ELECTROCARDIOGRAPHIC RISK FACTORS FOR SUDDEN DEATH

Cover: Rhythm strip of a patient who died suddenly within two years after 24-hour electrocardiography. The lack of short-term heart rate variability on this apparently normal electrocardiogram is an important indicator of an increased risk for sudden death. See figure 5.3, upper panel (same patient).

ELECTROCARDIOGRAPHIC RISK FACTORS FOR SUDDEN DEATH

A study with 245 cases of sudden death during a two-year follow-up after 24-hour electrocardiography in 6693 patients

ELECTROCARDIOGRAFISCHE RISICOFACTOREN VOOR PLOTSELINGE DOOD

Een onderzoek met 245 gevallen van plotselinge dood in de twee jaar na 24 uurs electrocardiografie bij 6693 patiënten

PROEFSCHRIFT

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aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus Prof. Dr. C.J. Rijnvos
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aan Margriet
aan Annemijn en Jelle
aan mijn ouders

CONTENTS

1. Introduction

Approximately 45% of all mortality in the industrialized world is caused by cardiovascular diseases. Up to 40% of all coronary heart disease deaths are estimated to occur suddenly.[1] The mechanism generally believed to be responsible for the fatal event is ventricular fibrillation either in the presence of a myocardial infarction or not.

RESEARCH ON SUDDEN DEATH AT THE THORAXCENTER, ROTTERDAM

Precursors of sudden death were studied in several projects at the Thoraxcenter, a joint institute of the departments of cardiology and cardiopulmonary surgery of the University Hospital Rotterdam-Dijkzigt engaged in patient care and clinical and basic research. Pool et al. described in 1978 two monitored cases of sudden death outside hospital.[2] In the IMIR[3] study early recognition of myocardial infarction in general practice was investigated as was done in the TRACE-project,[4] in which several tests for the diagnosis of myocardial infarction were made available to general practitioners. Velema et al. studied the prognostic value of arrhythmias detected by routine analysis of 24 hour electrocardiograms on the occurrence sudden death.[5] Roelandt et al. reported on terminal arrhythmias in a series of 20 patients who died during 24 hour electrocardiogram registration.[6] The studies of Velema and Roelandt were based on rhythm analysis with semi automatic analyzers developed for routine clinical use. Zeelenberg and coworkers developed methods for QRS detection by computer in 24 hour electrocardiograms[7] and implemented a system for detailed analysis of these recordings.[8] This system, ARGUS-TX, provides accurate quantification of ventricular arrhythmias as well as detailed measurements of RR intervals. In the IMPACT trial, an international multicenter randomized study on the antiarrhythmic effects of mexiletine, ARGUS-TX was used for the quantification of ventricular arrhythmias and proved to be reliable.[9]

AIM OF THE STUDY

The present study was designed to assess the relation between parameters derived from twelve lead and twenty four hour electrocardiography and the occurrence of sudden death. More specifically, the aim was to study the risk implications of QTc interval duration (a parameter of the total duration of depolarization and repolarization of the myocardium) in the 12 lead electrocardiogram and that of high QTc interval variability, low heart rate variability, and frequent ventricular arrhythmias in the 24 hour electrocardiogram. A further objective of the study was to determine the prognostic value of all electrocardiographic parameters taken together with other clinical data.

STRUCTURE OF THE THESIS

The epidemiology and etiology of sudden death is described in chapter two. Emphasis is placed on to those mechanisms which are detectable by electrocardiographic methods. In this chapter, the specific aims of the study are formulated. The methodological aspects of the study are presented in chapter three. General aspects of the nested case-referent study design are introduced and a description of the study population, the observed incidence of sudden death, and baseline characteristics are given. In chapter four the risk implications for sudden death of QTc prolongation in the twelve lead electrocardiogram are analysed and compared with the literature. In chapter five the risk implications of parameters concerning QTc and RR interval duration and variability as derived from 24 hour electrocardiography are studied. Detailed information on the computer-aided study analysis of the 24 hour electrocardiograms is supplied in the appendices of this chapter. In chapter six a prognostic model taking into account all electrocardiographic parameters in addition to routine clinical characteristics is developed. Chapter seven provides a general discussion of the findings of this study and their implications. Finally, an english and dutch summary are supplied.

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2. Sudden Cardiac Death

"The readiness with which the ventricles are thrown into the fibrillar condition varies remarkably in different conditions of the cardiac tissues. In a normally contracting and vigorous heart it usually requires a faradic current of considerable strength to produce the result in question. But in certain changed conditions of the organ it becomes extremely easy to throw the ventricles into the fibrillar movement." JA McWilliam, 1887.[1]

HISTORY

Already hieroglyphes indicate the familiarity of the Egyptians with the phenomenon of sudden death.[2] Several cases of sudden death are mentioned in the Bible: Ananias, charged by Peter to have lied to God, dropped dead.[3] Another early case of sudden death was Phidippides the marathon runner who collapsed after his announcement of the defeat of the Persians to the notables of Athens (490 B.C.). After him many other cases were described in history, often in a situation in which grief or anger played a role: King Philip V is said to have dropped dead when he realised the Spaniards had been defeated, and Pope Innocent IV succumbed suddenly to the "morbid affects of grief on his system" soon after the disastrous overthrow of his army by Manfred.[3]

Pope Clement XI ordered Lancisi to investigate the sudden death epidemic in the city of Rome and in 1706 he reported that some groups in the population were affected more than others: most were wealthy males living in a luxurious style; females and people continent with respect to food, drink, and sexual life were preserved.[4] He suggested that multiple factors were involved.

