichotomous thresholds, also several categories or continuous estimates of the heart-rate adjusted QT may be studied. As women have systematically longer (about 10 ms)heart rate adjusted QT intervals[5,9,20-22], it seems that the threshold value for prolonged QT_c and QT_{lr} should be higher in women than in men.

Using data from large population-based follow-up studies, such as the Rotterdam Study, may offer an opportunity to circumvent the problem of the lack of standards by establishing specific reference values for each ECG computer program or manual measurement technique separately. For each method, age- and sex-specific normal values of QT interval can be assessed, together with threshold values for prolonged heart-rate adjusted QT interval. Thresholds should depend on the additional risk associated with a certain length of the heart-rate adjusted QT interval, for example a two- or threefold risk for cardiovascular morbidity or mortality. This would facilitate uniform diagnoses of those with prolonged heart-rate adjusted QT intervals, and link them to established levels of risk. Consequently, prevalence of prolonged heart-rate adjusted QT can be compared between different populations. More importantly, this would enable physicians to target preventive measures at patients with QT intervals inferring increased cardiovascular risk. At present, in the absence of these measurement-technique specific reference values, prolonged QT interval remains a tricky diagnosis.

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Chapter 3

PROGNOSTIC STUDIES

CHAPTER 3.1

PROLONGED QT INTERVAL PREDICTS CARDIAC AND ALL-CAUSE MORTALITY IN THE ELDERLY: THE ROTTERDAM STUDY

Abstract

Objective To examine the association between heart-rate adjusted QT prolongation and cardiac and all-cause mortality in the population-based Rotterdam Study among men and women aged 55 years or older and to compare the prognostic value of heart rate adjusted QT interval, using different formulas to correct for heart rate.

Background. In several studies it has been suggested that a prolonged QTc interval on the ECG is an independent predictor of cardiovascular disease and mortality. However, only few studies were performed in non-hospitalized populations showing controversial results.

Methods After exclusion of participants with arrhythmias or bundle branch block on the ECG, the study population consisted of 2,083 men and 3,158 women. During the 3 to 6 years (mean 4 years) follow-up period, 217 (10.4%) men and 236 (7.5%) women died. The QT interval was computed by the Modular ECG Analysis System (MEANS). Data were analyzed using Cox' proportional hazards model.

Results. Participants in the highest quartile of heart-rate adjusted QT interval had about a 70% age- and sex-adjusted increased risk for both all-cause mortality (hazard ratio (HR) 1.8; 95%CI:1.3-2.4) and cardiac mortality (HR 1.7; 95%CI:1.0-2.7) compared to those in the lowest quartile. In women, increased risk associated with prolonged QT for cardiac death was more pronounced than in men. These risk estimates did not change after adjustment for potential confounders, including history of myocardial infarction, hypertension and diabetes mellitus.

Conclusions. A prolonged heart-rate adjusted QT interval is an independent predictor for cardiac and all-cause mortality in older men and women. The risk associated with prolonged QT is hardly affected by the heart-rate correction formula used.

Introduction

Prolonged heart-rate adjusted QT interval on the 12-lead electrocardiogram (ECG) is associated with an increased risk for ventricular arrhythmias, sudden death, and coronary heart disease. This relation has been reported in patients with the long QT syndrome[1], in patients after myocardial infarction[2,3], and in diabetic patients with autonomic neuropathy[4]. Only few studies have been performed in the population at large[5-7] and they have shown controversial results. In the Dutch Civil Servants Study[5], men and women with prolonged heart-rate adjusted QT had a twofold increased risk for death from coronary heart disease. In the Zutphen Study[6], a two- to fourfold increased risk for coronary heart disease mortality associated with prolonged heart-rate adjusted QT was observed in middle-aged men and a threefold increased risk in elderly men. In contrast to these findings, prolonged heart-rate adjusted QT was not associated with total mortality, sudden cardiac death or coronary artery disease mortality in both men and women in the Framingham Heart Study[7].

The duration of the QT interval is strongly correlated with heart rate. Previous studies on prognostic implications of prolonged QT interval all used Bazett's formula[8] to adjust QT for heart rate, but its adequacy has been questioned. Several new formulas have been proposed[9-12]. In clinical practice, the formula which best predicts heart disease will be most valuable. In analogy, the definition of prolonged QT should be based on prognostic implications for clinical endpoints, for example a two- or threefold risk for cardiac mortality.

Until now, the threshold value for prolonged QT, notably the value to distinguish between normal and prolonged QT, was often based on the distribution of QT interval duration in the male population. As women have systematically longer heart-rate adjusted QT intervals, clinically useful threshold values for prolonged QT in men and women may differ.

In the present study we examined the association between heart-rate adjusted QT prolongation and cardiac and all-cause mortality in men and women aged 55 years or older, participating in the population-based Rotterdam Study. We compared the prognostic value of heart-rate adjusted QT interval, applying different formulas

available to correct QT for heart-rate.

Methods

Study population and baseline data collection

This study is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence and risk factors for chronic diseases in the elderly. Objectives and methods of the Rotterdam Study have been described in detail elsewhere[13]. Briefly, in the Rotterdam Study all men and women aged 55 years or older, living in the district Ommoord of the city of Rotterdam, were invited to participate (response rate 78%). Of 7,129 participants the baseline data, collected from 1990 to 1993, included an ECG, information on history of cardiovascular disease, established cardiovascular risk factors, and use of medications.

A digitally stored ECG was available in 6,160 (86%) participants. An ECG was missing in 14% of the participants, mainly due to temporary technical problems of the ECG recorder. Blood pressure was calculated as the average of two consecutive measurements with a random zero mercury manometer. Body mass index was calculated as weight/length^2 in kg/m^2. Hypertension was defined as systolic blood pressure above 160 mmHg or diastolic blood pressure above 95 mmHg or use of antihypertensive medication for the indication hypertension. Diabetes mellitus was defined as a non-fasting blood glucose above 11.1 mmol/l or use of anti-diabetic medication. History of myocardial infarction (MI) was defined as self-reported MI with hospital admission, or MI on the ECG[14]. Presence of angina pectoris was established through the Rose questionnaire[15].

After exclusion of participants with arrhythmias (n=256) or complete left or right bundle branch block (n=290), and of subjects without follow-up data, mainly because they moved to unknown addresses (n=345), the study population consisted of 2,093 men and 3,176 women.

Follow-up procedures

The follow-up period, starting at the baseline examination and for the present analysis lasting until April 1996, comprised 3 to 6 (mean 4) years. With respect to

the vital status of participants, information was obtained at regular intervals from the municipal health service in Rotterdam. Information on fatal and non-fatal endpoints was obtained from the general practitioners (GPs) working in the study district of Ommoord. These 20 GPs, covering about 85% of the cohort, all have their practice computerized and report possible non-fatal and fatal events of participants on computer file to the Rotterdam Study data-center on a regular basis. All possible events reported by the GP are verified by research physicians from the Rotterdam Study through patient records of the participating GPs and medical specialists. In April 1996, the medical records of participants with GPs outside the Ommoord area, about 15% of the cohort, were checked by research physicians and of all possible events additional information for coding was collected. Causes and circumstances of death were obtained shortly after reporting of death by the municipal health service or the GP, by questionnaire from the GP and by scrutinizing information from hospital discharge records in case of admittance or referral.

Overall, follow-up information was available for 94% of the population of the present study. Compared to subjects included in the present study, subjects without follow-up on average were 3.5 years older (73.9 years), had a lower prevalence of hypertension (25% versus 30%) and diabetes (10% versus 14%). No other differences in baseline characteristics were found.

Classification of events was based on the International Classification of Diseases, 10th edition (ICD-10)[16]. We defined cardiac mortality as death from myocardial infarction (ICD-10: I21-24), chronic ischemic heart disease (ICD-10: I25), pulmonary embolism or other pulmonary heart disease (ICD-10: I26-28), cardiomyopathy (ICD-10: I42-43), cardiac arrest (ICD-10: I46), arrhythmias (ICD-10:I47-49), heart failure (ICD-10: I50), or sudden cardiac death. Sudden cardiac death was defined as death occurring instantaneously or within 1 hour after onset of symptoms or unwitnessed death, in which a cardiac cause could not be excluded[17,18].

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

ECG interpretation and measurements

A 12-lead resting ECG was recorded with an ESAOTE-ACTA cardiograph at a sampling frequency of 500 Hz, and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain ECG measurements and interpretations. The MEANS program has been extensively evaluated[19-21].

The MEANS program determines the overall QT interval for all twelve leads together on a representative beat, which results from selective averaging of dominant beats. To adjust QT for heart rate we used five formulas that have also been used in other population-based studies:

1) Bazett's formula[8]: $QTc = QT*RR^{1/2}$;
2) Fredericia's cubic root[22]: $QTc = QT*RR^{1/3}$;
3) Linear regression formula[10]: $QTc = QT + \beta*(1-RR)$ with $\beta=0.140$ in men and $\beta=0.163$ in women.
4) The normogram method[12]: $QTc= QT + \beta*(1-RR)$, with $\beta=0.116$ for heart rates less than 60 beats per minute, $\beta= 0.156$ for heart rates from 60 through 99 beats per minute and $\beta= 0.384$ for heart rates of 100 beats per minute or more.
5) QT index (QTI)[11]: QTI=QT/QTp, where QTp is the predicted interval and equals QTmax / (1 + 0.01*HR), with QTmax=656 ms, and HR is the heart rate in beats per minute.
In formula 1 to 4, QTc can be interpreted as the length of the QT interval at a heart rate of 60 beats per minute. In formula 5, QTI reflects the length of the measured QT interval relative to the predicted QT interval. For example, a QTI of 110 can be interpreted as a 10% prolongation of the QT interval.

Left ventricular hypertrophy (LVH) was determined using voltage as well as repolarization criteria. Negative T-waves were defined as negative T-wave deflections of at least 1.0 mm in any of leads I-III, aVR, aVF, and V2-V6.

Data Analysis

Differences in baseline characteristics between those with and without follow-up data were examined by means of one way analysis of covariance, adjusting for age

and gender when appropriate.

To evaluate whether certain patient characteristics could confound the relationship between QTc and the endpoints studied, differences in the distribution of cardiovascular risk indicators between subjects in quartiles of Bazett's QTc interval were examined through the use of one-way analysis of covariance, adjusting for age and gender.

For the five correction formulas under study, heart-rate adjusted QT values were categorized in sex-specific quartiles. By means of Cox' proportional hazards analysis, age- and sex-adjusted hazards ratios for cardiac and all-cause mortality for subjects in the three highest quartiles, with the lowest quartile as a reference group, were calculated for each formula separately. We adjusted for two sets of confounders: (1) age and sex, and (2) all potential confounders resulting from the analysis of covariance.

Influence of age and history of myocardial infarction on the risk for cardiac death

Table 1. General characteristics of the study population. Values are means (standard deviation) or percentages. P-values are presented for equality of values in sex-specific quartiles of Bazett's QTc interval, adjusted for age and sex using one-way analysis of covariance.

Characteristics	All	Q1*	Q2†	Q3‡	Q4§	p-value
Age (y)	68.2 (8.7)	67.2	68.2	68.2	71.4	<0.01
Systolic blood pressure (mmHg)	139.1 (22.2)	136.9	138.6	138.9	141.6	<0.01
Diastolic blood pressure (mmHg)	73.6 (11.5)	71.9	73.1	73.8	75.3	<0.01
Body mass index (kg/m^2)	26.3 (3.7)	26.0	26.1	26.5	26.8	<0.01
Current cigarette smoking (%)	21.4	19.0	20.2	24.1	22.3	<0.01
Serum cholesterol (mmol/l)	6.7 (1.2)	6.6	6.6	6.7	6.7	NS
Hypertension (%)	29.1	26.6	27.1	27.3	35.1	<0.01
Diabetes mellitus (%)	11.9	9.6	9.6	11.7	16.2	<0.01
History of MI‖ (%)	12.2	11.1	9.3	11.5	16.7	<0.01
History of angina pectoris (%)	6.5	6.6	6.9	6.2	6.2	NS
Electrocardiographic LVH¶ (%)	4.7	5.7	4.1	3.5	5.6	<0.01
Negative T-wave (%)	7.4	9.3	6.2	6.7	7.6	<0.05

*Q1: lowest quartile of QTc (<406 ms in men; <418 ms in women)
†Q2: second quartile of QTc (406-421 ms in men; 418-432 ms in women)
‡Q3: third quartile of QTc (421-437 ms in men; 432-446 ms in women)
§Q4: highest quartile of QTc (>437 ms in men; >446 ms in women)
‖ MI = myocardial infarction; ¶ LVH= left ventricular hypertrophy

associated with prolonged QTc was examined through Cox' proportional hazards analysis within strata of these possible effect modifiers.

To estimate the risk associated with published threshold values for prolonged QTc interval, we studied risk for cardiac and all-cause mortality of subjects with Bazett's QTc intervals above 420 ms, 440 ms, and 460 ms, relative to those with Bazett's QTc-intervals below 420 ms.

All analyses were performed for men and women separately.

Results

The participants of the present study were on average 68 years old. Most cardiovascular risk indicators under study, apart from serum cholesterol and history of angina pectoris, showed a positive association with heart-rate adjusted QT-interval duration (Table 1).

Prognostic value of heart-rate adjusted QT interval obtained with different formulas

Risk for all-cause mortality (Table 2) and cardiac mortality (Table 3) in the three upper quartiles of heart-rate adjusted QT interval, relative to those in the lowest quartile, was hardly influenced by the correction formula used. For men, the highest age-adjusted hazard ratios (HR) in the fourth quartile were obtained for QTI, both for all-cause mortality (HR 1.8; 95%CI 1.2-2.9) and cardiac mortality (HR 1.7; 95%CI 0.8-3.6). For women, the highest hazard ratios in the fourth quartile were obtained for Bazett's formula, both for all-cause mortality (HR 1.9; 95%CI 1.3-2.9) and cardiac mortality (HR 2.4; 95%CI 1.1-5.3).

In all formulas, but least pronounced in Bazett's formula, the risk for cardiac mortality in the second quartile of heart-rate adjusted QT interval seemed to be lower than in the first quartile, suggesting a J- or U-shaped curve, especially in women.

Depending on the correction formula used, men in the highest quartile of heart-rate adjusted QT interval had a 50 to 80 percent increased risk for all-cause mortality and a non statistically significant 30 to 70 percent increased risk for cardiac mortality. In women in the highest quartile of heart-rate adjusted QT interval the increa-

Table 2. Age-adjusted hazard ratios for *all-cause mortality* of men and women in the three highest quartiles of heart-rate adjusted QT, relative to those in the lowest quartile, using five different formulas to adjust the QT interval for heart rate.

Formula	Group	Percentile			Hazard ratio	Hazard ratio	Hazard ratio
		25th	50th	75th	Q2*	Q3†	Q4‡
1. Bazett[8]	M§	406	421	437	0.9 (0.6-1.4)	1.2 (0.8-1.9)	1.5 (1.0-2.3)
	F¦	418	432	446	1.3 (0.8-2.0)	1.5 (1.0-2.3)	1.9 (1.3-2.9)
	All¶				1.2 (0.8-1.6)	1.4 (1.0-2.0)	1.8 (1.3-2.4)
2. Fredericia[22]	M	401	413	426	1.0 (0.6-1.6)	1.4 (0.9-2.2)	1.6 (1.1-2.4)
	F	408	420	432	1.0 (0.7-1.5)	1.1 (0.7-1.7)	1.6 (1.1-2.3)
	All				1.0 (0.7-1.3)	1.2 (0.9-1.7)	1.6 (1.2-2.1)
3. Linear	M	400	411	424	0.9 (0.5-1.4)	1.5 (1.0-2.3)	1.5 (1.0-2.3)
regression[10]	F	410	421	433	1.0 (0.7-1.6)	1.1 (0.7-1.7)	1.7 (1.2-2.4)
	All				0.9 (0.7-1.3)	1.3 (1.0-1.7)	1.6 (1.2-2.1)
4. Normogram[12]	M	403	414	427	1.1 (0.7-1.7)	1.6 (1.0-2.5)	1.7 (1.1-2.6)
	F	410	421	433	1.1 (0.7-1.7)	1.2 (0.8-1.9)	1.7 (1.2-2.5)
	All				1.1 (0.8-1.5)	1.4 (1.0-1.9)	1.7 (1.3-2.2)
5. QTindex[11]	M	98.3	101.5	104.8	1.3 (0.8-2.1)	1.8 (1.1-2.9)	1.8 (1.2-2.9)
	F	100.5	103.4	106.6	1.0 (0.6-1.5)	1.2 (0.8-1.8)	1.8 (1.2-2.6)
	All				1.1 (0.8-1.5)	1.4 (1.1-2.0)	1.8 (1.3-2.3)

*Q2 = second quartile; †Q3 = third quartile; ‡Q4 = fourth quartile

§M= male; ¦F= female;¶ All: combining sex-specific quartiles

sed risks for cardiac mortality were more pronounced than in men.

All risk estimates were independent from other cardiovascular risk indicators, as additional adjustment for body-mass index, cigarette smoking, hypertension, diabetes mellitus, history of MI, electrocardiographic LVH, and presence of negative T-waves did not materially change the results.

Subgroup analysis showed that the risk for all-cause mortality associated with heart-rate adjusted QT was more pronounced in those under 70 years of age than in older subjects (HR of the highest versus lowest quartile of Bazett's QTc interval 2.8; 95%CI 1.5-5.2 versus 1.5; 1.1-2.0). History of MI did not modify the association of all-cause and cardiac mortality with heart-rate adjusted QT, but the number of cases of cardiac death was too small to allow for definite conclusions.

Table 3. Age-adjusted hazard ratios for *cardiac mortality* of men and women in the three highest quartiles of heart-rate adjusted QT, relative to those in the lowest quartile, using five different formulas to adjust the QT interval for heart rate.

Formula	Group	Percentile			Hazard ratio	Hazard ratio	Hazard ratio
		25th	50th	75th	Q2*	Q3†	Q4‡
1. Bazett[8]	M§	406	421	437	0.7 (0.3-1.5)	0.7 (0.3-1.5)	1.3 (0.7-2.4)
	F¦	418	432	446	1.0 (0.4-2.6)	1.8 (0.8-4.1)	2.4 (1.1-5.3)
	All¶				0.8 (0.5-1.5)	1.1 (0.6-1.9)	1.7 (1.0-2.7)
2. Fredericia[22]	M	401	413	426	1.0 (0.4-2.2)	1.1 (0.5-2.5)	1.6 (0.8-3.3)
	F	408	420	432	0.5 (0.2-1.3)	1.2 (0.5-2.5)	1.9 (0.8-4.4)
	All				0.7 (0.4-1.3)	1.1 (0.7-2.0)	1.7 (1.1-2.8)
3. Linear	M	400	411	424	0.9 (0.4-2.1)	1.2 (0.6-2.7)	1.6 (0.8-3.3)
regression[10]	F	410	421	433	0.5 (0.2-1.4)	1.3 (0.6-2.9)	2.1 (1.1-4.2)
	All				0.7 (0.4-1.4)	1.3 (0.7-2.2)	1.8 (1.1-3.0)
4. Normogram[12]	M	403	414	427	1.0 (0.5-2.3)	1.0 (0.5-2.2)	1.5 (0.5-2.3)
	F	410	421	433	0.6 (0.2-1.6)	1.3 (0.6-2.9)	2.1 (1.0-4.1)
	All				0.8 (0.5-1.5)	1.3 (0.7-2.2)	1.7 (1.1-2.9)
5. QTindex[11]	M	98.3	101.5	104.8	1.2 (0.6-2.7)	1.1 (0.5-2.5)	1.7 (0.8-3.6)
	F	100.5	103.4	106.6	0.4 (0.2-1.2)	1.1 (0.5-2.3)	1.7 (0.9-3.3)
	All				0.8 (0.5-1.5)	1.1 (0.6-1.9)	1.7 (1.0-2.7)

*Q2 = second quartile; †Q3 = third quartile; ‡Q4 = fourth quartile

§M= male; ¦F= female;¶ All: combining sex-specific quartiles

Risk associated with published threshold values for prolonged QTc

Participants with Bazett's QTc intervals above 420 ms had an increased risk for all-cause mortality (HR 1.6; 95%CI 1.2-2.1 in men and HR 1.6; 95%CI 1.1-2.2 in women). For this threshold value, the positive association between QT interval and cardiac mortality was not statistically significant in both men and women (HR 1.3; 95%CI 0.8-2.2 in men and HR 1.5; 95%CI 0.9-2.9 in women). Increasing the threshold for prolonged QTc to 440 ms resulted in higher risk estimates for all-cause mortality (HR 1.8; 95%CI 1.3-2.5 in men and HR 1.7; 95%CI 1.2-2.5 in women) and cardiac mortality (HR 1.6; 95%CI 0.9-2.9 in men and HR 1.9; 95%CI 1.0-3.7 in women). Those with Bazett's QTc intervals above 460 ms had a more than twofold risk for all-cause mortality (HR 2.4; 95%CI 1.5-3.8 in men and HR 2.1; 95%CI 1.4-

3.2 in women) and cardiac mortality (HR 2.2; 95%CI 1.0-5.2 in men and HR 2.3; 95%CI 1.1-5.1 in women).