Thus, far before the 20th century the first notions about the extent of the problem of sudden death as well of the factors which have a relation with its occurrence were developed.

SELECTED CASE REPORTS

The two following case reports were selected from the sudden deaths in the present study. In this chapter these cases will be referred to as illustrating examples.

Sudden death case 1. A 50-year-old man collapsed suddenly when he opened a gate while he was hiking in the mountains. He was resuscitated and transported to a hospital by helicopter but deceased upon arrival. At autopsy a fresh thrombus was found in the left anterior descending coronary artery. One year before the patient had an anteroseptal myocardial infarction complicated by ventricular fibrillation. At cineangiography four months later his left ventricular ejection fraction was 22%, and at exercise testing his maximum workload was reduced. His medication consisted of a beta blocker, diuretics and oral anticoagulants.

Sudden death case 2. A 62-year-old woman died suddenly when she wanted to rescue her cats because her neighbours house was on fire. Her general practitioner reported that "she died instantaneously of (non-documented) ventricular fibrillation provoked by the fright of the fire". Three months before the fatal event she had had a large, uncomplicated inferolateral myocardial infarction.

In the sudden death of case 1 apparently acute coronary thrombosis initiated the fatal event. In the second case excitation of the central nervous system in a patient with a vulnerable heart may have been the initiating mechanism. A further discussion on the initiating mechanisms is provided under "Etiology" later in this chapter.

DEFINITION

A definition of sudden cardiac death could be: "Unexpected, natural death due to cardiac causes in an individual with or without known preexisting heart disease within one hour of the onset of the terminal event. In the case of unwitnessed death, the victim has been seen to be well within the preceding 24 hours".[5,6] This definition includes patients dying unexpectedly during sleep. Essential elements in the definition are: 1) natural death, 2) unexpected occurrence, 3) rapid development, and 4) cardiac cause.

Deaths from non-natural causes such as accidents, homicide, and suicide are not included in this definition. The unexpectedness of the sudden death is crucial and is related to the history of disease and the presence of disability prior to death. Individuals who have severe limitations of activities because of physical or mental illness are usually not considered as sudden, unexpected deaths.[7] The above definition uses a time interval of one hour between onset of complaints and death. A problem with this definition is the fact that death may not have been witnessed and therefore formally should be excluded. This exclusion, however, leads to the negligence of an important number of deaths who die within a short time after onset of complaints, for the faster the demise the smaller the opportunity of witnessing. In order to include this latter group of often instantaneous deaths, the above definition is extended to those victims in whom death was unwitnessed but who were seen to be well in the preceding 24 hours. Although not always specified as such, in most definitions of sudden death it is sudden *cardiac* death which is aimed at, thus in the definition of sudden cardiac death natural, non-cardiac causes of death are excluded (e.g. pulmonary embolism, aortic dissection, stroke). Stroke, although generally believed to account for 10 to 20 percent of sudden death,[6] does not fit the definition of sudden cardiac death for two reasons. Firstly, only very few stroke patients die within one hour after onset of complaints.[8] Secondly, the cause of death is non-cardiac.

Several definitions of sudden cardiac death are faced in the literature. Differences regard mostly the time interval from onset of complaints to death. In large community based studies one often uses a 24 hour definition because of difficulties to obtain detailed information on the terminal process. In smaller studies aimed at the pathology of sudden cardiac death and with more detailed clinical observations frequently a more strict time criterion is used. Nowadays, a special group of sudden death patients emerges in the literature paradoxically referred to as "survivors of sudden death". These are patients who

would have died suddenly had they not been resuscitated. Depending on the aims of a study this group of patients may be considered as sudden deaths.

EPIDEMIOLOGY

Incidence

The most extensive data on the incidence of sudden cardiac death originate from the United States, where the annual toll is estimated to be more than 300,000, that is an overall incidence of 1.4 per 1000 person-years.[9] Eighty to ninety percent of sudden deaths occur on the basis of coronary heart disease,[10,11] in which it, in the one hour definition, is the initial and terminal expression of coronary heart disease in over half of the decedents.[12] In both men and women the incidence increases with age (table 2.1[9]): the incidence below age 55 is about a third of that above this age.[12] However, the proportion of deaths due to coronary heart disease that are sudden decreases with advancing age.[9,13] Sudden cardiac death has a huge preponderance in males compared with females – approximately three times as many men than females die suddenly (table 2.1).[14] Thus, the majority of sudden death victims are males above age 55.

In the Netherlands few data are available on the incidence of sudden death, since the death certificates used by the Central Bureau of Statistics do not require information on the timing between onset of complaints and death. In a study in Rotterdam, 26% of 459 deaths occurring in this municipality during one month in 1983 died within one hour of onset of complaints.[15,16] Extrapolated to the Rotterdam population (in 1983 ±557,000 inhabitants and 6,558 deaths) this would yield an approximate incidence of 3 per 1000 person-years. In the Imminent Myocardial Infarction Rotterdam study (IMIR) the incidences of sudden death for males and females were 2.5 and 0.7 per 1000 person-years respectively.[17]

Risk factors

Much of the current knowledge on risk factors for sudden death in the general population originates from the Framingham study.[18,19] In this study a cohort of 5,128 persons aged 30 to 62 years on entry is followed up biennially for development of coronary heart disease in

Table 2.1: Incidence of sudden death in the Framingham study, 26-year follow-up[14]

	Incidence (per 1000 person-years)	
Age (yr)	Men	Women
35-44	0.4	0.0
45-54	1.1	0.3
55-64	2.1	0.6
65-74	3.1	1.3
75-84	4.3	3.2
35-84	1.6	0.6

Table 2.2: Risk factors/indicators* for sudden cardiac death: univariate relative risks+ based on age adjusted absolute risks reported in the Framingham study.

Factor	RR		reference
	men	women	
Systolic blood pressure			12
<140	-		
140-159	1.7		
160-179	3.0		
≥180	3.8		
Diastolic blood pressure			9
<85	-		
85-94	1.8		
≥95	1.9		
Serum cholesterol			18
low	-	-	
medium	1.5	8.7	
high	1.3	17	
Cigarette smoking			18
none	-		
<20/day	1.3		
20/day	1.8		
>20/day	2.4		
Metropolitan relative weight			18
low	-	-	
medium	1.7	1.9	
high	2.4	3.3	
Diabetic status	1.1	3.0	19
Glucosuria	3.2	12	19
Standard 12 lead electrocardiogram			18
IV conduction disturbance	9.1	9.0	
left ventricular hypertrophy	5.4	0.9	
nonspecific ST/T abnormality	1.6	2.4	
ventricular ectopy	2.9	1.6	
heart rate			
<65	-		
66-73	2.3		
74-79	2.8		
80-87	4.3		
>88	5.4		
Coronary heart disease			18
age 45-54	12	-	
age 55-64	7	4.9	
age 65-65	4.3	6.6	
age 75-84	2.7	2.3	
Cardiac failure	7.2	4.3	18

* a factor implies a causal relation between a variable and sudden death, an indicator points to an association between the two and is not necessarily causal;
+ for the calculation of relative risks the category of a variable with lowest absolute risk was taken as reference.

general and sudden death in particular. During 26 years of follow-up 147 men and 50 women died suddenly, i.e. within one hour of onset of symptoms.[18,19] In table 2.2 univariate relative risks for sudden death are reported, predominantly based on this 26-year follow-up. The well-known risk factors of coronary heart disease, blood pressure, serum cholesterol level and cigarette smoking behavior also exhibit a clear effect on the incidence of sudden death, as do relative weight, diabetic status and glucosuria. Ventricular ectopy at a standard 12 lead electrocardiogram showed an excess sudden death incidence, but often occurred concurrently with left ventricular hypertrophy, intraventricular block or non-specific ST/T abnormalities, each of which was associated with sudden death.

Persons with overt established coronary heart disease were at 3-fold to 12-fold increased risk depending on age, the relative risk diminishing with advancing age. When overt coronary disease was established, the major coronary risk factors had little discernable effect on the risk for sudden death.

ETIOLOGY

Introduction

The etiology of sudden cardiac death is multifactorial. Because ventricular tachyarrhythmia is the final fatal mechanism in approximately 85% of all sudden deaths[20-23] we concentrate in the following sections on this mechanism.

The factors involved in the evolution of sudden death commonly are categorized into three groups: substrate, modulator and trigger (figure 2.1).[24,25]