Overall, the risk for all-cause mortality associated with a certain threshold value was somewhat higher in men than in women, while the risk for cardiac mortality associated with a certain threshold value was higher in women than in men.

Discussion

Results from the present study show that prolonged heart-rate adjusted QT interval predicts all-cause and cardiac mortality in older men and women, independent from other cardiovascular risk indicators. The risk for all-cause and cardiac mortality associated with heart-rate corrected QT is hardly influenced by the formula used for correction.

Our results support the association between prolonged heart-rate adjusted QT and cardiac mortality reported in two previous studies in non-hospitalized populations in the Netherlands[5,6]. In these studies measurement of QT interval was performed manually in a subset of leads, and absolute values of QTc interval are systematically smaller than those measured by the MEANS program in the population of the Rotterdam Study. In the Zutphen Study[6], elderly men with Bazett's QTc intervals above 420 ms had a threefold risk for coronary heart disease death (HR 3.1;95%CI 1.3-7.6). This is even higher than the risk for cardiac mortality associated with prolonged QTc above 460 ms in men in the Rotterdam Study. This may partly be explained by the definition of endpoints, as our definition of cardiac mortality is wider than the definition of coronary heart disease mortality in the Zutphen Study. In the Dutch Civil Servants Study[5] among 3,000 healthy middle-aged men and women, Bazett's QTc above 440 ms was associated with a twofold risk for both all-cause mortality (odds ratio (OR) 1.8 in men and OR 1.9 in women) and cardiac mortality (OR 2.0 in men and OR 1.9 in women), after 15 years. No clear differences in risk estimates between men and women, such as we found, were reported. This may partly be explained by differences in population characteristics, as our population is older and selective survival may play a role, especially in men. Men with heart disease die on an earlier age than women and the men who survive until older

age may be healthier than women of the same age.

It has been suggested that the absence of the association between Bazett's QTc interval and cardiac death in the Framingham Heart Study[7] may be explained by a U-shaped relationship, conferring increased mortality in those with short and in those with prolonged QT intervals. Although we did find a U-shaped relationship of heart-rate adjusted QT with cardiac mortality in women with all correction formulas, this was least pronounced in Bazett's formula, and virtually absent for all formulas in men. In an additional analysis (data not shown) we found a statistically significant positive linear association of Bazett's QTc interval with all-cause and cardiac mortality in men and women. This suggests that the U- or J-shaped association is weak and the risk associated with QT prolongation is present over the whole range of QT interval duration.

The relationship between prolonged heart-rate adjusted QT and future cardiac mortality may be attributed to ventricular electrical instability and dispersion of repolarization, which give rise to early afterdepolarizations[23]. As in these mechanisms parasympathetic activity exhibits beneficial effects, an unfavorable balance in sympathetic and parasympathetic activity may play an important role. This is in accordance with the positive association of QTc interval with blood pressure and heart rate. In addition, patchy myocardial fibrosis, with or without clinical symptoms, may lead to ventricular electrical instability and dispersion of repolarization. This is supported by the positive associations of heart-rate adjusted QT interval with a history of MI in our study.

Women have longer heart-rate adjusted QT intervals than men (median of Bazett's QTc 432 ms versus 421 ms in the present study). It has been suggested that, based on the distribution of heart-rate adjusted QT interval, the threshold for prolonged QT should be higher in women than in men. However, the risk for cardiac mortality associated with certain threshold levels of prolonged QTc is at least as high in women as in men. Therefore, the threshold for prolonged heart-rate adjusted QT in women should be comparable to that in men.

As the prevalence of prolonged heart-rate adjusted QT is higher and the relative risk for cardiac mortality is somewhat higher in women than in men, the proportion of

cardiac deaths attributable to prolonged QT interval is larger in women than in men. It should be emphasized, however, that the absolute risk for cardiac death is larger in men than in women.

The risk associated with heart-rate corrected QT interval is hardly influenced by the correction formula used. In an additional analysis (data not shown) the unadjusted QT interval itself had hardly any prognostic value for cardiac mortality. When we added RR interval as an independent variable to the model, we found hazard ratios similar to those for Bazett's formula. Although all formulas may be used for risk stratification, there is no reason to discard Bazett's formula, which is most frequently used in reported studies as well as in the medical practice.

In this study we used the extensively validated MEANS computer program[21,24] to measure the QT interval, without supervision of human ECG interpreters. The use of a computer program offers a standardized and efficient way to interpret ECGs, without the intra- and inter-observer variation of human observers measuring and interpreting ECGs. The results of the present study imply, that heart-rate adjusted QT interval obtained with the MEANS program can be used to identify subjects at risk for future cardiac and all-cause mortality in the population at large and in a clinical setting. As system-specific thresholds for prolonged QT interval corrected with Bazett's formula, obtained by the MEANS program, 440 or 460 ms can be used. If another measurement technique is used, absolute values of QTc interval and precision of the QT measurement may differ systematically from our method[21], and this would require modifications of the thresholds applied.

In conclusion, QTc interval is an independent predictor of cardiac and all-cause mortality in men and women. In clinical practice, prolonged heart-rate adjusted QT can be easily determined, manually as well as by computer, and may be used to identify subjects at increased risk for future mortality.

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CHAPTER 3.2

QTc DISPERSION PREDICTS CARDIAC MORTALITY IN THE ELDERLY: THE ROTTERDAM STUDY

Abstract

Background Increased QTc dispersion has been associated with an increased risk for ventricular arrhythmias and cardiac death in selected patient populations. We examined the association between computerized QTc-dispersion measurements and mortality in a prospective analysis of the population-based Rotterdam Study among men and women aged 55 years or older.

Methods and Results QTc dispersion was computed by the Modular ECG Analysis System (MEANS) as the difference between the maximum and minimum QTc-interval in 12 leads and in 8 leads (i.e. the 6 precordial leads, the shortest extremity lead and the median of the 5 other extremity leads). After exclusion of those without a digitally stored ECG the population consisted of 2358 men and 3454 women. During the 3 to 6.5 (mean 4) years of follow-up, 568 (9.8%) subjects died. Degree of QTc dispersion was categorized into tertiles. Data were analyzed using Cox' proportional hazards model, adjusting for age. For QTc dispersion in 8 leads, those in the highest tertile relative to the lowest tertile, had a twofold risk for cardiac death (hazard ratio 2.5; 95%CI 1.6-4.0) and sudden cardiac death (HR 1.9; 95%CI 1.0-3.7), and a forty percent increased risk for total mortality (HR 1.4; 95%CI 1.2-1.8). Additional adjustment for potential confounders, including history of myocardial infarction, hypertension, and overall QTc, did not materially change the risk estimates. Hazards ratios for QTc dispersion in 12 leads were comparable to those found for QTc dispersion in 8 leads.

Conclusion QTc dispersion is an important predictor of cardiac mortality in older men and women.

Chapter 3.2

Introduction

Recent clinical studies have suggested that the interlead variability of the QT interval in the standard electrocardiogram (ECG), defined as QT dispersion, reflects regional differences in ventricular repolarization.[1,2] Increased dispersion of recovery time is believed to increase the risk for serious ventricular arrhythmias.[3-6] It is hypothesized that an important entity underlying QT dispersion is patchy myocardial fibrosis, resulting from myocardial ischemia, ventricular dilatation, and neurohormonal activation.[3,7] This is supported by findings of increased QT dispersion in patients with acquired long QT interval,[1,8] myocardial infarction,[2,9,10] hypertrophic cardiomyopathy,[11,12] hypertension and left ventricular hypertrophy,[13] and in diabetic patients with autonomic neuropathy.[14] Moreover, QT dispersion has been associated with increased risk for ventricular arrhythmias and sudden death in patients with chronic heart failure,[15] mitral valve prolaps,[16] myocardial infarction,[17] and familial long QT syndrome,[1] and with an increased risk for cardiac mortality in patients with peripheral arterial disease[7] and myocardial infarction.[18]

In these previous studies QT dispersion was measured retrospectively and manually in a limited number of cases and controls, by one or more observers using a digitizing tablet. Evidence from large, prospective studies on the prognostic implications of QT dispersion is lacking. The use of a computer program to measure QT dispersion facilitates large studies and excludes intra- and interobserver variability.

We assumed that the risk associated with increased QT dispersion not only applies to patient populations, but also to the population at large. Therefore, we examined whether increased QT dispersion, established by computer, was associated with a higher risk for total mortality, cardiac death, sudden cardiac death, and non-fatal cardiac disease in a large non-hospitalized population of older adults.

Methods

Study population and baseline data collection

This study is part of the Rotterdam Study, a population-based cohort study aimed at

assessing the occurrence and risk factors for chronic diseases in the elderly. Objectives and methods of the Rotterdam Study are described in detail elsewhere.[19] Briefly, in the Rotterdam Study all men and women aged 55 years or older, living in the Rotterdam district Ommoord, were invited to participate (response rate 78%). Of 7,129 participants, the baseline data, collected from 1990 to 1993, included an ECG, information on history of cardiovascular disease, established cardiovascular risk factors and use of medications.

A digitally stored ECG was available in 6,160 (86%) participants. An ECG was missing in 14% of the participants, mainly due to temporary technical problems of the ECG recorder. Blood pressure was calculated as the average of two consecutive measurements with a random zero mercury manometer. Body mass index was calculated as weight/length^2 in kg/m^2. Hypertension was defined as systolic blood pressure above 160 mmHg or diastolic blood pressure above 95 mmHg or use of anti-hypertensive medication for the indication hypertension. Diabetes mellitus was defined as a non-fasting blood glucose above 11.1 mmol/l or use of anti-diabetic medication. History of myocardial infarction (MI) was defined as self-reported MI with hospital admission, or MI on the ECG. Presence of angina pectoris was established through the Rose questionnaire.[20]

After exclusion of 345 subjects without follow-up data, mainly because they moved to unknown addresses, and 3 subjects with ECGs of poor technical quality which could not be interpreted by the computer program, the study population consisted of 2,358 men and 3,454 women.

Follow-up procedures

The follow-up period, starting at the baseline examination and in the present analysis lasting until April 1996, was 3 to 6.5 (mean 4) years. With respect to the vital status of participants, information was obtained at regular intervals from the municipal health service in Rotterdam. Information on fatal and non-fatal endpoints was obtained from the general practitioners (GPs) working in the study district of Ommoord. These GPs, covering around 85% of the cohort, all have their practice computerized and report possible fatal and non-fatal events of participants on computer file to the Rotterdam Study data-center on a regular basis. All possible

events reported by the GP were verified by research physicians from the Rotterdam Study through patient records of the participating GPs and medical specialists. In April 1996, the medical records of participants with GPs from outside the Ommoord area, around 15% of the cohort, were checked by research physicians and of all possible events additional information for coding was collected.

Cause and circumstances of death were established, shortly after reporting of death by the municipal health service or the GP, by questionnaire from the GP and by scrutinizing information from hospital discharge records in case of admittance or referral.

Overall, complete follow-up information was available for 94% of the population of the Rotterdam study. Participants in whom no follow-up information was available were similar to those included in the present study. Those without follow-up were on average 3.5 years older (73.9 years), had a lower prevalence of hypertension (25% versus 30%), and diabetes (10% versus 14%). No other differences in baseline characteristics were found.

Classification of fatal and non-fatal events was based on the International Classification of Diseases, 10th version.[21] We defined cardiac mortality as death from myocardial infarction (ICD-10: I21-24), chronic ischemic heart disease (ICD-10: I25), pulmonary embolism or other pulmonary heart disease (ICD-10: I26-28), cardiomyopathy (ICD-10: I42-43), cardiac arrest (ICD-10: I46), arrhythmias (ICD-10:I47-49), heart failure (ICD-10: I50), or sudden cardiac death. Sudden cardiac death was defined as death occurring instantaneously or within 1 hour after onset of symptoms or unwitnessed death, in which a cardiac cause could not be excluded.[22, 23] Non-fatal cardiac events were defined as myocardial infarction (ICD-10: I21-24), chronic ischemic heart disease (ICD-10: I25), coronary artery bypass graft (no ICD-10 code), or percutaneaous transluminal coronary angioplasty (no ICD-10 code).

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

ECG interpretation and measurements

A 12-lead resting ECG was recorded with an ESAOTE-ACTA cardiograph with a sampling frequency of 500 Hz, and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain ECG measurements and diagnostic interpretations. The MEANS program has been extensively evaluated by the developers themselves and others.[24-26] To adjust QT for heart rate, we calculated QT_c according to Bazett's formula: $QT_c = QT/\sqrt{RR}$, where RR is the RR interval in seconds.[27]

Normally, the MEANS program determines an overall end of T waves for all 12 leads together using a representative beat, that results from selective averaging of dominant beats, and thus QTc dispersion in not disclosed. The program was, therefore, adjusted to determine the end of the T wave per lead. Taking the location of the overall end of the T wave as a starting point, the program searches forward and backward to establish the lead-specific end of the T wave. If the T wave amplitude is less than 50 μV, the T wave is considered to be flat and the lead is excluded from further analysis. QTc dispersion is determined as the difference between the maximum and minimum QTc in all considered leads. Analogously, QT dispersion is determined as the difference between the maximum and minimum QT interval, without correction for heart rate, in all considered leads.

QTc dispersion measured by the MEANS program was validated against two human observers on a set of 100 ECGs (unpublished data, 1997). Both observers independently marked the end of the T wave in each lead with the cursor on a high-resolution computer screen. We found a mean QTc dispersion difference between MEANS and pooled data from both observers of 5.1 (SD 29.3) ms. These results are comparable with the interobserver variability between the two human observers (mean 6.7 (SD 28.4) ms). Therefore, we concluded that the performance of the program was comparable to that of human observers.

Left ventricular hypertrophy (LVH) was determined using voltage as well as repolarization criteria. A negative T-wave was defined as at least 1.0 mm negative deflection of the T-wave in lead II, aVF, or the precordial leads.

Chapter 3.2

Lead selection for QTc dispersion

Traditionally, QTc dispersion is defined as the difference between the maximum and minimum QTc-interval in 12 leads. However, in the standard 12-lead ECG, only two of the six extremity leads are actually recorded. The other four are derived mathematically from these two leads.

It can be shown that, if there is a shortest T wave in one of the extremity leads, the other five extremity leads must have the same end of T (see appendix). As a consequence, true QTc dispersion cannot exist among these leads and QTc dispersion measured in these leads can only be the result of measurement inaccuracy.

Therefore, we defined QTc dispersion as the difference between the maximum and the minimum QTc interval in 8 leads, i.e. the 6 precordial leads, the shortest extremity lead and the median of the 5 other extremity leads. In addition, we computed QTc dispersion in 12 leads. ECGs in which QTc dispersion could be measured in less then 9 of the 12 leads were excluded (n=16 of the 5812 subjects in the present study).

Data Analysis

Differences in baseline characteristics between those with and without follow-up data were examined using one-way analysis of covariance, adjusting for age and gender when appropriate.

Degree of QTc dispersion in both 8 and 12 leads was categorized in tertiles, with inter-tertile values of 39 ms and 60 ms (in 8 leads), and 47 ms and 66 ms (in 12 leads) respectively. Also QT dispersion in 8 and 12 leads was categorized in tertiles. All analyses were performed for both 8 and 12 lead measures of dispersion.

To evaluate the association between QTc dispersion and potentially confounding factors, differences in the distribution of selected baseline characteristics between subjects in tertiles of QTc dispersion were examined by means of one-way analysis of covariance, adjusting for age and gender when appropriate.

Cox' proportional hazards model was used to examine the risk for cardiac and total

mortality and non-fatal cardiac events in relation to tertile of baseline QTc and QT dispersion, adjusted for two sets of confounders: (1) age and gender (the latter only when non sex-specific risks were estimated), and (2) all possible confounders, excluding other ECG abnormalities, resulting from the analysis of covariance ($p<0.05$). The lowest tertile of QTc dispersion or QT dispersion was taken as the reference category. In order to minimize the effect of missing data in the multivariate analysis, missing values of categorical variables were replaced by dummies. Missing values of continuous variables were replaced by the average value and a dummy variable (to indicate that the participant's individual value was missing) was added to the model.[28]

To compare predictive value of QTc dispersion with that of other commonly used cardiovascular risk indicators, age and sex-adjusted hazard ratios for cardiac mortality of important cardiovascular risk indicators were computed.

Influence of age and history of MI on the risk for cardiac death associated with

Table I. Baseline characteristics of study participants according to tertiles of QTc dispersion, values are means (standard deviation) or percentages. P-values are presented for equality of tertile specific values (T1-T3) for tertiles of QTc dispersion in 8 leads, adjusted for age and gender using one way analysis of covariance.

Characteristic	All (n=5812)	T1* <39 ms	T2† 39 - 60 ms	T3‡ >60 ms	p-value
Age	69.3 (9.0)	68.4	69.1	70.0	<0.01
Gender (% women)	59.4	58.4	59.1	60.5	NS
Systolic blood pressure	139.4 (22.4)	138.0	138.5	141.3	<0.01
Diastolic blood pressure	73.5 (11.6)	73.1	73.2	74.0	<0.05
Body mass index (kg/m^2)	26.3 (3.7)	26.5	26.4	26.2	NS
Cholesterol (mmol/l)	6.6 (1.2)	6.6	6.6	6.6	NS
Current smoking (%)	23.1	22.0	23.0	23.9	NS
Use of cardiovascular medication (%)	36.0	34.4	36.1	37.2	NS
Hypertension (%)	29.6	27.4	28.4	32.2	<0.01
Diabetes (%)	12.7	11.2	11.9	14.4	<0.01
Angina pectoris (%)	6.8	7.1	7.5	6.0	NS
Myocardial infarction (%)	13.0	11.5	12.5	14.5	<0.05
Overall QTc (ms)	431 (29)	429	430	434	<0.01
Negative T-wave (%)	7.8	5.6	7.6	9.4	<0.01
LVH§ on ECG (%)	4.9	3.4	4.8	6.1	<0.01

* T1= lowest tertile of QTc dispersion; † T2= middle tertile of QTc dispersion; ‡ T3= highest tertile of QTc dispersion; § LVH=left ventricular hypertrophy

increased QTc dispersion was examined through subgroup analyses for these possible effect modifiers.

Results

Baseline characteristics of participants in different tertiles of QTc dispersion are presented in table I. Statistically significant differences existed between the three comparison groups with regard to age, systolic and diastolic blood pressure, hypertension, diabetes mellitus, history of MI, overall QTc interval, presence of negative T-waves, and electrocardiographic LVH.

The distribution of QTc dispersion, measured in both 8 and 12 leads, in cases of cardiac death during the follow-up period was shifted to the right compared to survivors (Figure 1). In addition, QTc dispersion in 12 leads was shifted to the right compared to the distribution in 8 leads, reflecting larger dispersion in 12 leads than in 8 leads.

During the 3 to 6.5 (mean 4) years of follow-up, 568 (9.8%) subjects died; 166 (2.9%) died of a cardiac cause and 73 (1.3%) died suddenly. In 193 (3.3%) of the subjects at least one non-fatal cardiac event occurred. Cardiac mortality according to tertile of QTc dispersion is presented in men and women is presented in Figure 2a and 2b. It appears that in men increased risk for cardiac mortality starts at a lower level of QTc dispersion than in women.

Participants in the highest tertile relative to the lowest tertile of QTc dispersion in 8 leads, had a more than twofold age- and sex-adjusted risk for cardiac death (hazard ratio 2.5; 95%CI 1.6-4.0) and sudden cardiac death (HR 1.9; 95%CI 1.0-3.7), and an increased risk for total mortality (HR 1.4; 95%CI 1.2-1.8) and non-fatal cardiac events (HR 1.3; 95%CI 0.9-1.8), although the latter result was not statistically significant (Table II). Additional adjustment for hypertension, diabetes, and history of MI, did not materially change hazards ratio estimates for cardiac and all-cause mortality, although the 95% confidence intervals of the adjusted hazards ratios for sudden death events included one. Inclusion of other ECG abnormalities, notably LVH, negative T waves and maximum QTc interval, in this model did not influence the results.