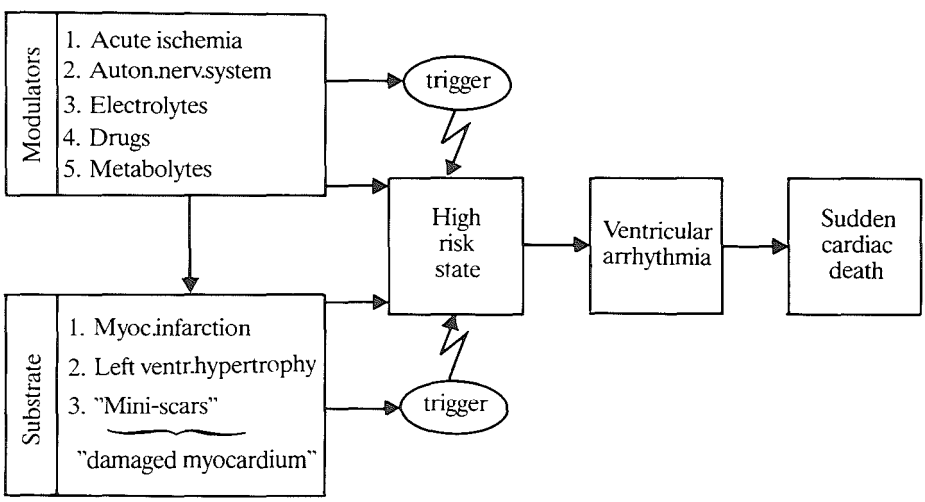

Figure 2.1: Component causes in the occurrence of sudden cardiac death: substrate, modulators and trigger.

In "substrate" those factors are joined that damaged the normal structure of the myocardium. The major factor in this group is myocardial infarction producing scarred tissue and electrical unstable areas at its borderzone. Also left ventricular hypertrophy and small areas of fibrosis (micro-infarctions) damage the normal structure of the myocardium. These factors have in common that they are permanent once present, thus creating a milieu - a substrate - in which ventricular fibrillation more readily can occur.

"Modulators" are those risk factors that temporarily increase the risk for sudden death; their contribution to the total risk is reversible (as opposed to the substrate risk factors). Modulators are acute ischemia, autonomic nervous system influences, electrolyte and metabolyte disturbances and drugs.

The premature ventricular complex is the trigger which initiates the fatal ventricular arrhythmia in a situation in which substrate and modulators created a high risk state. Thus, the premature ventricular complex can be seen as the sparkle that ignites the "explosive mixture" of substrate and modulators. However, in absence of an "explosive mixture" the sparkle is harmless.

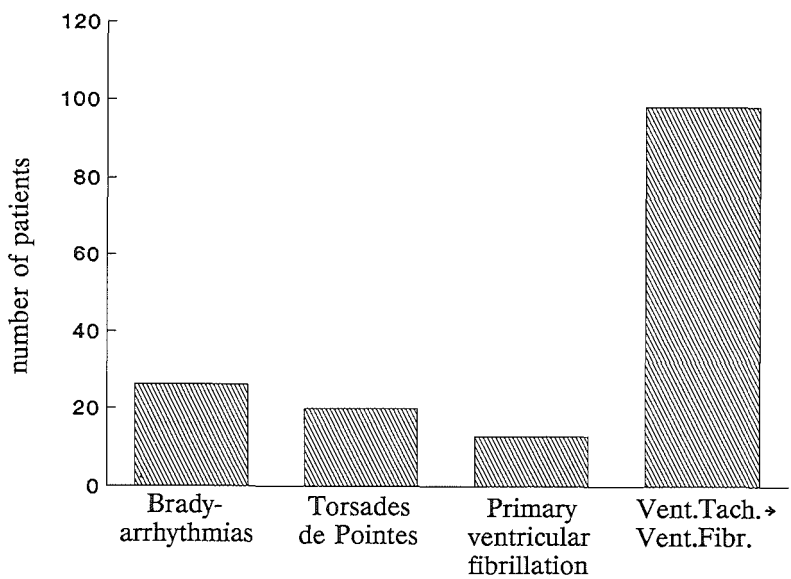

Figure 2.2: Distribution of different terminal events leading to sudden death during ambulatory monitoring. After Bayés de Luna et al.[20]

Electrocardiographic correlates

Electrocardiography in patients who died suddenly during ambulatory recording of the electrocardiogram enlightens the electrical events leading to the fatal event. In a review on 157 of such cases Bayés de Luna and Coumel concluded that in 84% ventricular tachyarrhythmias were the final electrical event, in the remaining 16% bradyarrhythmias eventually caused the sudden death.[20]

The 131 ventricular tachyarrhythmias could be divided into 13 primary ventricular fibrillations (10%), 98 ventricular tachycardias (75%) and 20 Torsades de Pointes* (15%) (figure 2.2). Of course, it should be realised that this distribution is based on patients in whom a medical reason existed to perform ambulatory electrocardiography, who form a selection of all patients dying suddenly. Studies in patients with out-of-hospital cardiac arrest, however, indicate a similar distribution of terminal arrhythmias: 67 - 93% ventricular tachyarrhythmias and the remainder bradyarrhythmias.[21-23]

The onset of the fatal tachyarrythmia differed for the Torsade de Pointes group and the ventricular fibrillation group (table 2.3).[27] In the latter group the sinus rate slowly increased during the last hours, especially in those patients in whom ventricular tachycardia or fibrillation started without a preceding pause. The heart rate just before death was high (92.0 beats per minute) in the ventricular tachycardia/fibrillation group as compared with that in the Torsades de Pointes group (60.6 beats per minute). In patients who developed ventricular fibrillation while out-of-hospital also a significant increase of heart rate was noted: upon arrival of a mobile coronary care unit a rate of 84 beats per minute was recorded as compared with a rate of 98 beats per minute immediately before ventricular fibrillation.[28] This increase of heart rate and the high terminal heart rate probably reflects a high sympathetic drive.