Table 2. Hazards ratios in subjects in the middle (T2) and highest (T3) tertile relative to the lowest tertile of QTc dispersion measured in 8 leads, adjusted for age and sex (Model A) and for all possible confounders (Model B).

End point	Subgroup	Model A*		Model B†	
		T2‡	T3§	T2	T3
		39-60 ms	>60 ms	39-60 ms	>60 ms
Total mortality	All	1.3 (1.1-1.7)	1.4 (1.2-1.8)	1.3 (1.0-1.6)	1.3 (1.1-1.6)
	Men	1.5 (1.0-2.0)	1.4 (1.0-1.9)	1.4 (1.0-2.0)	1.2 (0.8-1.6)
	Women	1.2 (0.9-1.7)	1.5 (1.1-2.0)	1.1 (0.8-1.5)	1.4 (1.0-1.9)
Cardiac mortality	All	2.1 (1.3-3.4)	2.5 (1.6-4.0)	1.9 (1.2-3.1)	2.0 (1.3-3.2)
	Men	3.3 (1.6-6.9)	2.5 (1.2-5.2)	3.2 (1.5-6.6)	1.8 (0.9-3.9)
	Women	1.2 (0.6-2.5)	2.5 (1.4-4.6)	1.1 (0.5-2.2)	2.1 (1.2-4.0)
Sudden cardiac death	All	1.8 (0.9-3.5)	1.9 (1.0-3.7)	1.7 (0.8-3.3)	1.6 (0.8-3.1)
	Men	3.0 (1.1-8.1)	2.4 (0.9-6.6)	3.0 (1.1-8.1)	2.0 (0.7-5.6)
	Women	0.9 (0.3-2.5)	1.6 (0.6-3.8)	0.9 (0.3-2.4)	1.5 (0.6-3.6)
Non-fatal cardiac events	All	0.9 (0.6-1.3)	1.3 (0.9-1.8)	0.8 (0.6-1.2)	1.1 (0.8-1.6)
	Men	0.8 (0.5-1.3)	1.2 (0.8-1.8)	0.8 (0.5-1.3)	1.0 (0.5-1.6)
	Women	1.0 (0.5-2.0)	1.6 (0.9-3.0)	0.9 (0.5-1.9)	1.5 (0.8-2.8)

Table 3. Hazards ratios in subjects in the middle (T2) and highest (T3) tertile relative to the lowest tertile of QTc dispersion measured in 12 leads, adjusted for age and sex (Model A) and for all possible confounders (Model B).

End point	Subgroup	Model A*		Model B†	
		T2‡	T3§	T2	T3
		47-66 ms	>66 ms	47-66 ms	>66 ms
Total mortality	All	1.3 (1.0-1.6)	1.3 (1.1-1.6)	1.2 (1.0-1.6)	1.2 (0.9-1.4)
	Men	1.5 (1.1-2.1)	1.2 (0.8-1.6)	1.5 (1.1-2.0)	1.0 (0.7-1.4)
	Women	1.1 (0.8-1.5)	1.4 (1.1-1.9)	1.0 (0.8-1.4)	1.3 (1.0-1.7)
Cardiac mortality	All	1.9 (1.2-3.0)	2.2 (1.4-3.4)	1.7 (1.1-2.8)	1.8 (1.1-2.7)
	Men	2.9 (1.5-5.6)	1.9 (1.0-3.8)	2.7 (1.4-5.3)	1.4 (0.7-2.9)
	Women	1.2 (0.6-2.3)	2.4 (1.4-4.3)	1.1 (0.5-2.1)	2.0 (1.1-3.6)
Sudden cardiac death	All	1.8 (0.9-3.4)	1.7 (0.9-3.1)	1.2 (0.5-2.8)	1.9 (0.9-4.0)
	Men	2.1 (0.8-5.8)	1.9 (0.7-5.5)	3.6 (0.8-16.3)	4.7 (1.1-19.5)
	Women	1.8 (0.6-5.8)	2.6 (1.0-6.6)	0.7 (0.1-3.9)	2.0 (0.6-6.3)
Non-fatal cardiac events	All	0.9 (0.7-1.4)	1.3 (0.9-1.8)	1.0 (0.7-1.6))	1.4 (1.0-2.0)
	Men	0.9 (0.5-1.4)	1.3 (0.9-2.0)	0.9 (0.5-1.5)	1.3 (0.8-2.0)
	Women	1.2 (0.6-2.4)	1.2 (0.6-2.2)	1.4 (0.6-3.2)	1.4 (0.6-2.9)

* Model A: adjusted for age; † Model B: adjusted for age, overall QTc, and presence of hypertension, diabetes mellitus, history of myocardial infarction, negative T-wave, and left ventricular hypertrophy; ‡ T2=middle tertile of QTc dispersion; § T3= highest tertile of QTc dispersion.

QTc dispersion in both 8 and 12 leads ranks among the strongest predictors for cardiac mortality (Figure 3). The highest age- sex adjusted hazard ratios for cardiac mortality were found for LVH (HR 2.6; 95%CI 1.7-4.0) and QTc dispersion in 8 leads larger than 60 ms (HR 2.5; 95%CI 1.6-4.0), while in the multivariate model QTc dispersion in 8 leads larger than 60 ms was the strongest predictor for cardiac mortality, followed by history of MI (HR 2.0; 95%CI 1.5-2.5). The corresponding multivariate hazard ratio for cardiac death for QTc > 440 ms was identical to the age-and sex adjusted hazard ratio, notably 2.3 (95%CI: 1.0-2.1).

Subgroup analysis showed that the risk for cardiac death associated with increased QTc dispersion for participants in the highest relative to the lowest tertile of QTc dispersion was not modified by age, but was more pronounced in those without a history of MI (HR 3.5; 95%CI 1.8-6.9) than in those with a history of MI (HR 1.8;95% CI 0.8-3.9).

Figure 1. Distribution of QTc dispersion measured in 8 and 12 leads, in those who die from a cardiac cause and in survivors, among 5,812 men and women aged 55 year or older.

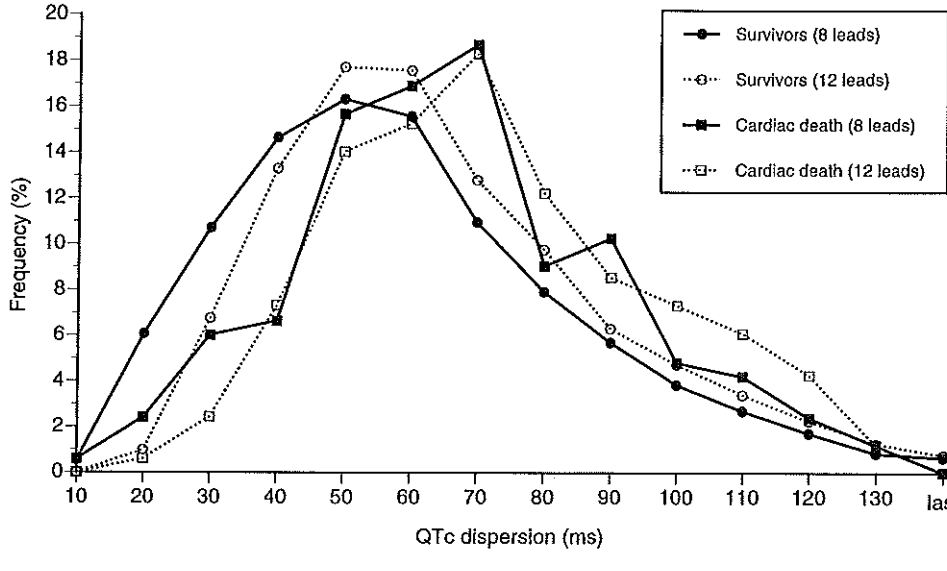


Figure 2a. Cardiac mortality (percentage) by tertile of QTc dispersion in 8 leads in men.

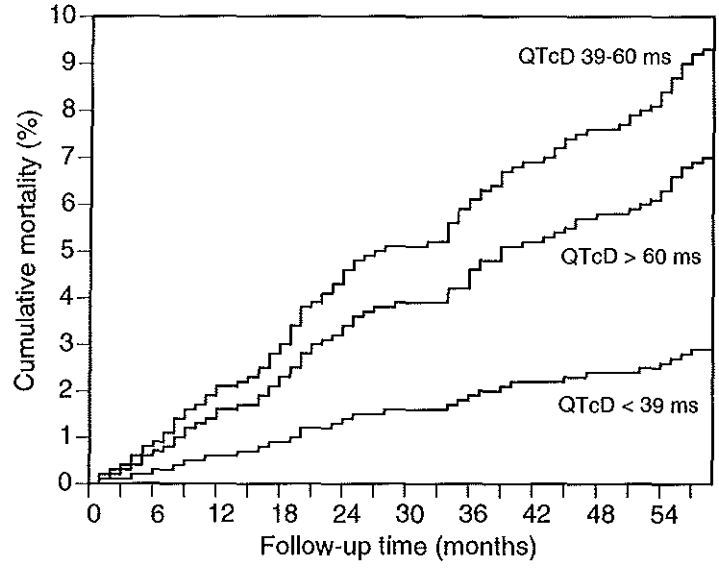
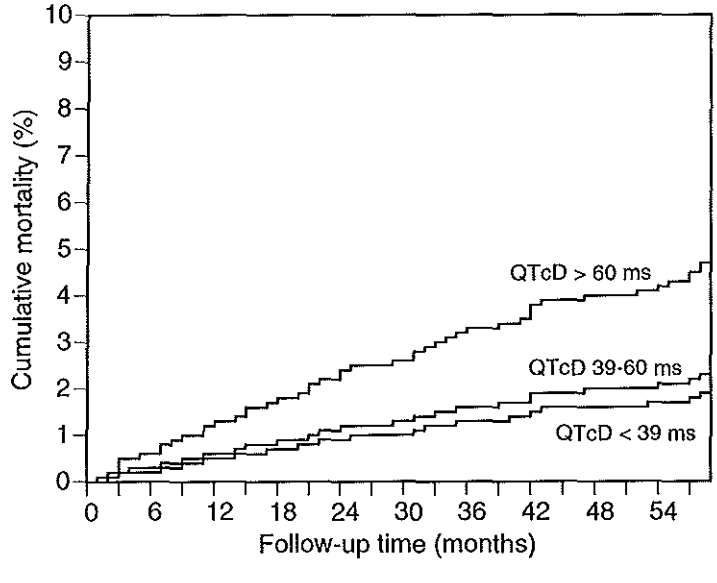


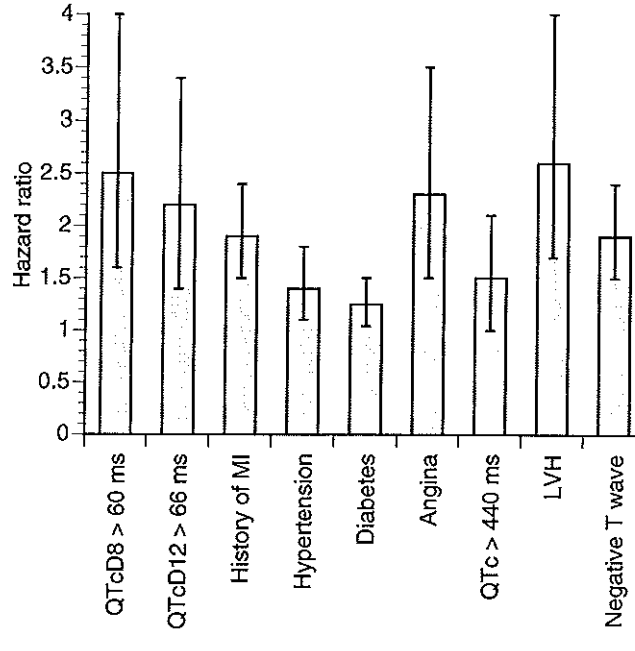
Figure 2b. Cardiac mortality (percentage) by tertile of QTc dispersion in 8 leads in women.



The risk estimates for the various endpoints associated with QT dispersion, without correction of the QT interval for heart rate, in 8 and 12 leads, were similar, but had wider confidence limits, compared to the risk estimates for QTc dispersion in 8 and 12 leads.

The risks associated with QTc dispersion based on 12 leads was very similar to the risk associated with QTc dispersion in 8 leads (Table III). Hazards ratios tended to be higher in QTc dispersion in 8 leads compared to QTc dispersion in 12 leads, but 95% confidence intervals hardly differed.

Figure 3. Age- ad sex adjusted hazard ratios QTc dispersion in 8 and 12 leads and other commonly used cardiovascular risk indicators and ECG abnormalities.



QTcD8 = QTc dispersion in 8 leads; QTcD12 = QTc dispersion in 12 leads

MI = myocardial infarction; LVH = left ventricular hypertrophy

Discussion

The results of this study show that increased QTc dispersion is a strong and independent risk factor for cardiac mortality in older men and women.

Previous studies were performed in patient populations. Their findings that QT dispersion is larger in those with myocardial infarction,[2, 9, 10] hypertension, left ventricular hypertrophy,[13] and in diabetes mellitus[14] are confirmed by ours. Increased risk for cardiac mortality associated with QTc dispersion has been reported in patients with peripheral artery disease[7] and myocardial infarction.[18] Our findings provide support for an association of increased QTc dispersion and cardiac death in those with and without coronary heart disease. However, differences in mean values of QTc dispersion in those who die from a cardiac cause compared to survivors, were much more pronounced in these earlier studies: 25 to 30 ms versus 4 to 6 ms in the Rotterdam Study. This may be explained by differences in severity of the underlying disease in the population at large compared to patient populations. Also differences in measurement techniques may play a role.

Our findings are in accordance with the hypothesis that QTc dispersion is due to patchy myocardial fibrosis, resulting from myocardial ischemia, ventricular dilatation, and neurohormonal activation, as we found a positive association of QTc dispersion with many cardiovascular risk indicators.

Irrespective of the technique used, QTc dispersion is difficult to measure. The end of repolarization, assessed as the end of the T-wave, is a gradual process, and therefore hard to define. The definition of the end of the T-wave is further complicated by low-amplitude T-waves and the presence of U-waves. Differences in measurement techniques, either by hand or computer, are known to be the source of large variations in absolute values of QT intervals.[26] Prior studies have shown that measurement of QTc dispersion suffers from large measurement error and has a poor reproducibility in both manual and computerized measurements.[29-33] Therefore, reported risk estimates are likely to be substantially diluted.

QTc dispersion in 12 leads was larger than QTc dispersion in 8 leads. As this difference is probably mainly due to measurement error it seems preferable to measure QTc dispersion in 8 leads, although any difference between QTc dispersion

in 8 and 12 leads hardly has any effect on the risk associated with QTc dispersion.

We conclude that QTc dispersion is a strong and independent predictor of cardiac mortality in older men and women. Further studies are warranted to study the mechanism underlying QTc dispersion and to search for the most accurate measure of this mechanism.

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Chapter 3.2

Appendix

Relationship between extremity leads

In the standard 12-lead ECG, only two of the six extremity leads are actually recorded, for instance leads I and II, and the other four are derived from mathematical relationships imposed by the lead system. Thus, for the amplitudes in the extremity leads at any time instant it holds that III = II − I, aVR = −(I + II)/2, aVL = (I − III)/2, and aVF = (II + III)/2. If all T waves end at the same moment, of course QT dispersion (QTD) = 0. Suppose the T wave in one lead, say I, is shorter than in the other ones, ending at some time instant t1. Then, lead I being zero, III = II for t > t1. This means that II and III must end at the same time. Let us assume this moment to be t2. In the time interval t1-t2 lead I = 0 and, using the above basic relationships, aVR = −II/2, aVL = −III/2, and aVF = II = III. Thus, the T waves in all augmented leads end when also the T waves in the leads II and III end, i.e., at t2. Mutatis mutandis the argument can be applied to any extremity lead other than I, Einthoven or augmented. It is always true that if there is a shortest T wave in one of the extremity leads ending at some time instant t1, the T waves in the other five extremity leads must all end at the same time instant t2 > t1. As a consequence, QTD cannot exist among these leads and any QTD measured can only be the result of measuring inaccuracy. The only possible true dispersion is between these five leads and the single short lead, viz. QTD = t2–t1.

CHAPTER 3.3

T AXIS: A NEW RISK INDICATOR FOR CARDIAC EVENTS IN THE ELDERLY

Abstract

Background The electrical T axis was hypothesized to be a general marker of repolarization abnormality, indicative of subclinical myocardial damage. The aim of this investigation was to assess the prognostic importance of the T axis for fatal and non-fatal cardiac events in a prospective cohort study among men and women aged 55 years and older.

Methods The study population consisted of 2,352 male and 3,429 female participants in the population-based Rotterdam Study. Electrocardiographic measurements were determined by a computer program. T axes were categorized as normal, borderline, and abnormal. Data were analyzed using Cox' proportional hazards models, adjusting for age and sex.

Results During the 3 to 6 (mean 4) years of follow-up, 165 (2.8%) fatal and 192 non-fatal (3.3%) cardiac events occurred. Subjects with an abnormal T axis had increased risks for cardiac death (hazard ratio 3.9; 95%CI 2.8-5.6), sudden cardiac death (4.4; 2.6-7.4), non-fatal cardiac events (2.7; 1.9-3.9), and combined fatal or non-fatal cardiac events (3.2; 2.5-4.1). Additional adjustment for established cardiovascular risk indicators resulted in lower, but still highly significant risks for all endpoints. The risks associated with an abnormal T axis were higher than those of any other cardiovascular risk indicator. Additional subgroup analyses indicated that the risk for cardiac death was not substantially modifed by age, sex, or history of myocardial infarction.

Conclusions The T axis is a new, strong, and independent risk indicator of fatal and non-fatal cardiac events in the elderly.

Chapter 3.3

Introduction

Ischemia and hypertrophy of the myocardium carry an increased risk for fatal and non-fatal cardiac events. Electrocardiographic (ECG) changes of ventricular repolarization may reflect, possibly subclinical, myocardial damage. Consequently, repolarization abnormalities as manifested by various ECG parameters, such as changes in the ST-T segment[1-8] and increased QT dispersion[9], have been found to predict the occurrence of coronary heart disease. However, a disadvantage of most of these parameters is that their measurement is tedious, has poor reproducibility, and requires analysis of all ECG leads.

We therefore sought to find a simpler ECG measurement to represent disturbances of ventricular repolarization. Electrical activity of the heart during repolarization is represented by the orientation of the electrical T axis. This suggests that the T axis may provide an alternative measure of repolarization abnormality. The purpose of this investigation was to determine whether an abnormal T axis is a marker of increased risk for cardiac events in older adults.

Methods

Study population and baseline data collection

The present investigation is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk indicators for chronic disease in the elderly. Objectives and methods of the Rotterdam Study have been described in detail elsewhere[10]. Briefly, in the Rotterdam Study all men and women aged 55 years or older, living in the Rotterdam district of Ommoord, were invited to participate (response rate 78%). Of 7,129 participants, baseline data were collected from 1990 to 1993, including established cardiovascular risk indicators, use of medications, history of cardiovascular disease, and an ECG.

Hypertension was defined as systolic blood pressure above 160 mmHg or diastolic blood pressure above 95 mmHg or use of antihypertensive medication for the indication hypertension. Diabetes mellitus was defined as a non-fasting blood glucose level above 11.1 mmol/l or use of antidiabetic medication. History of myocardial

infarction was defined as self-reported myocardial infarction with hospital admission. Presence of angina pectoris was established through the Rose questionnaire[11]. Digitally stored ECGs of 6,160 (86%) participants were available. Missing ECGs were mainly due to temporary technical problems with the ECG recorder.

After exclusion of 345 subjects without follow-up data, mainly due to unknown addresses, and 34 subjects with ECGs that could not be processed by the computer program, the study population consisted of 2,352 men and 3,429 women.

Follow-up procedures

The follow-up period, starting at the baseline examination and for the present analysis lasting until April 1996, was 3 to 6 (mean 4) years. With respect to the vital status of participants, information was obtained at regular intervals from the municipal health authorities in Rotterdam. Information on fatal and non-fatal endpoints was obtained from the general practitioners (GPs) working in the study district of Ommoord. These GPs, covering about 85% of the cohort, all have their practice computerized and report possible fatal and non-fatal events of participants on computer file to the Rotterdam Study data-center on a regular basis. All possible events reported by the GPs were verified by research physicians from the Rotterdam Study by consulting the patient records of the participating GPs and of medical specialists. In April 1996, the medical records of participants under the care of GPs outside the Ommoord area, about 15% of the cohort, were also checked by research physicians.