Table 2.3: Heart rate differences before the onset of Torsades de Pointes and ventricular fibrillation. After Leclercq et al.[27]

	Torsades de Pointes (n=13)	VT/VF (n=49)
HR 3 hours before death	77.5 (2.5)	82.8 (20.0)
HR just before death	60.6 (2.5)	92.0 (26.7)
HR trend	-16.9	9.2
long RR cycle present	13 (100%)	22 (44%)

VT, ventricular tachycardia; VF, ventricular fibrillation; HR, heart rate in beats per minute (mean and standard deviation).

* Torsades de Pointes: a fast irregular rhythm (rate 150-300 beats per minute) in which the peaks ("pointes") of the QRS complexes twist ("torsade") around the iso-electric line. A "torsade" covers 5-10 "pointes". The coupling interval of the first QRS complex is long (500-800 ms) and the arrhythmia most often is self terminating.[26]

Pathology

Coronary cardiac death. Most victims of sudden cardiac death had coronary artery disease.[10,29] Coronary artery stenosis, defined as one or more coronary vessels with a ≥75% area stenosis, was present in 94% in a series of 220 autopsied cases of sudden cardiac death.[21] Old or recent myocardial infarction was found in approximately 70% of all sudden cardiac death victims.[21,30,31]

However, reports on the acute pathologic phenomena in sudden cardiac death are less unanimous. In pathological series acute coronary thrombosis (compare selected case 1) was reported as fatal mechanism in 20 to 93% of sudden cardiac death cases.[32-35] A second mechanism, ventricular fibrillation unrelated to new acute myocardial ischemia was reported in 22 to 64% of sudden death victims.[21,22,36,37] From a recent study on 168 cases of sudden death Davies concluded that these seemingly conflicting data at least partly can be explained from the composition of the patient groups studied.[38] In patients with an old myocardial infarction at autopsy, a known clinical history of ischemic heart disease or three vessel disease a lower frequency of acute thrombosis was found than in the patients with acute myocardial infarction at autopsy, prodromal symptoms or single vessel disease. In figure 2.3 a summarizing view on the occurrence of the two mechanisms of sudden death in relation to the extent of damage to the myocardium is given. Van Dantzig put these differences into words by proposing two pathways which sudden ischemic cardiac death might follow: "Firstly, that of a slowly evolving disease with chronic injury to myocardium that may end in a sudden electrical event. On the other hand, there may be a situation in which a sudden coronary arterial event may be the initiating factor for acute ischemia and death."[33] Both processes may be compatible with the ulceration-thrombosis cycle of coronary disease proposed by Forrester which was based on observations of

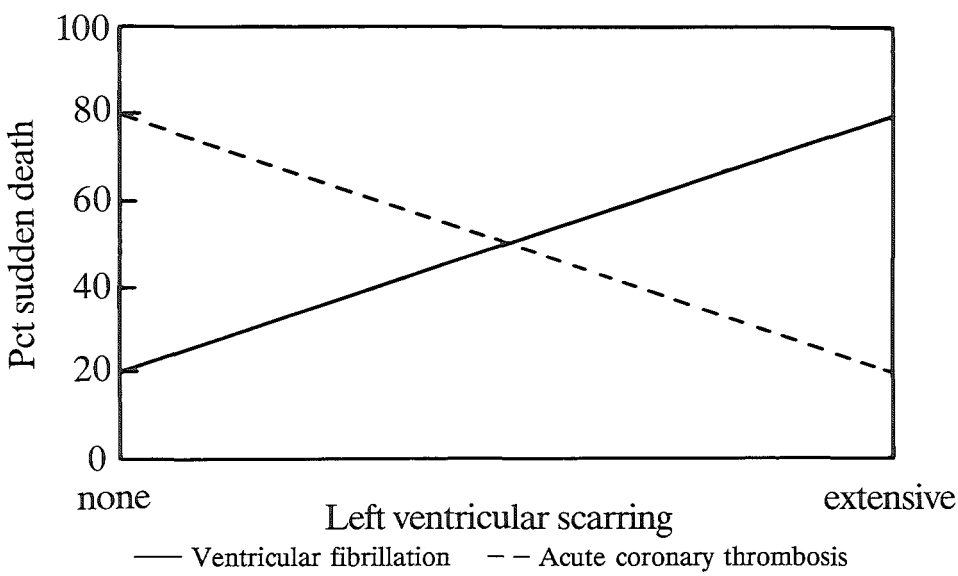

Figure 2.3: Two mechanisms of sudden death in relation to the extent of myocardial damage.

coronary arteries of living man with use of fiberoptic angioscopes.[39] This theory alludes mainly to mechanisms that cause injury of the myocardium (the substrate, see below), but does not deal with possible electrical causes of sudden death.