Shortly after a report of death by the municipal health service or the GP, cause and circumstances of death were established by questionnaire from the GPs and by scrutinizing information from hospital discharge records.

Overall, complete follow-up information was available for 94% of the population. Differences in baseline characteristics between those with and without follow-up data were examined using one-way analysis of covariance, adjusting for age and sex when appropriate. Those without follow-up data were on average older (73.9 versus 70.4 years) and had a lower prevalence of hypertension (25% versus 30%) and diabetes (10% versus 14%). No other differences in baseline characteristics were found.

Classification of fatal and non-fatal events was based on the 10th revision of the International Classification of Diseases (ICD-10)[12]. We defined cardiac mortality as death from myocardial infarction or other heart diseases (ICD-10: I21-28, 42, 43, 46-50), or sudden cardiac death. Sudden cardiac death was defined as death occurring within one hour after onset of symptoms, or unwitnessed death while a cardiac cause could not be excluded[13,14]. Non-fatal cardiac events were defined as myocardial infarction or chronic ischemic heart disease (I21-25), coronary artery bypass graft, or percutaneaous transluminal coronary angioplasty (no ICD-10 codes).

All events were classified independently by two research physicians. If there was disagreement, a consensus was reached in a separate session. Finally, all events were verified by a medical expert in the field of cardiovascular disease. In case the expert disagreed with the research physicians, the expert's judgment was considered final.

ECG measurements and interpretation

A 12-lead resting ECG was recorded with an ACTA electrocardiograph (ESAOTE, Florence) at a sampling frequency of 500 Hz, and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS)[15]. MEANS computes a representative averaged beat for each of the 12 leads from which ECG measurements and a diagnostic interpretation are derived. The program is also able to perform a classification according to the Minnesota Code[16]. MEANS has been extensively evaluated, both by the developers themselves[15,17] and by others[18,19].

T axes were computed from vectorcardiographic X, Y and Z leads which can, in good approximation, be reconstructed from the standard ECG leads[20,21]. The mean spatial axis is obtained by vectorially adding the instantaneous heart vectors during the T wave. The mean frontal axis is then taken to be the angle between the X axis and the projection of the mean spatial axis on the frontal XY plane; the mean horizontal axis is the angle between the X axis and the projection of the mean spatial axis on the horizontal XZ plane.

An overall QT interval was determined from the common QRS onset and T offset for all 12 leads together. To adjust for heart rate, Bazett's formula ($QTc = QT/\sqrt{RR}$)

was used[22].

Taking the location of the overall end of T as a starting point, the computer program determines the end of the T wave in each separate lead. QT dispersion was computed as the difference between the maximum and the minimum QT interval in the six precordial leads, the shortest extremity lead and the median of the five other extremity leads[9].

ST-T depression was taken as Minnesota Code 4.1 or 4.2. T-wave inversion was defined as Minnesota Code 5.1 or 5.2. Myocardial infarction by ECG was based on a comprehensive set of criteria that partly derive from the Minnesota Code. Electrocardiographic left ventricular hypertrophy was determined using voltage as well as repolarization criteria.

Data analysis

Based on previously published reports[23-26], both frontal and horizontal T axes were classified into three groups: "normal" (15° to 75°), "borderline" (−15° to 15° and 75° to 105°), and "abnormal" (−180° to −15° and 105° to 180°).

Differences in baseline characteristics between those with normal, borderline, and abnormal T axes were examined using one-way analysis of covariance, adjusting for age and sex when appropriate.

Cox' proportional hazards analysis[27] was used to determine the risk for cardiac death, sudden cardiac death, non-fatal cardiac events, and fatal or non-fatal cardiac events associated with borderline and abnormal T axes, taking subjects with normal T axes as the reference group. We adjusted for two sets of possible confounders: age and sex (model A), and age, sex, and established cardiovascular risk indicators: body mass index, cholesterol, current cigarette smoking, diabetes, hypertension, history of angina, and history of myocardial infarction (model B).

Subgroup analyses were carried out to assess the modifying influence of age, sex, and history of myocardial infarction on the risk for cardiac mortality associated with an abnormal T axis.

Table 1. Baseline characteristics of all participants and according to three categories of the frontal T axis.* Category-specific values have been adjusted for age and sex using one-way analysis of covariance.

Characteristic	All (n=5,781)	Normal† (n=4,690)	Borderline‡ (n=482)	Abnormal§ (n=609)
Age (year)	69.3 ± 9.0	68.2	71.6	75.4
Female sex (%)	59.4	61.3	50.7	50.8
Systolic blood pressure (mmHg)	139.4 ± 22.4	138.5	141.7	144.5
Diastolic blood pressure (mmHg)	73.5 ± 11.6	73.3	73.7	74.7
Body mass index (kg/m^2)	26.3 ± 3.7	26.3	26.5	26.4
Cholesterol (mmol/l)	6.6 ± 1.2	6.6	6.7	6.4
Current smoking (%)	21.0	21.1	20.0	21.7
Use of cardiovascular medication (%)	36.0	32.0	44.2	59.2
Hypertension (%)	29.6	28.3	31.8	37.8
Diabetes mellitus (%)	12.7	11.3	16.8	14.8
History of angina pectoris (%)	6.8	5.7	9.2	12.5
History of MI‖ (%)	7.1	4.4	15.9	21.5
QTc interval (ms)	431 ± 27	430	430	438
QTc dispersion (ms)	53 ± 29	56	61	66
ST depression (%)	10.3	4.0	18.4	52.3
T-wave inversion (%)	8.1	2.0	13.3	50.9
MI by ECG (%)	9.3	7.0	15.5	22.1
LVH¶ by ECG (%)	4.9	1.6	5.2	29.6

* Values are means ± SD or proportions;
† Normal = 15° < T axis < 75°; ‡ Borderline = −15° < T axis < 15° or 75° < T axis < 105°; § Abnormal = −180° < T axis < −15° or 105° < T axis < 180°;
‖ MI = myocardial infarction; ¶ LVH = left ventricular hypertrophy.

Results

Table 1 shows baseline characteristics of all participants and of those with normal, borderline, and abnormal frontal T axes, after adjusting for age and sex. Most variables have a clear association with the T axis. Similar results were obtained for the horizontal T axis.

During the follow-up period, 165 (2.8%) subjects died from a cardiac cause, of whom 73 (1.3%) died suddenly. Non-fatal cardiac events were experienced by 192 (3.3%) participants. Eleven individuals had a non-fatal cardiac event followed months or years later by a fatal cardiac event during the follow-up period. Table 2

Table 2. Number of fatal and non-fatal cardiac events and incidence rates for three categories of the frontal T axis.

Endpoint	Normal* (n=4,690)		Borderline† (n=482)		Abnormal‡ (n=609)	
	n	rate§	n	rate	n	rate
Cardiac death	78	4.2	23	12.9	64	27.4
Sudden cardiac death	34	1.9	10	5.8	29	13.2
Non-fatal cardiac event	130	6.9	20	11.3	42	18.9
Fatal or non-fatal cardiac event	203	10.7	40	21.6	103	41.2

*Normal = 15° < T axis < 75°; †Borderline = –15° < T axis < 15° or 75° < T axis < 105°; ‡Abnormal = –180° < T axis < –15° or 105° < T axis < 180°.
§Per 1,000 person-years.

shows the number of events and the crude incidence rates for subjects in different categories of the frontal T axis.

Subjects with an abnormal frontal T axis had about a fourfold age- and sex-adjusted risk for cardiac death (hazard ratio (HR) 3.9; 95%CI 2.8-5.6) and sudden cardiac death (HR 4.4; 95%CI 2.6-7.4) (Table 3). In addition, a marked increased risk for non-fatal cardiac events (HR 2.7; 95%CI 1.9-3.9) and for fatal and non-fatal cardiac events combined (HR 3.2; 95%CI 2.5-4.1) was observed. The risks associated with a borderline T axis were also significantly increased for all outcomes, except non-fatal cardiac events.

After adjustment for different established cardiovascular risk indicators (model B), the hazard ratios associated with an abnormal T axis attenuated, but remained statistically highly significant for all endpoints.

For comparison purposes, Table 3 also shows the risk for cardiac death associated with each of the other cardiovascular risk indicators. For both models, the risk associated with an abnormal T axis proved to be higher than that of any other risk indicator.

Subgroup analyses indicated that relative risk estimates for cardiac death associated with an abnormal frontal T axis were only slightly modified by age (HR 4.3 (95%CI 2.4-8.0) for age ≤ 75 years and 3.6 (95%CI 2.4-5.5) for age > 75), by sex (HR 3.7 (95%CI 2.3-6.0) for males and 4.2 (95%CI 2.5-6.8) for females), and by history of myocardial infarction (HR 3.2 (95%CI 2.0-5.0) in subjects without and 3.0 (95%CI

Table 3. Hazard ratios (95% CI) of abnormal and borderline T axis and cardiovascular risk indicators for cardiac death, sudden death, non-fatal cardiac events, and fatal or non-fatal cardiac events.

End point	Variable	Model A*	Model B†
Cardiac death	Borderline T axis‡	2.1 (1.3-3.3)	1.7 (1.0-2.8)
	Abnormal T axis§	3.9 (2.8-5.6)	2.9 (2.0-4.3)
	History of MI	3.0 (2.0-4.4)	1.9 (1.3-2.9)
	History of angina	2.4 (1.6-3.7)	1.9 (1.2-3.0)
	Diabetes mellitus	2.4 (1.6-3.4)	1.9 (1.3-2.8)
	Hypertension	1.4 (1.0-1.9)	1.4 (1.0-1.9)
	Current smoking	1.4 (0.9-2.0)	1.5 (1.0-2.2)
	Cholesterol > 8 mmol/l	1.3 (0.8-2.2)	1.1 (0.6-1.9)
	BMI > 25 kg/m^2	0.9 (0.6-1.2)	0.9 (0.6-1.2)
Sudden death	Borderline T axis	2.1 (1.1-4.4)	1.7 (0.8-3.6)
	Abnormal T axis	4.4 (2.6-7.4)	3.1 (1.7-5.5)
Non-fatal cardiac event	Borderline T axis	1.4 (0.9-2.2)	1.1 (0.7-1.8)
	Abnormal T axis	2.7 (1.9-3.9)	1.8 (1.3-2.7)
Fatal or non-fatal cardiac event	Borderline T axis	1.6 (1.1-2.3)	1.3 (0.9-1.9)
	Abnormal T axis	3.2 (2.5-4.1)	2.3 (1.7-3.0)

* Model A: each variable entered separately, adjusting for age and sex; † Model B: T axis and cardiovascular risk indicators entered simultaneously, adjusting for age and sex.
‡ Borderline T axis = $-15° <$ T axis $< 15°$ or $75° <$ T axis $< 105°$;
§ Abnormal T axis = $-180° <$ T axis $< -15°$ or $105° <$ T axis $< 180°$.

1.6-5.5) in subjects with a history of myocardial infarction).

All analyses were also carried out for abnormal and borderline horizontal T axes with essentially similar results (data not shown).

Discussion

The T axis is a strong and independent risk indicator of cardiac events in our study population of older adults. Its prognostic importance was higher than that of any other established cardiovascular risk indicator.

To the best of our knowledge, this is the first study to report on the prognostic value of the T axis. In diagnostic vectorcardiography, the abnormal T axis has for long been known to provide a global measure of repolarization abnormalities[26]. Such

abnormalities have been attributed to ischemic changes in the heart, but the mechanisms underlying ventricular repolarization are far from having been clarified as we are only beginning to discover the characteristics and complex interrelationships of different types of cells in the myocardium. Thus, the physiological meaning of an abnormal T axis remains unclear.

In previous studies, ST-T changes, either "silent" or in combination with other ischemic or hypertrophic changes, have been associated with coronary heart disease[2,6-8]. In the present study, most ECG variables were strongly associated with the T axis (Table 1). When we adjusted for age, sex, and these other ECG variables in the multivariate analysis, an abnormal T axis still proved to be associated with an almost threefold risk for cardiac death (HR 2.8; 95%CI 1.8-4.5), suggesting that an abnormal T axis carries additional information beyond that available through other ECG variables. Thus, the T axis appears an important, general marker for (subclinical) myocardial damage.

Our results were obtained in a population of older adults. Considering the strong relationship between T axis and ST-T changes and the fact that the latter have been identified as an important predictor for coronary heart disease in a wide diversity of populations, we expect the T axis to be an important predictor for cardiac events in younger age groups as well, but this remains to be established.

The thresholds to distinguish between different T-axis categories were based on values reported in previous studies[23-26]. Most of these studies mention normal ranges for the axis of the maximal T vector in the frontal or horizontal plane, but not for the (mean) T axis. Since the normal spatial T loop often has an elongated, spindle-like shape, we considered the difference between the maximal and mean T axes to be negligible.

The precise choice of threshold values does not appear to be very critical. When we decreased all thresholds by 15° and repeated our analyses, the results remained essentially the same. We also considered a dichotomization of T axes based on percentiles, taking the upper and lower limits of intervals that contained 75 or 90 percent of the T axes as boundaries, but again results did not change substantially. However, for risk stratification or screening purposes "optimal" boundaries may

need to be determined.

It may come as a surprise that there is little to choose between horizontal and frontal T axes. At first sight one would perhaps expect one to carry more information than the other. It must, however, be understood that, except for the case that the spatial T axis is lying exactly in either the horizontal or the frontal plane, any change in its direction will be projected on both planes and that both horizontal and frontal T axis will represent this information.

The calculation of T axes by computer is difficult to replicate by humans. However, many modern electrocardiographs can synthesize the vectorcardiogram from the recorded 12-lead ECG and optionally print projections of the spatial P-QRS-T loop in the frontal and horizontal planes, from which T axes are easily derived. Alternatively, the frontal T axis can readily be estimated similarly to the physician's derivation of the frontal QRS axis: using the same leads, the procedure is simply applied to the T wave instead of the QRS complex. When we simulated this procedure by computer, using only the peak-to-peak amplitude of the T waves in leads I and aVF, and repeated our analyses, very similar results were obtained (e.g., the age- and sex-adjusted hazard ratio for cardiac death associated with an abnormal T axis was 3.85; 95%CI 2.68-5.51 versus 3.94; 95%CI 2.78-5.58 in our previous analysis). Whether determined automatically or manually, measurement of the T axis is likely to be less troubled by noise and problems of definition than many of the existing amplitude and interval measurements in the ECG.

In conclusion, the T axis seems to be an important, general marker of myocardial damage and is a strong, independent predictor for fatal and non-fatal cardiac events. If confirmed, its measurement should be considered in identifying individuals prone to develop coronary heart disease both in clinical practice and in screening programmes.

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CHAPTER 3.4

BOTH DECREASED AND INCREASED HEART RATE VARIABILITY ON THE STANDARD 10-SECOND ELECTROCARDIOGRAM PREDICT CARDIAC MORTALITY IN THE ELDERLY: THE ROTTERDAM STUDY

Abstract

Decreased heart rate variability (HRV) has been associated with an adverse prognosis in patients after myocardial infarction. Studies in the population at large show contradictory results. We examined the association between heart rate variability on a standard 10-second electrocardiogram (ECG) and cardiac and all-cause mortality in the Rotterdam Study, a population-based cohort study in men and women aged 55 years or over. HRV, taken as the standard deviation of normal RR intervals (SDNN), was computed by the Modular ECG Analysis System (MEANS), using only RR intervals between two adjacent normal dominant beats. After exclusion of subjects without a digitally stored ECG, and those with less than 6 normal RR intervals, or with arrhythmias, the study population consisted of 2,088 men and 3,184 women. During the 3 to 6 (mean 4) years of follow-up 69 (3.4%) men and 63 (2.1%) women died from a cardiac cause. SDNN was categorized into quartiles, with 25-, 50- and 75-percentile values of 9.6, 15.2, and 25.9 ms. Cox' proportional hazards model was used to examine the age- and sex-adjusted risk for cardiac, non-cardiac, and total mortality in relation to quartiles of SDNN, using the third quartile of SDNN as the reference category. Subjects in the lowest quartile relative to those in the third quartile of SDNN, had an 80 percent age- and sex-adjusted increased risk for cardiac mortality (HR 1.8; 95%CI:1.0-3.2). The corresponding hazard ratios for non-cardiac mortality and all-cause mortality were 1.3 (95%CI:0.9-1.8) and 1.4 (95%CI:1.0-1.8), respectively. Interestingly, for subjects in the highest quartile of SDNN compared to those in the third quartile an even more pronounced risk for cardiac mortality was present (HR 2.3; 95%CI:1.3-4.0). Additional adjustment for possible confounders, including diabetes, body mass index, and heart rate, did not materially change the risk estimates. HRV measured in the standard 10-second ECG can be used to identify older men and women with an increased risk for cardiac mortality. Increased HRV is an even stronger indicator of cardiac mortality than decreased HRV.

Introduction

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

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

The report of the Task Force on HRV recommends that, in order to standardize clinical studies, only two types of HRV measurements should be used[1]: (a) short term measurements on 5 minute electrocardiograms (ECGs) made under physiologically stable conditions, processed by frequency-domain methods, and (b) 24-hour recordings processed by time-domain methods. However, two prior population-based studies, restricted to men, have reported an association between decreased HRV, measured in 10-beat ECGs[18] and 20-second ECGs[17], and total and cardiac mortality. Provided the predictive value of HRV measurements is established, the standard 12-lead ECG would offer a useful tool for risk stratification in large populations, as it is much easier and less costly to obtain than the standardized 5-minute ECG or the 24-hour holter ECG.

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

Methods

Study population and baseline data collection

This study is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence and risk factors of chronic diseases in the elderly. Objectives and methods of the Rotterdam Study are described in detail elsewhere[22]. Briefly, in the Rotterdam Study all men and women aged 55 years or older, living in the Rotterdam district Ommoord, were invited to participate (response rate 78%). Of 7,129 participants baseline data, collected from 1990 to 1993, included an ECG, information on history of cardiovascular disease, cardiovascular risk factors, and use of coffee, alcohol, and medications.

A digitally stored ECG was available in 6,160 (86%) participants. An ECG was missing in 14% of the participants, mainly due to temporary technical problems of the ECG recorder. Blood pressure was calculated as the average of two consecutive measurements with a random zero mercury manometer. Body mass index was calculated as weight/length^2 in kg/m^2. Hypertension was defined as systolic blood pressure above 160 mmHg or diastolic blood pressure above 95 mmHg or use of antihypertensive medication for the indication of hypertension. Diabetes mellitus was defined as a non-fasting blood glucose above 11.1 mmol/l or use of antidiabetic medication. History of myocardial infarction (MI) was defined as self-reported MI with hospital admission, or MI on the ECG. Presence of angina pectoris was established through the Rose questionnaire[23].

Subjects with arrhythmias (n=232: 162 atrial fibrillation, 14 atrial flutter, 23 atrial rhythm, 32 ideoventricular rhythm, 1 supraventricular tachycardia) and subjects in whom less than 6 intervals on the ECG could be analyzed for HRV measurements (n=251), were excluded. In addition, 345 subjects without follow-up data (mainly because they moved to unknown addresses) and 71 subjects with ECGs of poor technical quality, in which cardiac rhythm could not be analyzed, were excluded. The final study population consisted of 2,088 men and 3,184 women.

Follow-up procedures

The follow-up period, starting at the baseline examination and in the present analy-

sis lasting until April 1996, was 3 to 6 (mean 4) years. Information on the vital status of participants was obtained at regular intervals from the municipal authorities in Rotterdam. Information on fatal and non-fatal endpoints was obtained from the general practitioners (GPs) working in the study district of Ommoord. These GPs, covering about 85% of the cohort, all have their practice computerized and report possible fatal and non-fatal events of participants on computer file to the Rotterdam Study data center on a regular basis. All possible events reported by the GPs are verified by research physicians from the Rotterdam Study through patient records of the participating GPs and medical specialists. In April 1996, the medical records of those participants with GPs from outside the Ommoord area (about 15% of the cohort) were checked by research physicians and of all possible events additional information for coding was collected.

Cause and circumstances of death were obtained, shortly after reporting of death by the GP or municipal authorities, from the GP by questionnaire and by scrutinizing information from hospital discharge records in case of admittance or referral.

Complete follow-up information was available for 94% of the population of the Rotterdam study. Differences in baseline characteristics between those with and without follow-up data were examined using one-way analysis of covariance, adjusting for age and gender when appropriate. Those without follow-up were on average older (73.9 years versus 70.4 years), had a lower prevalence of hypertension (25% versus 30%) and diabetes (10% versus 14%). No other differences in baseline characteristics were found.

Classification of fatal and non-fatal events was based on the International Classification of Diseases, 10th version (ICD-10)[11]. We defined cardiac mortality as death from myocardial infarction (ICD-10: I21-24), chronic ischemic heart disease (ICD-10: I25), pulmonary embolism or other pulmonary heart disease (ICD-10: I26-28), cardiomyopathy (ICD-10: I42-43), cardiac arrest (ICD-10: I46), arrhythmias (ICD-10: I47-49), heart failure (ICD-10: I50), or sudden cardiac death. Sudden cardiac death was defined as death occurring within one hour after onset of symptoms or unwitnessed death, in which a cardiac cause could not be excluded[24, 25].

All events were classified independently by two research physicians. If there was

disagreement, a consensus was reached in a separate session. Finally, all events were verified by a medical expert in the field of cardiovascular disease. In case of discrepancies, the judgment of this expert was considered definite.

ECG interpretation and measurements

A 12-lead resting ECG was recorded with an ACTA cardiograph (EsaOte, Florence) with a sampling frequency of 500 Hz, and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain ECG measurements and diagnostic interpretations. The MEANS program has been evaluated extensively[26-29].

Only RR intervals between two adjacent normal dominant beats were used to compute mean heart rate (HR) and HRV, taken as the standard deviation of normal RR intervals (SDNN). Both premature ventricular and supraventricular complexes were considered abnormal. The overall QT interval was determined on a representative beat for all twelve leads together. To adjust QT for heart rate, we calculated QT_c according to Bazett's formula[30]. Left ventricular hypertrophy (LVH) was determined using voltage as well as repolarization criteria. Negative T-waves were defined as negative T-wave deflections of at least 1.0 mm in any of the leads I-III, aVR, aVF, and V2-V6.

Data analysis

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

To evaluate the association between HRV and potentially confounding factors and other ECG characteristics, differences in the distribution of selected baseline characteristics between subjects in quartiles of SDNN were examined by one-way analysis of covariance, adjusting for age and gender when appropriate. As a U-shaped relationship was apparent between several determinants and SDNN in which the lowest risk was present in the third quartile, separate analyses were performed for decreased HRV (comparing the lowest three quartiles) and increased HRV (comparing the highest two quartiles). All determinants that showed a statistically

significant ($p<0.05$) association with SDNN in one of these analyses, was considered a possible confounder.

Cox' proportional hazards model was used to examine the risk for cardiac, non-cardiac and total mortality in relation to quartiles of SDNN, adjusted for two sets of confounders: (1) age and sex, and (2) all possible confounders resulting from the analysis of covariance. The third quartile of SDNN was taken as the reference category. In order to minimize the effect of missing data in the multivariate analysis, missing values of categorical variables were replaced by dummies[31]. Missing values of continuous variables were replaced by the average value and a dummy variable to indicate whether an imputed value was added to the model.

Subgroup analyses were performed to examine whether age (below or over 75 years), sex, history of MI, and presence of ectopic beats influenced the association between SDNN and cardiac mortality.

Results

Baseline characteristics of participants in quartiles of SDNN are shown in Table 1.

In the analysis of determinants of decreased HRV, statistically significant differences existed between the three comparison groups with regard to age, sex, body mass index, and diabetes mellitus. The ECG characteristics associated with decreased SDNN were mean RR interval and overall QTc interval. Increased HRV, comparing the highest two quartiles, was associated with age, sex, mean RR, presence of negative T-waves, and premature ventricular and supraventricular complexes.

During follow-up, 222 (10.6%) men and 238 (7.5%) women died; 69 (3.4%) men and 63 (2.1%) women died from a cardiac cause. Subjects in the lowest quartile relative to those in the third quartile of SDNN, had an 80 percent age- and sex-adjusted increased risk for cardiac mortality (hazard ratio (HR) 1.8; 95%CI:1.0-3.2) (Table 2).

The corresponding hazard ratios for non-cardiac mortality and all-cause mortality were 1.3 (95%CI:0.9-1.8) and 1.4 (95%CI:1.0-1.8), respectively. Interestingly, for

subjects in the highest quartile of SDNN compared to those in the third quartile we found an even more pronounced increased risk for cardiac mortality (HR 2.3; 95%CI:1.3-4.0).

The risk for cardiac mortality associated with both decreased and increased SDNN were more pronounced in women than in men, in subjects with a history of MI and in subjects younger than 75 years (Table 2). Both decreased and increased HRV seemed to be associated with non-cardiac mortality in women only.

Table 1. Baseline characteristics, values are means (standard deviation) or percentages. P-values are indicated for equality of quartile-specific values in quartiles of SDNN, adjusted for age and gender.

Characteristic	All (n=5272)	Q1 <9.6	Q2 9.6-15.2	Q3 15.2-25.9	Q4 >25.9
Age (years)	68.7 (8.8)	70.6**	69.1	67.4	68.0*
Women (%)	60.4	59.9*	64.4	62.1	54.9**
Systolic blood pressure (mmHg)	139.4 (22.3)	140.7	139.7	139.5	137.2
Diastolic blood pressure (mmHg)	73.6 (11.5)	74.2	73.7	73.5	73.0
Body mass index (kg/m^2)	26.4 (3.7)	26.7*	26.4	26.3	26.1
Serum Cholesterol (mmol/l)	6.6 (1.2)	6.7	6.6	6.6	6.7
Cigarette smoking (%)	21.4	21.4	20.8	20.7	22.7
Coffee intake (mg/day)	482 (238)	483	481	474	490
Alcohol intake (mg/day)	10.3 (15.3)	10.7	9.9	10.0	10.9
Hypertension (%)	29.3	31.5	30.1	29.4	26.0
Diabetes (%)	12.3	14.8*	12.0	11.3	10.9
Angina pectoris (%)	6.7	6.9	7.0	7.0	5.7
Myocardial infarction (%)	12.1	13.3	11.4	11.3	12.0
Cardiovascular drug use (%)	33.9	34.6	34.2	34.5	32.2
Negative T-wave (%)	6.8	7.5**	8.4	5.2	7.4**
LVH on ECG (%)	4.4	4.0	4.9	4.3	4.3
Mean RR interval (ms)	867 (140)	801**	858	898	911*
Overall QTc (ms)	430.9 (26.2)	438**	432	428	426
Presence of PVC (%)	2.8	2.9	2.2	2.6	3.9*
Presence of PSVC (%)	2.7	0.6	0.2	0.2	10.3*

LVH=left ventricular hypertrophy; PVC= premature ventricular complex; PSVC=premature supraventricular complex.; *: $p<0.05$; **: $p<0.01$

Table 2. Age-adjusted hazards ratios for cardiac, non-cardiac, and all-cause mortality of subjects in quartiles of heart rate variability (SDNN in ms), relative to those in the third quartile.

Outcome	Group	Hazard ratio (95% CI) Q1 <9.6	Q2 9.6-15.2	Q3* 15.2-25.9	Q4 >25.9
Cardiac mortality	All	1.8 (1.0-3.2)	1.7 (1.0-3.1)	1	2.3 (1.3-4.0)
	Men	1.3 (0.6-2.8)	1.6 (0.7-3.4)	1	2.0 (1.0-4.2)
	Women	2.5 (1.1-5.8)	2.0 (0.8-4.8)	1	2.7 (1.1-6.4)
	No MI	1.6 (0.8-3.0)	1.3 (0.6-2.5)	1	2.0 (1.0-3.9)
	MI	2.4 (0.8-7.2)	3.2 (1.0-9.6)	1	3.2 (1.1-9.8)
	<=75	2.0 (0.8-5.4)	2.8 (1.1-7.2)	1	3.8 (1.6-9.5)
	> 75	1.6 (0.8-3.2)	1.2 (0.6-2.5)	1	1.6 (0.8-3.2)
Non-cardiac mortality	All	1.3 (0.9-1.8)	1.2 (0.9-1.7)	1	1.1 (0.8-1.6)
	Men	1.1 (0.7-1.7)	0.8 (0.5-1.3)	1	0.9 (0.5-1.4)
	Women	1.5 (0.9-2.5)	1.7 (1.1-2.8)	1	1.6 (1.0-2.7)
All-cause mortality	All	1.4 (1.0-1.8)	1.3 (1.0-1.8)	1	1.4 (1.0-1.9)
	Men	1.1 (0.8-1.7)	1.0 (0.7-1.5)	1	1.1 (0.7-1.6)
	Women	1.7 (1.1-2.6)	1.8 (1.2-2.7)	1	1.9 (1.2-2.9)

Q1, Q2 , Q3, Q4 = first to fourth quartile
*: reference category

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

Additional adjustment for body mass index, diabetes mellitus, overall QTc interval, mean RR interval, and presence of negative T-waves, did not substantially change the hazards ratios for all endpoints.

Discussion

Results of this study show that both decreased and increased HRV, measured in the standard 10-second ECG, are associated with cardiac mortality in the elderly. These

risks were more pronounced in women, those younger than 75, and subjects with a history of MI. In addition, the results indicate that both decreased and increased HRV are associated with death from non-cardiac causes in women, but not in men.

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

Prior studies assessing the risk associated with HRV in the general population, consistently show an association of decreased HRV with cardiac and all-cause mortality in middle-aged populations[17, 18-20]. An association of increased HRV with mortality has never been reported in middle-aged subjects. In elderly populations however, contradictory results have been reported on the risk associated with both decreased and increased HRV. In the Framingham Heart Study[16], a linear association between decreased SDNN and all-cause mortality was present in men and women aged 63 years or older, suggesting the absence of an association of increased HRV with mortality. In the Zutphen Study[17], the risk associated with reduced HRV was less pronounced in men aged 65 years or older than in middle-aged men, and an association of increased HRV with all-cause mortality was present only in elderly men. Finally, in the Bronx Aging Study[21], in men and women aged 75 to 85 years no association was present between decreased HRV and cardiac and all-cause mortality, but an association of increased HRV with cardiac events was present in women.

The absence of an association of increased HRV with mortality in some of these

studies may partly be explained by exclusion criteria and procedures to measure HRV. On visual inspection, one can clearly see that increased HRV is accompanied by irregular sinus arrhythmias. However, using the conventional editing rules and measures for HRV, this irregular HRV cannot be distinguished from normal sinus arrhythmia. When these irregular sinus beats are considered abnormal, estimated risks associated with increased HRV might be reduced. However, proper definitions for abnormal sinus beats are lacking. Also age-differences between study populations are likely to account for part of the discrepancies.

Presumably, increased HRV, unlike decreased HRV, is hardly influenced by the autonomic nervous system but may rather be due to sinus node dysfunction[32, 33]. With increasing age, pathological changes occur in the sinoatrial node, including an increase in collagen and elastic fibers[34]. Pathological studies performed in patients with sick sinus syndrome showed that an increased amount of fibrous tissue was present in the sinus node, apart from defects due to coronary arteriosclerosis[35]. It has been shown that intrinsic sinus node function, which is measured after autonomic blockade, deteriorates with age, resulting in prolonged RR intervals and increased, irregular HRV[36, 37]. In the present study, those with increased HRV had on average longer RR intervals. The finding that the risk associated with increased HRV was more pronounced for cardiac mortality than for non-cardiac and all-cause mortality, indicates that increased HRV is influenced by ischemic heart disease.

Decreased HRV is probably largely due to changes in autonomic balance[38, 39]. Autonomic dysfunction, i.e. sympathetic overactivity and a decrease in vagal activity, results in increased heart rates and, consequently, decreased HRV. Changes in autonomic balance result from coronary heart disease, but can also be due to other disease processes[2, 3, 30-42], as is suggested by the increased risk of decreased HRV with non-cardiac mortality observed in our study.

In conclusion, HRV measured in the standard 10-second ECG can be used to identify older men and women with an increased risk for cardiac mortality. In elderly men and women increased HRV is an even stronger indicator for cardiac mortality than decreased HRV.

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CHAPTER 3.5

THE CARDIOVASCULAR RISK PROFILE IN THE ELDERLY: ADDITIONAL VALUE OF THE RESTING ELECTROCARDIOGRAM

Abstract

Coronary heart disease is a common disease that frequently occurs without warning symptoms and may even present itself with sudden death as the first symptom. The electrocardiogram (ECG) is an inexpensive and noninvasive instrument to determine the presence of coronary heart disease as well as other abnormalities, known to be associated with future cardiovascular events. We examined the predictive value of conventional and new ECG abnormalities for future coronary heart disease in older men and women participating in the Rotterdam Study. In particular, we assessed whether ECG abnormalities are of additional prognostic value compared to the conventional cardiovascular risk indicators that are commonly available in general practice. ECG abnormalities were assessed by the Modular ECG Analysis System (MEANS). After exclusion of those without a digitally stored ECG the population consisted of 2352 men and 3429 women. To develop a risk function for cardiac mortality, based on ECG abnormalities and established cardiovascular risk indicators, we used logistic regression analysis. First, for each ECG abnormality a bivariate analysis was performed, taking age differences into account. Second, a multivariate model was applied, simultaneously including the established cardiovascular risk indicators and all ECG abnormalities that showed an association in the bivariate analysis. In addition, we estimated a "standard risk function" for cardiac mortality, based on only established cardiovascular risk indicators. The "ECG risk function", including both ECG abnormalities and conventional cardiovascular risk indicators, compared to the "standard risk function", improved predictive power for cardiac death. This finding was more pronounced in women than in men. In conclusion, both classical and new ECG abnormalities have independent predictive value for future coronary heart disease in older men and women. Using the ECG in addition to the standard cardiovascular risk profile may improve the identification of men and women at risk for cardiac mortality.

Introduction

Coronary heart disease is a common disease that frequently occurs without warning symptoms[1-6] and may even present itself with sudden death as the first symptom[7-9]. Since in most developed countries the proportion of elderly people in the population is expected to increase in the next decades, prevention of coronary events in older men and women is of growing importance. However, most studies on coronary heart disease involved middle-aged populations and therefore the applicability of their results to the elderly may be limited. Early identification of persons at risk for coronary heart disease is an important first step in designing appropriate preventive measures. In many countries, including the UK and the Netherlands, identification of subjects prone to develop cardiovascular disease is primarily the task of the general practitioner.

Current risk profiling in general practice is primarily based on assessment of hypertension, diabetes, hypercholesteremia, obesity, and cigarette smoking[10]. The electrocardiogram (ECG) is an inexpensive and noninvasive instrument to determine the presence of coronary heart disease as well as other abnormalities, such as prolonged QTc interval or atrial fibrillation, known to be associated with future cardiovascular events. Since computer programs for ECG interpretation with good performance have become available[11, 12], the use of ECGs in primary care becomes more feasible. Especially in the elderly, in whom medical histories may be troubled by concomitant diseases, the ECG could serve as a useful diagnostic and prognostic instrument.

Recently, new ECG characteristics, including increased QTc dispersion, abnormal T axis, and decreased or increased heart rate variability (HRV), have been identified as important risk indicators for fatal and nonfatal cardiac events (unpublished data, 1997). The predictive value of the new ECG characteristics, in addition to conventional ECG abnormalities is largely unknown.

The value of the ECG in risk profiling in the elderly should be viewed from a clinical perspective. Even if ECG abnormalities are strong predictors for future coronary heart disease, it is only valuable to clinical practice if it adds important

prognostic information to conventional cardiovascular risk profiling, in terms of improving the detection of subjects at increased, absolute risk for future heart disease. The added value of the ECG to cardiovascular risk profiling in the elderly has not been determined fully.

We examined the predictive value of conventional and new ECG abnormalities for future coronary heart disease in older men and women. In particular, we assessed whether ECG abnormalities are of additional prognostic value compared to the conventional cardiovascular risk indicators that are commonly available in general practice.

Methods

Study population and baseline data collection

This study is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence and risk factors for chronic diseases in the elderly. Objectives and methods of the Rotterdam Study are described in detail elsewhere[13]. Briefly, in the Rotterdam Study all men and women aged 55 years or older, living in the Rotterdam district of Ommoord, were invited to participate (response rate 78%). Of 7,129 participants, the baseline data, collected from 1990 to 1993, included an ECG, information on history of cardiovascular disease, established cardiovascular risk factors, and use of medications.

A digitally stored ECG was available in 6,160 (86%) participants. An ECG was missing in 14% of the participants, mainly due to temporary technical problems of the ECG recorder. Blood pressure was calculated as the average of two consecutive measurements with a random zero mercury manometer. Body mass index was calculated as weight/length^2 in kg/m^2. Hypertension was defined as systolic blood pressure above 160 mmHg or diastolic blood pressure above 95 mmHg or use of antihypertensive medication for the indication hypertension. Diabetes mellitus was defined as a non-fasting blood glucose above 11.1 mmol/l or use of antidiabetic medication. History of symptomatic coronary heart disease (CHD) was defined as a self-reported myocardial infarction or the presence of angina pectoris established through the Rose questionnaire[14].

After exclusion of 345 subjects without follow-up data, mainly because they moved to unknown addresses, and 34 subjects with ECGs that could not be processed by the computer program, the study population consisted of 2,352 men and 3,429 women.

Follow-up procedures

The follow-up period, starting at the baseline examination and in the present analysis lasting until April 1996, was 3 to 6 (mean 4) years. With respect to the vital status of participants, information was obtained at regular intervals from the municipal health service in Rotterdam. Information on fatal and non-fatal endpoints was obtained from the general practitioners (GPs) working in the study district of Ommoord. These GPs, covering around 85% of the cohort, all have their practice computerized and report possible fatal and non-fatal events of participants on computer file to the Rotterdam Study data center on a regular basis. All possible events reported by the GP were verified by research physicians from the Rotterdam Study through patient records of the participating GPs and medical specialists. In April 1996, the medical records of participants with GPs from outside the Ommoord area, around 15% of the cohort, were checked by research physicians and of all possible events additional information for coding was collected.

Shortly after reporting of death by the municipal health service or the GP, cause and circumstances of death were established by questionnaire from the GP and by scrutinizing information from hospital discharge records in case of admittance or referral.

Overall, complete follow-up information was available for 94% of the population of the Rotterdam study. Differences in baseline characteristics between those with and without follow-up data were examined using one-way analysis of covariance, adjusting for age and gender when appropriate. Participants in whom no follow-up information was available were on average 3.5 years older (73.9 years) than those included in the study and had a lower prevalence of hypertension (25% versus 30%) and diabetes (10% versus 14%). No other differences in baseline characteristics were found.

Classification of fatal and non-fatal events was based on the International Classification of Diseases, 10th version (ICD-10)[15]. We defined cardiac mortality as death from myocardial infarction (ICD-10: I21-24), chronic ischemic heart disease (ICD-10: I25), pulmonary embolism or other pulmonary heart disease (ICD-10: I26-28), cardiomyopathy (ICD-10: I42-43), cardiac arrest (ICD-10: I46), arrhythmias (ICD-10: I47-49), heart failure (ICD-10: I50), or sudden cardiac death. Sudden cardiac death was defined as death occurring instantaneously or within one hour after onset of symptoms or in case of unwitnessed death, in which a cardiac cause could not be excluded[16, 17].

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

ECG interpretation and measurements

A 12-lead resting ECG was recorded with an ACTA cardiograph (ESAOTE, Florence) with a sampling frequency of 500 Hz, and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS). MEANS computes a representative averaged beat for each of the 12 leads, from which ECG measurements and diagnostic interpretations are derived[18]. The program is also able to perform a classification according to the Minnesota Code[19]. The MEANS program has been evaluated extensively[11, 18, 20-22].

T axes were calculated from vectorcardiographic X, Y, Z leads which can, in good approximation, be reconstructed from the standard ECG leads[23, 24]. The mean spatial axis is obtained by vectorially adding instantaneous heart vectors during the T wave. The mean frontal axis is then taken to be the angle between the X axis and the projection of the mean spatial axis on the XY plane.