Non-coronary death. The most common non-coronary causes of sudden cardiac death are hypertrophic obstructive cardiomyopathy, left ventricular hypertrophy due to aortic valve stenosis and abnormalities of the cardiac conduction system. Approximately 10 to 20 percent of all cases of sudden death is not due to coronary artery disease.[10,11]

The pathology in some rare cases of sudden cardiac death may enlighten its pathophysiological mechanisms. In several patients with the long QT syndrome (see "Autonomic nervous system" later in this chapter) inflammatory or degenerative changes were found in the left stellate ganglion,[40,41] supporting the theory that imbalance between the left and right sympathetic nervous system can result in sudden cardiac death.

Substrate

Myocardium healed after ischemic injury may show lasting changes predisposing to the occurrence of ventricular arrhythmias. Studies in dogs showed that after healing of experimental myocardial infarction connective tissue had invaded the epicardial border zone separating the muscle bundles.[42] In these regions action potentials were normal, however, activation was very slow, which may predispose to the occurrence of ventricular reentry arrhythmias, especially if other provoking factors (modulators, see below) are present. Comparable observations were obtained in hearts and endocardially resected preparations from patients with sustained ventricular tachycardias in the chronic phase of myocardial infarction.[43] Again, the destroyed architecture of myocardial tissue at the borderzone of the infarction appeared to be a major source of reentrant arrhythmias.

Modulators

Acute ischemia. Ischemia occurring in the first 10 minutes after coronary occlusion can cause ventricular tachycardia (possibly degenerating into fibrillation) due to circus movement reentry. The most important determinant for this reentry is the inhomogeneity in recovery of excitability within the ischemic zone.[44] Uncertainty exists as to the mechanisms of the initiating role of premature ventricular depolarizations.[44] Elevated sympathetic activity increases the likelihood for ventricular arrhythmias during regional ischemia.[44] Sudden reperfusion after an ischemic episode also can cause ventricular arrhythmias. Again, increased inhomogeneity of electrical activity, facilitating reentry plays an important role.[44] Enhanced automaticity can occur during reperfusion after ischemic periods of 20-30 minutes duration.

In humans the effects of acute ischemia can be studied only indirectly. In patients with angina outcome is closely related to the presence of electrocardiographically recorded ischemia.[45] The frequency of ischemic episodes increases in the early morning and wanes in the early afternoon and evening. The onset of acute myocardial infarction and of sudden death also exhibits circadian rhythms, with patterns that are remarkably similar to those observed for myocardial ischemia.[46-48] An implication of these concordant findings is that

when ischemia is most common (in the early morning), severe and prolonged episodes may progress and lead to acute myocardial infarction or sudden cardiac death.[49]

Autonomic nervous system. Transient factors that precipitate ventricular fibrillation, including nervous impulses to the heart, may be critically important in the research of sudden cardiac death.[50] However, in contrast to animal research, in humans this research has to use indirect parameters of neural activity since direct measurement almost always is impossible. Parameters used to study the influences of the nervous system are listed in table 2.4. Although these parameters reflect nervous system activity, it should be realised, however, that also other factors can influence them.

The Long QT Syndrome. The intriguing paradigm of the influence of the autonomic nervous system on the occurrence of ventricular arrhythmias is the Long QT Syndrome. This congenital syndrome is characterized by transient symptomatic episodes of dizziness or syncope starting early in life.[51-54] At electrocardiography the QTc interval (see appendix 2B for definition) most often is prolonged to values around 500 ms,[55,56] although marked spontaneous variations occur.[57] Routine gross and microscopic examination of hearts of long QT syndrome patients who died revealed no abnormalities apart from the finding of focal intracardiac neuritis and neural degenerations in some.[58,59]

Precipitating factors for the often lethal syncopal episodes include exercise, anxiety, fear, and sudden noises, each of which is commonly associated with a sudden increase in sympathetic neural activity.[60] At noxious psychic stimuli some electrocardiographic tracings show prolongation of the QT interval with a concomitant appearance of premature ventricular complexes and ventricular tachycardia degenerating into ventricular fibrillation.[61] Clinical and experimental data support the hypothesis that an imbalance in the cardiac sympathetic innervation forms the pathophysiologic basis of the Long QT Syndrome. Primary hypoactivity of the right cardiac sympathetic nerves reflexly results in hyperactivity of the left nerves.[54]

Electrophysiologic findings indicate that QT prolongation is due to heterogenous prolongation of repolarization resulting in increased dispersion of refractory periods across the ventricle.[60] The dispersion of total recovery time (the sum of endocardial activation time and dispersion of refractoriness) in left ventricles of patients with the Long QT Syndrome is more than twice than that in normal ventricles, and this is mainly due to a different dispersion of refractoriness.[62] The heterogeneity of repolarization commonly is

Table 2.4: Electrocardiographic parameters used to study influences the autonomic nervous system on the heart.