An overall QT interval was determined from the common QRS onset and T offset for all 12 leads together. To adjust for heart rate, Bazett's formula ($QTc = QT/\sqrt{RR}$) was used[25]. Taking the location of the overall end of T as a starting point, the program determines the end of the T wave in each separate lead. QT dispersion is

Table 1. Definition of ECG abnormalities

ECG finding	Definition
SILENTMI	Based on presence of pathological Q-waves or loss of R-wave potential in the precordial leads, in the absence of symptoms
LVH	Based on combination of voltage and ST-T wave criteria
IVB	Intra-ventricular block: prolonged QRS duration (incomplete or complete left or right bundle branch block, or intraventricular conduction defect)
AVB	Atrioventricular block (1st, 2nd, or 3rd degree); PR interval >0.20 ms
STD	ST-T depression: Minnesota Code 4.1 or 4.2
NEGT	T wave inversion : Minnesota Code 5.1 or 5.2
QTC	Prolonged QTc - Borderline 420 to 460 ms - Abnormal >460 ms
QTCD	Increased QTc dispersion - Borderline 47-66 ms - Abnormal >66ms
TAX	Deviation of the frontal T axis - Borderline: -15° < T axis < 15° or 75°<Taxis <105° - Abnormal: -180° < Taxis < -15° or 105° < Taxis < 180°
HRV	Decreased HRV - Abnormal SDNN <9.6 ms - Borderline SDNN 9.6 - 15.2 ms Increased HRV: SDNN > 25.9 ms
AFIB	Atrial fibrillation or atrial flutter
PVC	Premature ventricular complexes

computed as the difference between the maximum and the minimum QT intervals in the six precordial leads, the shortest extremity lead and the median of the five other extremity leads.

Definitions of ECG abnormalities used in the present study are shown in Table 1.

Data analysis

All analyses were performed for men and women separately. To determine the risk for cardiac mortality associated with ECG abnormalities we computed age-adjusted incidence rates of all endpoints in those with and without a certain ECG finding, using one-way analysis of covariance.

To develop a risk function for cardiac mortality, based on ECG abnormalities and

established cardiovascular risk indicators, we used logistic regression analysis. First, for each ECG abnormality a bivariate analysis was performed, taking age differences into account. Only ECG abnormalities that showed a clear association with cardiac mortality in this bivariate analysis (with $p<0.05$), were included in the next step. Second, a multivariate model was applied, simultaneously including all ECG abnormalities that showed an association in the bivariate analysis and the established cardiovascular risk indicators (notably body mass index, serum cholesterol, hypertension, diabetes mellitus and cigarette smoking, a history of symptomatic MI and presence of angina pectoris). The final "ECG risk function" was determined by including all ECG abnormalities which showed an association with cardiac mortality in this multivariate analysis (with $p<0.20$) and the established cardiovascular risk indicators in one logistic model. In addition, we estimated a "standard risk function" for cardiac mortality, using a multivariate logistic regression model in which only the established cardiovascular risk indicators described above were included, together with age.

Using the "ECG risk function" and the "standard risk function", the probability of cardiac death was determined for every individual men and women in the study. This probability was categorized into deciles of risk.To assess the value of a risk function two parameters were calculated. First, for each decile the incidence of cardiac death per 1,000 person-years was calculated. In addition, we calculated sensitivity for cardiac death of every decile as the proportion of all cases detected per decile. To examine whether the "ECG risk function" improves identification of those susceptible for cardiac mortality by the "standard risk function", we compared the incidence rate and the sensitivity of cardiac deaths in deciles of risk, estimated by both risk functions in the complete population. In addition, we compared incidence rates and sensitivity of cardiac death of the highest deciles of risk in subgroups of participants, notably in subjects younger and older than 75 years and in those with and without a history of symptomatic cardiovascular disease. For screening purposes the highest decile of risk will be of most interest.

Table 2. General characteristics of men and women participating in the Rotterdam Study. Values are means (standard deviations) or proportions.

Characteristic	Men n=2,352	Women n=3,429
Age (years)	68.2 (8.1)	69.9 (9.5)
Systolic blood pressure (mmHg)	138.8 (21.9)	139.8 (22.8)
Diastolic blood pressure (mmHg)	74.4 (11.7)	72.9 (11.5)
Body mass index (kg/m^2)	25.8 (2.9)	26.8 (4.0)
Total serum cholesterol (mmol/l)	6.3 (1.1)	6.8 (1.2)
Current cigarette smoking (%)	25.1	18.2
Hypertension (%)	25.7	32.2
Diabetes mellitus (%)	12.4	12.8
History of symptomatic MI (%)	12.7	4.3
Angina pectoris (%)	6.4	7.0

Results

General characteristics of men and women participating in the Rotterdam Study are presented in Table 2. Women were on average slightly older, had a higher body mass index and serum cholesterol, a higher prevalence of hypertension and smoked less. A history of symptomatic myocardial infarction was much more frequent in men than in women.

Most ECG abnormalities were more frequent in men than in women (Table 3). Repolarization abnormalities, including ST-T depression, T-wave inversion, and abnormal T axis, had a similar prevalence (about 10 percent) in men and women. Prolonged QTc interval, defined as QTc>460 ms, was more frequent in women (10.6% versus 5.8%).

The age-adjusted incidence of all coronary heart disease endpoints was higher in men than in women (Table 3). In both men and women, the highest age-adjusted incidence of cardiac death was found in subjects with an abnormal T axis (28.7 and 27.2 per 1,000 person-years, respectively). In men, a strong association of silent myocardial infarction with future coronary heart disease was found. This association was absent in women. Apart from silent myocardial infarction, most ECG abnormalities showed a stronger association with cardiac death in women than in men.

Table 3. Prevalence of ECG abnormalities and age-adjusted incidence rate (per 1,000 person years) of cardiac mortality in those with and without specific ECG abnormalities, in 2,352 men and 3,429 women aged 55 years or older, participating in the Rotterdam Study.

ECG finding		Men		Women	
		Prevalence (%)	Incidence rate of cardiac death	Prevalence (%)	Incidence rate of cardiac death
SILENT MI	No	92.7	8.1	94.6	6.2
	Yes	7.4	26.2	5.4	8.1
LVH	No	94.3	8.6	95.6	5.7
	Yes	5.7	24.8	4.4	19.8
IVB	No	90.2	8.4	94.7	5.7
	Yes	9.8	18.7	5.3	15.3
AVB	No	93.7	8.9	93.6	5.7
	Yes	6.3	15.1	6.4	17.1
STD	No	90.2	8.4	89.6	5.5
	Yes	9.8	19.0	10.4	13.3
NEGT	No	91.4	8.1	92.2	5.2
	Yes	8.6	24.9	7.8	21.7
AFIB	No	96.6	9.4	97.4	6.0
	Yes	3.4	10.1	2.6	27.2
PVC	No	93.9	9.2	95.9	6.0
	Yes	6.1	11.3	4.1	15.2
QTC	Normal	48.4	7.9	29.6	3.8
	Borderline	45.8	8.2	59.8	4.4
	Abnormal	5.8	13.7	10.6	8.8
QTCD	Normal	42.2	5.6	40.4	4.0
	Borderline	27.9	14.6	27.9	5.5
	Abnormal	29.9	9.6	31.7	9.9
TAX	Normal	78.2	6.5	83.0	4.0
	Borderline	9.9	12.2	7.3	10.7
	Abnormal	11.8	28.7	9.7	27.2
HRV	Decreased	24.4	6.9	24.9	7.7
	Borderline	22.7	10.0	27.1	5.0
	Normal	24.6	6.4	25.4	2.0
	Increased	28.3	13.0	22.7	6.9

Table 4. Coefficients and their standard errors for calculating the absolute four year risk of cardiac mortality in men and women.

	Men		Women	
Variable	Coef	Stand. Err.	Coef	Stand. Err.
Age (years)	0.065	0.016***	0.091	0.015***
Body mass index (kg/m^2)	-0.110	0.043*	0.016	0.029
Serum cholesterol (mmol/l)	-0.031	0.111	0.120	0.095
Cigarette smoking#	-0.288	0.300	0.921	0.331**
Hypertension #	0.572	0.266*	0.189	0.250
Diabetes #	0.704	0.297*	0.561	0.297
Symptomatic MI #	0.987	0.322**	0.929	0.349**
Angina pectoris #	0.826	0.349*	0.480	0.373
SILENT MI #	1.440	0.333*	---	---
LVH #	0.617	0.407	---	---
IVB #	0.535	0.312	---	---
AVB #	---	---	0.711	0.320*
NEGT #	---	---	0.224	0.328
QTCD borderline#	0.944	0.312**	0.399	0.345
QTCD abnormal #	0.180	0.330	0.940	0.309**
TAX borderline #	0.335	0.386	0.596	0.379
TAX abnnormal #	0.699	0.325*	0.922	0.327**
HRV decreased #	0.054	0.430	0.782	0.461
HRV borderline #	0.378	0.43	0.598	0.473
HRV increased #	0.588	0.401	0.926	0.473*
Intercept	-4.237	2.376	-14.554	2.102***

*: p<0.05, **: p<0.01, ***: p<0.001

Yes=1, no=0; for definitions see Table 1.

To obtain the probability that cardiac mortality will occur in 4 years in an individual person, multiply the coefficient (β1 to βp) for each variable (z1 to zp) by the measured value of that variable in a subject, summ these products and add the intercept (α). This provides the coefficient C (C=α+β1*z1+....+βp*zp) to calculate the probability of cardiac death P=1/1+exp (-C).

The components of the "ECG risk function" differed between men and women (Table 4). Silent myocardial infarction, left ventricular hypertrophy, and intraventricular block were included only in men, and atrioventricular block and T wave inversion were included only in women. In both men and women T axis, QTc dispersion, and heart rate variability were important predictors.

The absolute risk of cardiac mortality was markedly increased in the upper decile of risk of the "ECG risk function" and rates were about 50 percent higher in men as compared to women (Table 5). The incidence rates reflect the positive predictive

value of every decile of risk. For example, of 1,000 men detected in the highest decile, on average 66 will die from coronary heart disease in a period of one year, while 934 will survive. The sensitivity of the upper decile of risk for cardiac death, i.e. the percentage of all future cases included in that decile relative to all cases that occurred during on average 4 years, was 57.5% in men and 62.2% in women. Sensitivity estimates of the upper decile of risk assessed by the "ECG risk function" were higher than those assessed by the "standard risk function" in both men and women. Analogously, incidence rates for cardiac death in the upper decile of risk were higher using the "ECG risk function", especially in women.

In men with and without symptomatic CHD, both absolute risk of cardiac death and sensitivity of the upper decile of risk increased by using the "ECG risk function" instead of the "standard risk function" (Table 6). This increase was most pronounced for the sensitivity in men without symptomatic CHD (from 23.5% to 41.2%). In men younger than 75 years, the absolute risk for cardiac death and the sensitivity in the upper decile of risk were lower than in men older than 75 years. The differences between the "ECG risk function" and the "standard risk function" were similar in both groups.

Although absolute risks were smaller, prediction of cardiac death by using the "ECG risk function" instead of the standard risk function improved more in women than in men. Incidence rates in women with and without symptomatic CHD in the highest decile of risk increased with about 10 per 1,000 persons per year. Also sensitivity improved considerably (from 39.7% to 55.2% in those without, and from 66.7% to 79.2% in those with symptomatic CHD). Sensitivity for cardiac death in the upper decile of both risk functions was much better in women over age 75 than in those younger than 75. However, incidence rates of cardiac death in the upper deciles of risk were similar in both groups. Also the difference between both risk functions was not modified by age.

Discussion

In our population-based study among men and women aged 55 years or older, the "ECG risk function", including both ECG abnormalities and conventional cardiovascular risk indicators, compared to the "standard risk function", improved predic

Table 5. Incidence rate (per 1,000 persons-years) and the sensitivity of cardiac mortality according to decile of a risk estimated by the "standard risk function" and the "ECG risk function" in men and women.

Decile	Incidence rate (95% CI)		Sensitivity (95%CI)	
	Standard	ECG	Standard	ECG
MEN				
1	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-4.5)	0.0 (0.0-4.5)
2	2.3 (0.0-5.5)	2.3 (0.0-5.5)	2.5 (0.3-8.7)	2.5 (0.3-8.7)
3	4.6 (0.1-9.1)	1.1 (0.0-3.3)	5.0 (1.4-12.3)	1.3 (0.0-6.8)
4	3.3 (0.0-7.1)	2.30.0-5.6)	3.8 (0.8-10.6)	2.5 (0.3-8.7)
5	8.9 (2.7-5.1)	4.4 (0.1-8.7)	10.0 (4.4-18.7)	5.0 (1.4-12.3)
6	2.2 (0.0-5.2)	3.5 (0.0-7.5)	2.5 (0.3-8.7)	3.8 (0.8-10.6)
7	7.0 (1.4-12.6)	7.1 (1.4-12.7)	7.5 (2.8-15.6)	7.5-2.8-15.6)
8	9.1 (2.8-15.4)	7.1 (1.4-12.9)	10.0 (4.4 (18.7)	7.5-2.8-15.6)
9	14.1 (5.8-22.5)	12.2 (4.6-19.8)	13.8 (7.1-23.3)	10.0 (4.4-18.7)
10	61.1 (41.1-81.1)	65.9 (46.8-85.0)	45.0 (33.8-56.5)	57.5 (45.9-68.5)
WOMEN				
1	0.8 (0.7-2.2)	0.0 (0.0-0.0)	1.2 (0.0-6.6)	0.0 (0.0-4.4)
2	0.0 (0.0-0.0)	0.7 (0.0-2.2)	0.0 (0.0-4.4)	1.2 (0.0-6.6)
3	0.7 (0.0-2.2)	0.7 (0.0-2.2)	1.2 (0.0-6.6)	1.2 (0.0-6.6)
4	1.4 (0.0-3.3)	0.7 (0.0-2.2)	2.4 (0.3-8.5)	1.2 (0.0-6.6)
5	1.5 (0.0-3.5)	0.7 (0.0-2.2)	2.4 (0.3-8.5)	1.2 (0.0-6.6)
6	4.2 (0.9-7.6)	3.0 (0.0-5.9)	7.3 (2.7-15.2)	4.9 (1.3-12.0)
7	3.6 (0.4-6.7)	3.6 (0.4-6.8)	6.1 (2.0-13.7)	6.1 (2.0-13.7)
8	4.5 (0.9-8.2)	2.2 (0.0-4.8)	7.3 (2.7-15.2)	3.7 (0.8-10.3)
9	16.9 (9.5-24.3)	12.0 (5.9-18.1)	24.4 (15.6-35.1)	18.3 (10.6-28.4)
10	35.3 (24.1-46.3)	48.7 (35.3-62.1)	47.6 (36.4-58.9)	62.2 (50.8-72.7)

CI= confidence interval

Table 6. Incidence rate per 1,000 person-years and sensitivity for cardiac mortality in the upper decile of risk, using the "standard risk function" and the "ECG risk function" in subgroups of age and symptomatic coronary heart disease.

	Incidence rate (95%CI)		Sensitivity (95%CI)	
	Standard	ECG	Standard	ECG
MEN				
No CHD	60.4 (26.1-94.5)	63.6 (36.3-90.9)	23.5 (12.8-37.5)	41.2 (27.6-55.8)
CHD	62.5 (37.4-87.5)	68.1 (41.3-94.8)	82.8 (64.3-94.2)	86.2 (68.4-96.1)
<= 75 years	57.1 (21.6-92.6)	59.2 (31.0-87.4)	25.6 (13.0-42.1)	44.7 (28.6-61.7)
> 75 years	64.7 (39.7-89.5)	71.1(45.1-96.9)	63.4 (46.9-77.9)	70.7 (54.5-83.9)
WOMEN				
No CHD	34.2 (20.2-48.2)	43.7 (28.5-58.8)	39.7 (27.0-53.4)	55.2 (41.5-68.3)
CHD	47.5 (24.1-70.8)	58.8 (32.2-85.2)	66.7 (44.7-84.4)	79.2 (57.8-92.9)
<= 75 years	38.5 (0.0-91.8)	63.5 (12.5-114.3)	9.5 (1.2-30.4)	28.6 (11.3-52.1)
> 75 years	38.2 (25.8-50.5)	46.9 (33.1-60.6)	60.7 (47.3-72.9)	73.8 (60.9-84.2)

CI= confidence interval

tive power for cardiac death. This finding was more pronounced in women than in men. In the upper decile of risk according to the ECG risk function, incidence rates of cardiac mortality were almost as high in those without symptomatic CHD as in those with symptomatic CHD. Our findings lend support to the view that the ECG may aid the physician in cardiovascular risk profiling of individual patients.

We chose to define only one "ECG risk function", using the "hardest" endpoint, cardiac mortality for men and women separately. This improves practical applicability of the risk function. When we examined specific "ECG risk functions" of other endpoints, such as sudden cardiac death, non-fatal coronary heart disease events, and total fatal and non-fatal cardiac events, the results were similar as compared to the "ECG risk function" for cardiac mortality.

Comparison with previous studies is limited by our use of new ECG abnormalities, such as QTc dispersion, T axis deviation, and increased HRV. These new ECG abnormalities were strong predictors of cardiac mortality in men and women. Classical repolarization disturbances, notably ST-T depression and negative T-waves, showed a strong age-adjusted association with cardiac mortality, but lost their association when they were entered in a multivariate model together with the new ECG abnormalities. In previous studies, ST-T changes, either isolated or in combination with other ischemic or hypertrophic changes, have been associated with coronary heart disease[26-31]. However, the classical repolarization disturbances were highly correlated with T-axis abnormalities, which probably attenuated their predictive value.

Our data showed that silent myocardial infarction was an even stronger predictor for cardiac death in men than symptomatic myocardial infarction, but to our surprise we could show no association of silent myocardial infarction with cardiac death in women. A possible explanation is that the ECG criteria for myocardial infarction used by our computer program are less accurate for women than for men. In the Rotterdam Study, silent myocardial infarction is relatively more common in women than in men[6]. The relatively high prevalence and the absence of an association with cardiac death in women suggest that a large proportion of silent myocardial infarction in women may be false positive diagnoses. Published reports from the

Framingham Study also suggest that the risk associated with silent myocardial infarction is more pronounced in men than in women[3, 32].

In a separate analysis we studied the predictive value of the ECG without taking the conventional cardiovascular risk indicators into account (data not shown). The predictive value of the ECG abnormalities alone was similar to that of the "standard risk function". Although in clinical practice the ECG would never be used without knowledge on the conventional cardiovascular risk indicators, the ECG might be used as a first step in the identifying patients prone to develop cardiovascular disease.

In primary care, early identification of elderly subjects at risk for cardiac mortality may be improved by the use of ECGs in addition to established cardiovascular risk indicators. The availability of computer programs with good performance, such as the MEANS program, has a positive effect on the cost-effectiveness of ECGs in general practice. It is not unlikely that conservative strategies, such as reducing weight, blood pressure or serum cholesterol, will have a positive effect on the risk associated with the ECG risk profile. As the ECG also improved identification of women with symptomatic heart disease who are at risk for cardiac death, the ECG may also be useful in a hospital setting.

Ideally, a risk function should be assessed in a "learning population" and be validated in a "test population". However, at present we do not have enough follow-up data to split our study population in subgroups. Whether the associations we found hold in other populations of older men and women has to be assessed in future studies.

In conclusion, both classical and new ECG abnormalities have independent predictive value for future coronary heart disease in older men and women. Using the ECG in addition to the standard cardiovascular risk profile may improve the identification of men and women at risk for cardiac mortality.

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CHAPTER 4

GENERAL DISCUSSION

The research described in this thesis was initiated with the aim to determine the prognostic value of electrocardiographic characteristics for future cardiovascular disease in the elderly. More specifically, the objective was to study the electrocardiogram (ECG) in non hospitalized elderly subjects as part of the cardiovascular risk profile, and use electrocardiographic information over and beyond the traditional clinical ECG diagnoses, such as Q-wave infarction, left ventricular hypertrophy, and arrhythmias. The study of the prognostic value of the ECG encompasses two related questions with a different clinical perspective. First, which ECG characteristics reflect myocardial damage or disease, and how should they be assessed? This is a diagnostic question. Second: what is the prognostic value of certain ECG abnormalities? For both diagnostic and prognostic implications of the ECG, the mechanisms underlying the abnormalities is of limited relevance. Still, to understand the etiology of ECG changes may help to reveal the nature of myocardial disease, delineate subgroups of patients that share myocardial disorders, and indicate new ways for prevention and treatment. In the work presented in this thesis, emphasis was on descriptive, e.g. diagnostic and prognostic, rather than etiologic research. The findings, however, point at mechanisms that may be involved and require future study.

To reduce variability in ECG measurements coding schemes have been developed. Moreover, computerized ECG analysis has become available and this approach has been extensively used in the current studies. This markedly improves the utility and generalizability of more subtle or complicated ECG changes in diagnosis and prognosis outside the realm of clinical cardiology. In the following, the information the standard 12-lead ECG provides on diagnosis, prognosis and etiology in non hospitalized older adults will be discussed. In addition, practical implications are indicated and suggestions are made for future research.