Heart rate
Heart rate variability
QT interval
QT interval variability
Ventricular arrhythmias

thought to be characteristic of reentry, one of the major mechanisms of arrhythmia.[62,63] However, recently a hypothesis was advanced which holds that afterdepolarizations and triggered firing (another mechanism of arrhythmia) are responsible for the initiation of the arrhythmias.[63] These afterdepolarizations (oscillations in membrane potential that follow the upstroke of an action potential) have been recorded in patients with the Long QT Syndrome.[64,65]

Thus, available evidence suggests that the lengthening of the QT interval is neurogenic, that the long QT interval is associated with increased dispersion of repolarization, but also that afterdepolarizations occur. No consensus exists (yet) as to the exact mechanism of the ventricular arrhythmias.

Autonomic nervous system and QT interval. The influences of the autonomic nervous system on ventricular electrical activity and the resulting QT interval are complex.[60] Testing in vivo is complicated by the reflex responses in heart rate, blood pressure, ventricular afterload, and ventricular volume.

Vagal effects are predominantly indirect and secondary to heart rate changes. If atropine is administered heart rate increases, but the QTc interval remains constant. Blocking of sympathetic influences with the use of beta-blockers produces no major changes in QTc.[57] In the completely denervated hearts of heart transplant patients the QTc interval has been shown to be of normal duration.[57] Right sided block of the stellate ganglion in normal subjects prolonged QTc, while blocking of the left stellate ganglion did not affect QTc duration.[66] These findings correspond with those in animal experiments.[67]

Epidemiologic observations on the QT interval. In an international study patients with the Long QT Syndrome are followed.[55,56] Calculated from the data collected so far the incidence of sudden death and syncope was 1.3%, respectively 8.6% per year. Risk factors for these events were congenital deafness, history of syncope, female sex and a history of torsades de pointes or ventricular fibrillation, while left stellate ganglionectomy and beta-blockers had a beneficial effect.[55]

A controversy exists on the risk implications of QTc prolongation in post myocardial infarction patients*: in one review it was stated that "QTc has little, if any, predictive value",[57] while in another the opinion was advanced that "QTc represents a simple and valid method of identifying patients at high risk of sudden death".[68]

Enhanced activity of the sympathetic nervous system. Evidence from several sources supports the hypothesis that enhanced activity of the sympathetic nervous system can cause – or more prudent is associated with, the occurrence of sudden death. A summary of this evidence follows.

Abolishing the increased left sided sympathetic activity in patients with the Long QT Syndrome by left stellate ganglionectomy has a beneficial effect on the occurrence of sudden death,[55] although data from another small series of patients yielded deviant results.[69]

* See also discussion of chapter 4 in which the presently available literature on this topic is summarized.

Pooled data from long-term beta blocker trials yield a reduction of the incidence of sudden death of 32%.[70] One of the reasons why beta blockers prevent sudden death might be an antiarrhythmic mechanism, for in humans these drugs suppress ventricular ectopics both early[71,72] and late[73] after myocardial infarction.

Other evidence originates from observations in congestive heart failure patients in whom plasma noradrenaline was associated with the frequency of ventricular ectopic activity.[74] In animal research myocardial catecholamine release appeared to mediate a major role in the genesis of malignant ventricular arrhythmias during both myocardial ischemia and subsequent reperfusion.[75]

Lowered activity of the parasympathetic nervous system. Animal research has indicated that reduced parasympathetic nervous activity increases the likelihood of ventricular fibrillation during myocardial ischemia, especially when sympathetic hyperactivity coexists.[50,60,76,77] In a clinical study attenuated baroreceptor reflexes, which are an expression of enhanced sympathetic and reduced parasympathetic activity, were more common in patients who died suddenly post myocardial infarction as compared with survivors.[78] Low heart rate variability, corresponding to reduced parasympathetic tone, also is associated with an increased risk for sudden death (see below).

Behavioral influences. As mentioned in the historical introduction of this chapter psychological stress has been recognized for centuries as a precipitating factor in sudden death.[3] Case report 2 alludes to this phenomenon. A fully documented example was described by Olsson and regarded a 70-year-old post myocardial infarction patient who developed ventricular fibrillation after he had noticed that his wallet containing important documents was missing.[79]

The loss of a significant person was found six times more often in sudden death cases in comparison to a control group matched for age, sex and race.[80] Bereavement was also in other studies associated with increased mortality[3,81] supporting the hypothesis that the lack of social networks carries stress.[82] Low social class[83] and low levels of education[84] have been identified as stressors associated with increased cardiac and sudden death. An excess proportion of sudden deaths occurred on Mondays in the Manitoba study suggesting a stressful effect of reintroduction to work after a weekend respite.[85] A quite different form of stress showed its effects in a "natural experiment": the 1981 Athens earthquake: in the days after the event there was an excess of deaths from cardiac causes.[86] Animal experiments too have shown that severe behavioral stress could induce either death or extensive cardiac damage.[87]