Chapter 4

Diagnosis

Since the invention of electrocardiography in 1902 by Willem Einthoven, the electrocardiogram has gained an important position as a diagnostic tool in clinical cardiology[1]. Today, medical students and residents are taught how to interpret an ECG to diagnose myocardial infarction, ventricular hypertrophy, conduction disorders and arrhythmias. Although, intuitively, diagnostic ECG interpretation seems rather straightforward, in practice it proves to be a complex process, based on pattern recognition and experience. Thus, standardization of ECG diagnoses by well-defined and unambiguous criteria is important. Standardization became of special importance in the fifties, when large population-based studies were started to assess the prevalence and prognosis of ECG abnormalities. This led to the introduction in 1960 of the Minnesota Code as a standardized coding system for the ECG[2]. However, the Minnesota Code is a descriptive rather than a diagnostic system for ECG characteristics. This is probably the most important reason that it has never become a standard for ECG interpretation in clinical settings, even though it proved useful in epidemiologic studies.

Apart from conventional ECG diagnoses, such as myocardial infarction and left ventricular hypertrophy, new ECG characteristics, such as prolonged QTc interval, are increasingly being recognized to be of prognostic and, thus also, of diagnostic importance. Most of the new ECG abnormalities are based on just a few measurements of interval durations or amplitudes. Again, this seems to be rather uncomplicated, but, as for diagnostic ECG interpretation, proves to be rather difficult. For instance, the end of the T wave is hard to detect. Differences in measurement techniques are an important source of variation of absolute values of ECG measurements and consequently of prevalence estimates of ECG abnormalities (chapter 3.4). Therefore, standardization of measurement techniques is of utmost importance, with important consequences for ECG diagnoses.

In the last decade, computer programs for diagnostic ECG interpretation with good performance have become available[3]. In the CSE study, the diagnostic performance in patient populations of 15 computer programs for ECG interpretation has been evaluated against clinical evidence and experienced cardiologists. In the present

study, we evaluated the diagnostic performance of our computer program MEANS against three cardiologists, in a sample of the general population (chapter 3.1). The program was at least at good as trained research physicians using a standardized form for clinical ECG interpretation. Compared to human observers, the computer has many advantages. First, it offers a standardized way to interpret ECGs, circumventing inter-and intra-observer variability among different human observers. Second, computerized ECG interpretation is efficient and inexpensive. Moreover, digital ECGs can be stored more efficiently than hard copy ECGs. Finally, some ECG measurements, such as QRS or T axis, can only indirectly be estimated from the 12-lead ECG and are much better assessed from a computer reconstructed vectorcardiogram. However, variation between the individual computer programs for ECG interpretation is considerable. Standardization of ECG measurements and diagnostic interpretations in the population at large is urgently needed, especially for new ECG abnormalities, such as QT dispersion, heart rate variability, and T axis deviation. Similar to what was done in the CSE study in a clinical setting, a reference database could be used for this purpose. Enormous amounts of digital ECGs and follow-up data are available from population-based studies all over the world. These data could be used to construct such a reference database.

The diagnostic value of ECG abnormalities, regardless of the measurement technique used, depends on their reproducibility over time. Variation in serial ECG interpretation may result from random physiologic fluctuations, such as respiration movements or autonomic balance, and from intra- and inter-observer variability, which is obviously larger for more complex measurements and diagnoses. ECG diagnoses or codes based on a single threshold level, such as many Minnesota Codes, show large variability (chapter 2.2): a few microvolts or milliseconds difference may markedly affect the coding. The use of more than two diagnostic categories or even continuous values may this problem. In addition, when a diagnostic measurement or interpretation has a poor reproducibility, multiple measurements will in general improve diagnostic accuracy.

In evaluation or development of diagnostic ECG criteria, the prognostic value of each ECG diagnosis should play a decisive role. In this thesis, this was illustrated in our studies on diagnosis and prognosis of prolonged QTc interval (chapter 2.4 and

3.1). Our findings concerning diagnosis of silent myocardial infarction in women (chapter 2.3 and 3.5), notably the relatively high prevalence of silent myocardial infarction and the absence of a clear association of silent myocardial infarction with future heart disease in women, suggests that diagnostic criteria for silent myocardial infarction in women can be improved with regard to associated risk for future heart disease. In general, ECG criteria in women need to be evaluated and improved.

Nowadays, the ECG is often used as a diagnostic instrument in clinical practice as well as epidemiologic studies. However, commonly ECG interpretation still is performed by physicians only. Regrettably, most physicians are not familiar with computerized ECG interpretation. As reliable computer programs are available, their use in both medical practice and epidemiologic research should be expanded. Although computer interpretation may be used on its own, the quality of ECG interpretation particularly improves by combining the interpretation of more observers. A computer program may have difficulties with signal problems, whereas a human observer may have difficulties with complex diagnostic rules. Thus, ideally computer ECG interpretation is complementary to the interpretation by the physician.

Etiology

For most conventional ECG abnormalities, such as infarction patterns or ventricular hypertrophy, the underlying disease process is clear. However, in many of the recently defined ECG abnormalities, such as QTc dispersion and other parameters of myocardial repolarization, the underlying mechanism remains illusive. While their prognostic implications are becoming more clear with new research findings, their pathophysiologic relation to ischemic or other myocardial disease has not yet been disclosed.

With increasing age, physiological and pathological processes change the electrical properties of the cardiac muscle[4, 5]. These processes are mutually dependent and therefore hard to disentangle. Changes occurring at a cellular level include fatty degeneration, fibrosis, hypertrophy and hypotrophy of myocardial cells and conduction tissue[4, 6-9]. Apart from aging itself, ischemia or hypertrophy of the myocardium may accelerate these degenerative processes. Autonomic changes include increasing

sympathetic tone with older age[10], increase in sympathetic response to mental and physical stress, and an increased response to negative chronotropic drugs[11]. However, autonomic balance is not only associated with aging, but also with many other processes, such as respiration, diabetic neuropathy, left ventricular dysfunction and coronary heart disease. Thus, the mechanism underlying ECG findings associated with subclinical disease and autonomic balance, such as decreased and increased heart rate variability, prolonged QTc interval, QTc dispersion, ST-T abnormalities and T axis deviation, is complex and requires further attention. In epidemiologic studies the ECG may be used for etiologic purposes, as was demonstrated in studies investigating determinants and outcome of autonomic dysfunction[12-14]. However, in interpreting the results of such etiologic studies, the limitations described above should be kept in mind.

Particular problems arise in etiologic analyses in epidemiologic studies. Since for many ECG abnormalities the mechanism is unknown, it is hard to judge whether non electrocardiographic risk indicators for cardiac disease, such as blood pressure, body mass index and serum cholesterol level, should be treated as confounders in a multivariate analysis. Many non-electrocardiographic cardiovascular risk indicators are associated with the same mechanisms as electrocardiographic risk indicators. For instance, body mass index and blood pressure are associated with autonomic balance. Although these variables are commonly treated as possible confounders of the association between ECG abnormalities and heart disease, they may in fact be intermediates or otherwise be part of the causal pathway, and consequently they should be left out of the multivariate model. In most analyses we performed, the risk estimates were not materially influenced by additional adjustment for non-electrocardiographic risk indicators. This suggests that these non-electrocardiographic risk indicators were neither confounders nor intermediates in the association of ECG abnormalities with future heart disease.

The etiology underlying a disease or diagnosis may form the basis of treatment policies, which may improve the prognosis of a disease. In a clinical setting, the use of ECG abnormalities with an unknown etiology, has little direct therapeutic meaning.

To further elucidate the mechanism underlying ECG abnormalities, especially ECG parameters of repolarization, experimental studies could be performed. In a controlled setting, different mechanism simultaneously playing a role may be explored. This is important to establish a basis for clinical understanding of ECG abnormalities. However, practical diagnostic implications of such controlled electrocardiographic investigations may be limited. The strength of the ECG in clinical practice lies in its simplicity. The standard 12-lead ECG is fast and non-invasive. In the clinical situation, electrocardiographic tests under controlled situations, taking much more of time, will have to compete with many other diagnostic imaging techniques.

Prognosis

Prognosis is concerned with clinical outcome, regardless of the underlying mechanism, and is often described by the term "predictive value". In the assessment of predictive value of ECG abnormalities for groups of subjects, absolute rather than relative risks are of interest.

In many population-based studies (chapter 1), as well as in our own studies (chapter 3), it has been shown that the ECG can be used to identify men and women at increased risk for future heart disease and mortality. However, even if ECG abnormalities are strong predictors for future coronary heart disease, a risk indicator is only valuable to medical practice if it adds something to other commonly available elements of the cardiovascular risk profile, by further improving the detection of subjects at increased, absolute risk for future heart disease. Indeed, we found that the ECG may improve cardiovascular risk profiling in the elderly, especially in women (chapter 3.5). In older men and women, in whom the absolute risk for coronary heart disease is relatively high, the ECG may serve as a useful tool for risk stratification, to be used in addition to or even as a substitute for other well-known cardiovascular risk-indicators

New ECG risk indicators, in particular T axis deviation and QTc dispersion, are strong predictors of cardiac outcome. The risk for cardiac death associated with these new ECG abnormalities was at least as high as or even higher than the risk associated with conventional ECG abnormalities, such a myocardial infarction or

left bundle branch block.

In the prediction of cardiac mortality in the elderly, in men other ECG abnormalities appeared to be important than in women. ECG abnormalities which played a role in both men and women, often showed stronger associations in women. These findings may partly be explained by selective survival[15]. As in men the disease starts at an earlier age, many of those susceptible to the disease may have died already and the survivors may be less susceptible to the disease or express different disease manifestations.

Should the ECG be used to identify elderly persons at increased risk in medical practice or in cardiovascular screening? Even though the predictive value of ECGs in the elderly is clear, the answer to this question depends on related "costs" and "benefits". There are costs in terms of money and time. The ECG should be used in addition to and not instead of other preventive strategies, such as detection and treatment of high blood pressure and high serum cholesterol. There are also costs in terms of consequences for patients. For instance, an old men with a silent MI, who never knew he was ill, suddenly becomes a patient with heart disease. Especially at older age, changes is lifestyle may be experienced as a heavy burden. On the other hand, benefits it terms of a longer healthy life expectancy, may outweigh the costs.

Reduction of increased risk may be approached in a specific or general way. When the underlying disease is known, for instance a diagnosis of myocardial infarction or left ventricular hypertrophy, specific treatment may be installed. Recent studies have indicated that treatment of left ventricular hypertrophy reduces the incidence of coronary heart disease[16]. Subjects with silent myocardial infarction may benefit from the same treatment as patients with symptomatic myocardial infarction, particularly men.

If the underlying disease is largely unknown, subjects at high risk for cardiac disease will profit most from general cardiovascular preventive measures[17]. An improvement of the cardiovascular risk profile, for instance by treatment of hypertension or high cholesterol, will probably improve outcome in those with ECG abnormalities, with probably larger absolute yields.

Further research is needed to develop and evaluate preventive strategies for subjects

with ECG abnormalities. This may be assessed in clinical trials as well as in studies of determinants and outcome of serial changes in ECG abnormalities.

Conclusions

The results of our own studies and and of work by others, have expanded the potential for the ECG in the diagnosis of cardiac disease, and prognostic evaluation in cardiovascular risk assessment. While their mechanisms remain to be determined, several "new" ECG abnormalities may be detected using standardized or computerized measurement techniques. Further knowledge of the pathophysiological basis of ECG changes, such as T axis deviation and QTc dispersion, may help to further understand the nature and sequence of myocardial changes in coronary artery disease. Today, there is a range of powerful imaging techniques available for diagnosis of cardiovascular disease and the practice of risk profiling is constantly being defined. However, the ECG is inexpensive and non invasive, and new information remains to be disclosed as shown by our results. With the availability of sensitive and reproducible computerized ECG analysis, the prospect is offered of serial assessment of ECG abnormalities and direct monitoring of ECG changes in patients over time. For these reasons, the ECG will maintain its central position in cardiovascular diagnosis and prognosis, and has not lost any of its value about 100 years after discovery. Electrocardiography deserves further, preferably multidisciplinary, attention to further improve its value.

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CHAPTER 5

SUMMARY

In most developed countries, the proportion of elderly people in the population is expected to increase further in the next decades. Cardiovascular disease is a leading cause of death and disability in the elderly and the incidence rates of cardiac diseases in older adults are predicted to increase significantly in the years to come.

Since the invention of electrocardiography in 1902 by Willem Einthoven, the electrocardiogram (ECG) has gained an important position in clinical cardiology. In the last decade, computer programs for ECG interpretation with good performance have become available, improving the applicability of ECGs in medical practice and epidemiologic research. The ECG offers an inexpensive, noninvasive means to determine the presence of coronary heart disease as well as other cardiac abnormalities, such as ventricular hypertrophy and atrial fibrillation, known to be associated with the risk of future cardiovascular events. This suggests a potential for ECG analysis in cardiovascular screening. Especially in the elderly, in whom medical histories may be troubled by concomitant diseases and of which documentation is not always as reliable as one would like, the ECG could serve as a useful diagnostic and prognostic instrument, also outside the hospital.

The research described in this thesis was initiated with the aim to determine the prognostic value of electrocardiographic parameters for future cardiovascular disease in the elderly. The study of the prognostic value of the ECG encompasses two related questions with a different clinical perspective. First, which ECG parameters reflect myocardial damage or disease, and how should they be assessed? This is a diagnostic question. Second: what is the prognostic value of certain ECG abnormalities?

In **chapter 1**, a review of the literature on the prevalence and prognosis of ECG abnormalities in the elderly is given. To improve the comparability between studies, prevalence data are presented for all studies using the Minnesota Code for classification of ECG abnormalities. The prevalence of most Minnesota Codes showed wide variation across individual studies. Part of this variation may be due to a lack of standardization of coding procedures, for which computer programs may

offer a solution. The prevalence of abnormal ECG findings is relatively high in the elderly. The prevalence of most ECG abnormalities increases with age and is higher in men than in women. Most ECG abnormalities are associated with an increased risk of future coronary heart disease.

All diagnostic and prognostic studies described in **chapters 2 and 3** are part of the Rotterdam Study, a population-based study among 7,983 men and women aged 55 years or older, aimed at assessing the occurrence and risk factors for chronic diseases in the elderly.

To establish an efficient and standardized way for interpreting large numbers of ECGs in population-based studies, we assessed the performance of diagnostic ECG interpretation by both the ECG computer program MEANS (Modular ECG Analysis System) and research physicians, and compared it with the interpretation of cardiologists (**chapter 2.1**). We studied the diagnostic performance of three scenarios: use of the computer program alone (A), computer program and cardiologist combined (B), and computer program, research physician and cardiologist combined (C). To diagnose left ventricular hypertrophy and left and right bundle branch block the computer program alone gave satisfactory results. Preferably, however, findings of anterior and inferior MI by the program, need to be verified by a cardiologist. Diagnostic ECG interpretation by computer can be very helpful in population-based research, is at least as good as ECG interpretation by a trained research physician, but is much more efficient and, therefore, less expensive.

In clinical practice, the relevance of diagnostic or prognostic determinants heavily depends on its reproducibility in an individual. In view of this, knowledge about the reproducibility of ECG measurements and coding is essential. We assessed minute-to-minute, day-to-day, and year-to-year variability of computerized ECG measurements, composite scores, and Minnesota Code classification, in 101 non-hospitalized elderly men and women (**chapter 2.2**). Overall, variability between ECG measurements tended to increase with time. In a routine setting, electrode positioning had a relatively small effect on the total variability. ECG interval measurements were more reproducible than amplitude measurements. The best reproducibility was found for the overall QTc interval and the poorest

reproducibility for the Cardiac Infarction Injury Score. Minnesota Code discrepancies occurred frequently; 16%, 19% and 22% in the minute-to-minute, day-to-day, and year-to-year group, respectively. Part of this variability may be explained by the fact that most codes use a single threshold. For borderline measurements, a few milliseconds difference may dramatically change the coding. A way to deal with poor reproducibility of measurements in clinical practice is the use of repeated measurements to establish the presence or absence of an ECG diagnosis.

The estimated prevalence of ECG abnormalities is directly based on diagnostic criteria and measurement techniques. In **chapter 2.3**, we assessed the prevalence of different types of myocardial infarction (MI), notably "typical MI" (MI with symptoms and matching ECG abnormalities), "silent MI" (asymptomatic MI, diagnosed by ECG abnormalities only), and "non-Q-wave MI" (symptomatic MI, clinically diagnosed by raised cardiac enzyme levels, but without matching ECG abnormalities). Overall, the prevalence of "typical MI" was 4.1% (95%CI 3.5-4.9), of "non-Q-wave MI" 2.8% (95%CI 2.2-3.4), and of "silent MI" 3.9% (95%CI 3.2-4.5). Thus, in the elderly, MIs frequently occur without typical symptoms or ECG changes. Misclassification due to incomplete sources of information can be considerable and should be taken into account in the design and interpretation of epidemiologic studies. As all these silent manifestations of MI also convey an increased risk of symptomatic heart disease or death, they require further attention. In **chapter 2.4**, we studied variation in the prevalence of prolonged QT in the Rotterdam Study, based on several accepted definitions, and compared our results with those from other studies applying the same definitions. Prolonged QT is frequent both in men and women, and its prevalence increases with age. Women have longer heart-rate adjusted QT intervals than men. Depending on the formula used to adjust QT for heart rate and the threshold used to define prolonged QT, the prevalence of prolonged heart-rate adjusted QT varies from 6% in men and 9% in women using QT index, to 31% in men and 26% in women using a linear regression equation. In comparisons with other studies applying the same correction formulas and adjusting for age showed large discrepancies in prevalence estimates of prolonged heart-rate adjusted QT remain, probably largely attributable to

differences in measurement technique.

In **chapter 3**, the prognostic value of several relatively "new" ECG abnormalities, measured by the ECG computer program MEANS, for future cardiovascular disease and mortality is described. All studies in **chapter 3** are restricted to 2,358 men and 3,454 women, participating in the Rotterdam Study, for whom a digital ECG and follow-up information was available. During the 3 to 6 (mean 4) years of follow-up, 568 (9.8%) subjects died.

Prolonged heart-rate adjusted QT interval has been associated with an increased risk for ventricular arrhythmias, sudden death, and coronary heart disease in patient populations, but studies in the population at large have shown controversial results. We examined the association between heart-rate adjusted QT interval, using different formulas to correct for heart rate, and cardiac and all-cause mortality (**Chapter 3.1**). Participants in the highest quartile of heart-rate adjusted QT intervals had about a 70% age- and sex-adjusted increased risk for both all-cause mortality (hazard ratio (HR) 1.8; 95%CI:1.3-2.4) and cardiac mortality (HR 1.7; 95%CI:1.0-2.7) compared to those in the lowest quartile. These risk estimates do not change after adjustment for potential confounders. In women, increased risk associated with prolonged QT for cardiac death is more pronounced than in men. The risk associated with prolonged QT is hardly affected by the heart-rate correction formula used.

Increased QTc dispersion has been associated with an increased risk for ventricular arrhythmias and cardiac death in selected patient populations, using manual measurements. QTc dispersion has been hypothesized to reflect local differences in ventricular repolarization, resulting from myocardial ischemia and patchy myocardial fibrosis. QTc dispersion was computed by MEANS as the difference between the maximum and minimum QTc interval in 12 leads and 8 leads. For QTc dispersion in 8 leads, those in the highest tertile relative to the lowest tertile, had about a twofold risk for cardiac death (HR 2.5; 95%CI 1.6-4.0) and sudden cardiac death (HR 1.9; 95%CI 1.0-3.7), and a 40% increased risk for total mortality (HR 1.4; 95%CI 1.2-1.8) (**chapter 3.2**). Additional adjustment for potential confounders does not materially change the risk estimates. Hazard ratios for QTc dispersion in

12 leads are comparable to those found for QTc dispersion in 8 leads. QTc dispersion is an important predictor of cardiac mortality in older men and women.

In **chapter 3.3** we studied a new ECG characteristic, the electrical T axis, which we hypothesized to be a general marker of repolarization abnormality, indicative of subclinical myocardial damage. Subjects with an abnormal T axis have increased risks for cardiac death (HR 3.9; 95%CI 2.8-5.6), sudden cardiac death (HR 4.4; 95%CI 2.6-7.4), non-fatal cardiac events (HR 2.7; 95%CI 1.9-3.9), and combined fatal or non-fatal cardiac events (HR 3.2; 95%CI 2.5-4.1). Additional adjustment for established cardiovascular risk indicators results in lower, but still highly significant risks for all endpoints. The risks associated with an abnormal T axis are higher than those of any other cardiovascular risk indicator. The T axis is a new, strong, and independent risk indicator of fatal and non-fatal cardiac events in the elderly.

In **chapter 3.4** we examined the association between heart rate variability (HRV) on a standard 10-second ECG, and cardiac and all-cause mortality. HRV, calculated as the standard deviation of normal RR intervals (SDNN), was categorized into quartiles. The third quartile of SDNN was used as the reference category. Subjects in the lowest quartile compared to those in the third quartile of SDNN, have an 80% age- and sex-adjusted increased risk for cardiac mortality (HR 1.8; 95%CI:1.0-3.2). Interestingly, for subjects in the highest quartile of SDNN compared to those in the third quartile, an even more pronounced risk for cardiac mortality is present (HR 2.3; 95%CI:1.3-4.0). As has been suggested by many other studies, decreased HRV is probably largely due to changes in autonomic balance. Presumably, increased HRV is hardly influenced by the autonomic nervous system, but may rather be due to sinus node dysfunction.

Clinical relevance of electrocardiographic risk indicators largely depends on the added prognostic value of ECG abnormalities in addition to other cardiovascular risk indicators, in identifying subjects at increased risk for future heart disease. In **chapter 3.5** we studied the predictive value of conventional and "new" ECG abnormalities for cardiac mortality, when used in addition to the cardiovascular risk profile commonly available in general practice. In both men and women, the highest age-adjusted incidence of cardiac death was found in subjects with an abnormal T

axis (28.7 and 27.2 per 1,000 person-years, respectively). In men, a strong association of silent myocardial infarction with future coronary heart disease was found. This association was absent in women. Apart from silent myocardial infarction, most ECG abnormalities showed a stronger association with cardiac death in women than in men. The "ECG risk function" including both ECG abnormalities and conventional cardiovascular risk indicators, compared to the "standard risk function", improves the predictive power for cardiac death. This finding is more pronounced in women than in men. In the upper decile of risk according to the ECG risk function, incidence rates of cardiac mortality are almost as high in those without symptomatic coronary heart disease as in those with symptomatic coronary heart disease. Our findings lend support to the view that the ECG may aid the physician in cardiovascular risk profiling of individual patients.

In conclusion, in **chapter 4** the implications of the studies presented in this thesis are discussed and recommendations for future research are given. The ECG is an inexpensive and noninvasive diagnostic test with important prognostic properties, notably in non-hospitalized subjects. Development of ECG computer programs, that have been shown to perform well has certainly increased its applicability. As shown by our results, new information from the ECG remains to be disclosed. In addition, sensitive and reproducible ECG analysis by computer offers possibilities for serial ECG analysis. Even today, when powerful imaging techniques are available, the ECG maintains a central position in the diagnosis and prognosis of cardiovascular disease. Electrocardiography clearly deserves, preferably multidisciplinary, attention to further improve its value in epidemiologic research and cardiovascular risk profiling.

CHAPTER 6

SAMENVATTING

In veel westerse landen zal naar verwachting in de komende jaren het percentage ouderen in de bevolking verder toenemen. Hart-en vaatziekten vormen een belangrijke oorzaak van ziekte en sterfte bij ouderen en het valt daarom te verwachten dat de totale incidentie van hart-en vaatziekten de komende jaren eveneens sterk zal toenemen.

Sinds de uitvinding van electrocardiografie in 1902 door Willem Einthoven heeft het electrocardioam (ECG) een belangrijke plaats in de klinische cardiologie verworven. In de jaren '90 zijn goede computer programma's voor ECG interpretatie beschikbaar gekomen, die het gebruik van ECG's in de medische praktijk en in epidemiologisch onderzoek hebben bevorderd. Het maken van een ECG is goedkoop en niet erg belastend voor de patiënt en geschikt voor het vaststellen van coronaire hartziekten en andere afwijkingen, die samenhangen met de kans op het optreden van toekomstige cardiovasculaire ziekten. Het ECG kan aldus worden benut voor screening op toekomstig risico voor hart-en vaatziekten. Vooral bij ouderen, bij wie de anamnese bemoeilijkt kan worden door de aanwezigheid van meerdere ziekten, zou het ECG als een zinvol diagnostisch en prognostisch instrument kunnen dienen, ook buiten de kliniek.

Het onderzoek dat in dit proefschrift beschreven wordt, heeft tot doel de prognostische waarde van ECG kenmerken voor toekomstige hart- en vaatziekten bij ouderen te bepalen. Bij het bestuderen van de prognostische waarde van het ECG zijn twee verschillende vraagstellingen van belang. Ten eerste, welke ECG kenmerken reflecteren reeds aanwezige hartschade of hartziekte, en hoe moeten deze kenmerken worden bepaald? Dit is een diagnostische vraag. Ten tweede, wat is de prognostische waarde van bepaalde ECG afwijkingen?

In **hoofdstuk 1** wordt een overzicht gegeven van de literatuur over de prevalentie en de prognose van ECG afwijkingen bij ouderen. Om de verschillende onderzoeken zo vergelijkbaar mogelijk te maken, wordt de Minnesota Code gebruikt voor klassificering van ECG afwijkingen. Toch blijken grote verschillen te bestaan tussen studies onderling. Dit kan voor een deel verklaard worden door een gebrek aan

standaardisering van codeerprocedures, hetgeen opgelost zou kunnen worden met de tegenwoordig beschikbare computer programma's. De prevalentie van ECG afwijkingen bij ouderen is relatief hoog. Veel ECG afwijkingen komen vaker voor op hogere leeftijd en vaker bij mannen dan bij vrouwen. De meeste ECG afwijkingen zijn gerelateerd aan het optreden van toekomstige hartziekten.

In het onderzoek dat wordt beschreven in **hoofdstuk 2 en 3** is gebruik gemaakt van gegevens die verzameld zijn in het Erasmus Gezondheid Ouderen (ERGO) onderzoek, in het Engels 'Rotterdam Study' genoemd. Het ERGO onderzoek is een bevolkingsonderzoek bij 7983 mannen en vrouwen van 55 jaar en ouder, dat tot doel heeft het optreden van chronische ziekten bij ouderen te onderzoeken en de risicofactoren die daarbij een rol kunnen spelen.

Met als doel om te komen tot een efficiënte en gestandaardiseerde methode voor de interpretatie van grote hoeveelheden ECG's in bevolkingsonderzoeken, hebben we de diagnostische prestaties van het computer programma MEANS en onderzoeksartsen vergeleken met die van cardiologen, binnen ons bevolkingsonderzoek (**hoofdstuk 2.1**). We vergeleken de diagnostische prestaties van drie verschillende scenario's waarin: (A) ECG's alleen door het computer programma worden beoordeeld, (B) de door de computer gevonden afwijkingen worden geverifieerd door een cardioloog, of (C) alle ECG's zowel door de computer als de onderzoeksarts worden beoordeeld en de ECG's waarover zij van mening verschillen door de cardioloog worden beoordeeld. Het blijkt dat voor diagnostiek van linker ventrikel hypertrofie en linker- en rechter bundeltakblok het computerprogramma bevredigende resultaten geeft. Het verdient echter aanbeveling om alle voor- en achterwandinfarcten die door de computer worden gediagnostiseerd worden te laten verifiëren door een cardioloog. De computer presteert minstens zo goed als speciaal opgeleide onderzoeksartsen en computer interpretatie is bovendien efficiënter en dus een stuk goedkoper.

In de klinische praktijk wordt de relevantie van een diagnostische of prognostische bepaling in belangrijke mate bepaald door de reproduceerbaarheid van de meting in de individuele patiënt. Wij bestudeerden de reproduceerbaarheid binnen minuten, dagen en jaren van computermatige ECG metingen, samengestelde scores en

Minnesota Codes, in een steekproef van 101 deelnemers aan het ERGO onderzoek (**hoofdstuk 2.2**). De variabiliteit nam toe met de tijd die lag tussen de ECG's. De plaatsing van electroden heeft weinig invloed op de totale variabiliteit. Metingen van ECG intervallen zijn beter reproduceerbaar dan metingen van ECG amplitudes. Wij vinden de beste reproduceerbaarheid voor het QTc interval en de minst goede voor de Cardiac Infarction Injury Score. Discrepanties in Minnesota Codes komen veel voor: in 16% van de ECGs voor de vergelijking binnen minuten, in 19% van de ECGs voor de vergelijking binnen dagen en in 22% van de ECGs voor de vergelijking binnen jaren. Dit zou gedeeltelijk verklaard kunnen worden doordat de meeste codes een enkelvoudige drempelwaarde gebruiken. Voor metingen die dicht bij de drempelwaarde liggen kan een verschil van enkele milliseconden codering drastisch veranderen. In de medische praktijk kan slechte reproduceerbaarheid van metingen ondervangen worden door herhaalde metingen toe te passen om de aan- of afwezigheid van een ECG diagnose vast te stellen.

De geschatte prevalentie van ECG afwijkingen is gebaseerd op diagnostische criteria en meettechnieken. In **hoofdstuk 2.3** bepaalden we de prevalentie van verschillende typen myocardinfarct (MI), namelijk het 'typische MI' (MI met bijpassende symptomen en ECG afwijkingen), het 'stille MI' (MI zonder symptomen maar met karakteristieke ECG afwijkingen) en het 'luide MI' (MI met bijpassende symptomen maar zonder karakteristieke ECG afwijkingen, gediagnostiseerd met behulp van enzymbepalingen). De prevalentie van het 'typische MI' was 4,1% , van het 'stille MI' 3,9% , en van het 'luide MI' 2,8%. Bij ouderen komen hartinfarcten dus relatief vaak voor zonder symptomen of zonder ECG afwijkingen. Misclassificatie van MI door het gebruik van beperkte informatiebronnen kan aanzienlijk zijn en daar moet rekening mee worden gehouden bij de opzet en interpretatie van epidemiologische studies. Al deze manifestaties van MI geven een verhoogd risico op symptomatische hartziekten of sterfte en verdienen meer aandacht. **Hoofdstuk 2.4** geeft de resultaten van onderzoek naar de variatie in de prevalentie van verlengd QT gecorrigeerd voor hartfrequentie, gebaseerd op verschillende beschikbare definities, en onze resultaten worden vergeleken met die van andere studies die dezelfde definities gebruikten. Een verlengd QT interval komt vaak voor bij zowel mannen als vrouwen en de prevalentie neemt toe met de leeftijd. Bij vrouwen is het

voor hartfrequentie gecorrigeerde QT interval langer dan bij mannen. Afhankelijk van de formule die gebruikt wordt om QT te corrigeren voor hartfrequentie en van de drempelwaarde voor verlengd QT, varieert de prevalentie van 6% bij mannen en 9% bij vrouwen voor QT index tot 31% bij mannen en 26% bij vrouwen voor de lineaire regressie-correctie. Vergelijking met andere studies die dezelfde correctie formule gebruikten liet na correctie voor leeftijdsverschillen grote verschillen zien in prevalentieschattingen van gecorrigeerd QT interval, beide worden waarschijnlijk vooral veroorzaakt door verschillen in meettechnieken.

In **hoofdstuk 3** wordt de prognostische waarde van enkele 'nieuwe' ECG afwijkingen, bepaald met het computer programma MEANS, voor het optreden van toekomstige hartziekten beschreven. Alle studies in dit hoofdstuk werden verricht bij de 2358 mannen en 3454 vrouwen in het ERGO onderzoek, van wie zowel een digitaal ECG als follow-up informatie over het optreden van hart- en vaatziekten beschikbaar was. Gedurende de 3 tot 6 (gemiddeld 4) jaar follow-up zijn 568 (9,8%) deelnemers overleden.

Verlengd QT, gecorrigeerd voor hartfrequentie, is in verband gebracht met ventriculaire ritmestoornissen, plotselinge dood en coronaire hartziekten in onderzoek bij geselecteerde patiëntgroepen, maar studies in de algemene bevolking laten tegenstrijdige resultaten zien. Wij onderzochten de relatie tussen QT interval, gecorrigeerd voor hartfrequentie middels verschillende formules (QTc), en het risico op totale en cardiale sterfte (**hoofdstuk 3.1**). Deelnemers met QTc intervallen in hoogste 25% van de QTc verdeling hebben, na correctie voor leeftijd en geslacht, een 70% grotere kans om te sterven en om te sterven aan cardiale oorzaken, dan deelnemers met QTc intervallen in de laagste 25% van de verdeling. Dit risico wordt niet verklaard door andere risico factoren. Het risico bij een verlengd QT is groter voor vrouwen dan voor mannen. Het gebruik van verschillende correctieformules had weinig effect op de risicoschattingen.

Een toegenomen dispersie van het QTc interval is in voorgaand onderzoek in verband gebracht met een verhoogd risico op ventriculaire ritmestoornissen en hartsterfte onder geselecteerde patiëntgroepen. Hierbij waren de metingen met de hand werden uitgevoerd. QTc dispersie zou het gevolg kunnen zijn van lokale

verschillen in repolarisatiesnelheid van de hartspier, die veroorzaakt worden door ischaemie en vorming van littekenweefsel in de hartspier. Wat betreft QTc dispersie in 8 afleidingen hebben mensen in het hoogste tertiel ten opzichte van mensen in het laagste tertiel een tweemaal zo hoog risico op cardiale dood en plotselinge hartdood en een 40% hoger risico op totale sterfte (**hoofdstuk 3.2**). Correctie voor andere samenhangende variabelen heeft weinig invloed op deze risicoschattingen. De risico's voor cardiale sterfte geassocieerd met QTc dispersie in 12 afleidingen waren vergelijkbaar met die voor QTc dispersie in 8 afleidingen. QTc dispersie is een belangrijke voorspeller voor cardiale sterfte onder oudere mannen en vrouwen.

In **hoofdstuk 3.3** introduceren we een nieuw ECG kenmerk, de electrische T as. We stelden dat de T-as een algemene maat voor repolarisatiestoornissen zou kunnen zijn, die samenhangt met schade aan de hartspier. We onderzochten de prognostische waarde van de T-as voor fatale en niet-fatale cardiale problemen. In vergelijking tot mensen met een normale T-as hebben mensen met een abnormale T-as een vier maal zo hoog risico op cardiale dood en plotse hartdood en een bijna drie maal zo hoog risico op niet-fatale coronaire hartziekte. Correctie voor bekende risicofactoren voor hart- en vaatziekten resulteert in lagere, maar nog steeds statistisch significant verhoogde risico's voor alle eindpunten. De risico's die samenhangen met een abnormale T-as zijn hoger dan die van de andere cardiovasculaire risicoindicatoren. De T-as is een nieuwe, sterke risicoindicator voor fatale en niet-fatale hart- en vaatziekten bij ouderen.

In **hoofdstuk 3.4** onderzochten we de relatie tussen hartritmevariabiliteit (HRV) in het standaard 10-seconden ECG en cardiale sterfte. HRV werd bepaald als de standaard deviatie van alle normale RR intervallen (SDNN) en werd vervolgens verdeeld in kwartielen. Het derde kwartiel van SDNN werd gebruikt als referentie. Mensen in het laagste kwartiel vergeleken met die in het derde kwartiel hadden na correctie voor leeftijd en geslacht een 80% hoger risico op cardiale sterfte. Een interessante bevinding was dat mensen in het hoogste kwartiel SDNN vergeleken met die in het derde kwartiel zelfs een meer dan twee maal zo hoog risico hebben op cardiale sterfte. Zoals reeds in eerder onderzoek is gesuggereerd, wordt het risico gerelateerd aan verminderde HRV waarschijnlijk voornamelijk veroorzaakt door een slechte autonome balans. Verhoogde HRV daarentegen wordt waarschijnlijk

nauwelijks beïnvloed door autonome functie, maar is eerder het gevolg van een verminderde functie van de sinusknoop.

De klinische relevantie van electrocardiografische risicoindicatoren in sterk afhankelijk van de toegevoegde waarde van ECG afwijkingen aan het conventionele cardiovasculaire risicoprofiel, voor het identificeren van mensen met een verhoogd absoluut risico op hart- en vaatziekten. In **hoofdstuk 3.5** bestudeerden we de voorspellende waarde van ECG afwijkingen voor cardiale sterfte, wanneer het ECG gebruikt wordt als aanvulling op het gewone cardiovasculaire risicoprofiel, zoals dat bijvoorbeeld in de huisartsenpraktijk gebruikt wordt. Bij zowel mannen als vrouwen is na correctie voor leeftijd de hoogste incidentie van hartsterfte aanwezig bij mensen met een abnormale T-as (respectievelijk 28.7 en 27.2 per 1000 persoonsjaren). Bij mannen is er een sterk verband van 'stil myocardinfarct' met toekomstige hart-en vaatziekten, terwijl dit verband niet voor vrouwen geldt. Voor de meeste ECG afwijkingen, behalve het stille hartinfarct, is het risico voor cardiale sterfte hoger voor vrouwen dan voor mannen. De 'ECG risicofunctie', opgebouwd uit ECG afwijkingen en conventionele cardiovasculaire risicoindicatoren, geeft een betere voorspellende waarde voor cardiale sterfte dan de 'standaard risicofunctie', die alleen uit niet-electrocardiografische risicoindicatoren was opgebouwd. Dit verschil is groter bij vrouwen dan bij mannen. Onze resultaten steunen het idee dat het ECG de arts kan helpen bij risicoprofilering van individuele patiënten.

Tenslotte beschouwen we in hoofdstuk 4 de implicaties van de studies die in dit proefschrift worden beschreven en doen we aanbevelingen voor verder onderzoek. Het ECG is een goedkope, niet-invasieve diagnostische test met belangrijke prognostische eigenschappen. De ontwikkeling van goed presterende ECG computer programma's hebben de toepasbaarheid van het ECG vergroot, met name voor bevolkingsonderzoeken. Onze resultaten laten zien dat er nog steeds nieuwe informatie in het ECG ontdekt kan worden. Tegenwoordig zijn krachtige beeldvormende technieken beschikbaar, maar desondanks behoudt het ECG zijn centrale rol in diagnose en prognose van hart- en vaatziekten. Electrocardiografie verdient meer, liefst multidisciplinaire aandacht, om zijn waarde verder te kunnen benutten.

Dankwoord

Dit proefschrift is het resultaat van een bijzondere en vruchtbare samenwerking tussen vijf mensen werkzaam op het Instituut Epidemiologie & Biostatistiek en de afdeling Medische Informatica van de Erasmus Universiteit. Het feit dat ik deel mocht uitmaken van deze inspirerende samenwerking, is waarschijnlijk de meest waardevolle les die ik de afgelopen vier jaar heb geleerd. Ik hoop dat in de toekomst deze samenwerking zal voortleven, zowel binnen als buiten Rotterdam.

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delen, in de wetenschap dat ze daarna zelf ook beoordeeld zouden worden. Peter Klootwijk stelde zijn gloednieuwe apparatuur beschikbaar voor analyse van hartritmevariabiliteit. Ik heb er met plezier mee gewerkt, in goed gezelschap van Angela en Marianne, die mij veel hebben geleerd over de analyse van hartritme.

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Curriculum vitae

Margaretha Christine (Martine) de Bruyne was born on January 4, 1967 in Utrecht, the Netherlands. From 1979 to 1985 she attended Gymnasium-ß at the Gymnasium Celeanum in Zwolle.

In 1985 she started her medical studies at the University of Amsterdam and she obtained her medical degree in 1993. Starting in 1987, she also studied Medical Informatics at the University of Amsterdam. In 1988 and 1989 she was a student member of the faculty board of Medical Informatics. In April 1991 she graduated on the project 'Decision support in general practice based on the NHG standards'. In the same year she worked four months in the Advanced Computing Laboratory of the Imperial Cancer Research Fund in London, where she performed studies on the development and implementation of a protocol for treatment of hyperlipidaemia in the Oxford System of Medicine. In 1991 and 1992 she worked part-time for VVAA as an advisor for the development of MicroHIS, an information system for general practice.

In 1993 she started the work described in this thesis at the department of Epidemiology and Biostatistics and the Department of Medical Informatics, Erasmus University Medical School in Rotterdam (promotores Prof. dr. D.E. Grobbee and Prof. dr. ir. J.H. van Bemmel). She was managing editor of the 'Yearbook of Medical Informatics' published by the International Medical Informatics Association, from 1995 to 1997.

In 1996 she achieved the Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam.

From November 1997 she will probably be working at the Julius Centre for Patient-Oriented Research, where she will be involved with quality of care research in general practice.