Heart rate variability. The autonomic nervous system modulates heart rate. Three peaks can be discriminated in its power spectrum, corresponding with a periodicity of heart rate variations around 0.25, 0.10 and 0.03 Hz respectively.[88-90] The high frequency variations correspond with the respiratory frequency and are mediated through the parasympathetic nervous system.[88,90,91] The mid frequency variations parallel the spontaneous oscillations of the blood pressure and are influenced by both the sympathetic and parasympathetic nervous system.[88] The slow variations probably originate from fluctuations in peripheral

vasomotor tone associated with thermoregulation and lead to perturbations in central venous and arterial pressures.[92,93]

Two strategies are nowadays used to quantify heart rate variability: power spectral analysis and the calculation of simple statistics. Power spectral analysis has the ability to detect the peaks mentioned directly, but the technique is advanced and costly. In simpler approaches means and standard deviations in several combinations are used.[94,95] Most epidemiologic studies on the relation between heart rate variability and sudden death used the simple statistics. The Multicenter Post-Infarction Research Group reported that heart rate variability (taken as the standard deviation of all normal RR intervals in a 24-hour electrocardiogram) less than 50 ms was associated with a 5.3 times higher risk for mortality from all causes than heart rate variability over 100 ms.[96]

Electrolytes. Low serum potassium levels may be a risk factor for sudden death since an association between hypokalemia and ventricular arrhythmias has been observed.[97,98] This relation also comes forward from clinical trials using thiazide diuretics in hypertensive patients. Though reducing stroke mortality, no reduction in coronary heart disease was shown, and sudden death occurred more frequently in patients treated with diuretics. Evidence suggests that diuretic-induced hypokalemia may be responsible for the adverse effect on cardiovascular mortality.[99]

Drugs. The hypothesis on which the use of antiarrhythmic drugs is based presumes that a reduction of ventricular arrhythmias will diminish the number of opportunities in which they could deteriorate into ventricular fibrillation and sudden death. However, up to today clinical trials have failed to demonstrate improved survival.[100] In contrast, in the Cardiac Arrhythmia Suppression Trial (CAST), the largest trial thus far, the arms of the trial involving encainide and flecainide (class 1c antiarrhythmic drugs) were preliminary stopped because patients treated with active drug had a higher rate of death from arrhythmia than the patients assigned to placebo (4.5% and 1.2% respectively).[101] Although the basis for this finding is not entirely clear, the induction of lethal ventricular arrhythmias might have played an important role.[102] In this context it may be worthwhile to note that class 1c antiarrhythmic drugs prolong QT duration. Also other reports point to the proarrhythmic properties of antiarrhythmic drugs.[103,104]

Trigger: ventricular ectopy

In 40 out of 59 patients who had been resuscitated from out-of-hospital cardiac arrest ventricular tachyarrhythmias could be induced by programmed electrical stimulation.[105] Similar observations have been reported by others.[106] Thus, in most of these survivors of sudden death an artificial early ventricular depolarization was able to trigger another life threatening arrhythmia. Premature ventricular depolarizations had been related to the occurrence of sudden death already in a report on the Coronary Drug Program Study in 1973.[107] During a three-year follow-up of 2035 male survivors of myocardial infarction 10% of the patients with any premature ventricular complex in their resting baseline electrocardiogram died suddenly as compared with 5% of those with none.

Table 2.5: Lown grading system for ventricular arrhythmias[108]

Grade	Observed
0	no ventricular ectopic beats
1	occasional, isolated VPB*
2	frequent VPB (>1/min or 30/hr)
3	multiform VPB
4	repetitive VPB
a	couplets
b	salvos
5	early VPB

* VPB, ventricular premature beat. (N.B. In this thesis a slightly different nomenclature is used: "complex" rather than "beat", "doublet" in stead of "couplet" and "ventricular tachycardia" for "salvos".)

Classification of ventricular arrhythmias. In 1971 Lown introduced a system for the grading of ventricular arrhythmias (table 2.5).[108] It was assumed that higher grades were associated with a higher incidence of sudden cardiac death. Bigger and Weld criticized this system for the mutual exclusiveness of the classes: information on frequency, repetitiveness and multiformity of the premature ventricular complexes cannot be combined, also they found no clear hierarchy of the classes.[109,110] Therefore they proposed a classification in which the information on the characteristics of the ventricular arrhythmias are used next to each other.

Incidence of ventricular ectopy. The incidence of ventricular ectopy is associated with the degree of coronary artery disease.[100] It is low in apparently normal persons: ventricular premature complexes >10/hour occur in about 5% while multiform and repetitive complexes are rare. The morphology of the premature ventricular complexes in this group is more often of right ventricular origin and the complexes tend to disappear at higher heart rates.[111] Two weeks after myocardial infarction the incidence of ventricular ectopy is considerably higher: ventricular premature complexes >10/hour occur in about 20%, multiformity is observed in about half of the patients, doublets in 25% and ventricular tachycardia in 10%.[100]

Prognosis of ventricular ectopy. For apparently healthy persons with premature ventricular complexes on a standard 12 lead electrocardiogram the risk for sudden death is not clearly increased.[100] After myocardial infarction premature ventricular complexes >3 /hour and ventricular repetitiveness both doubled the risk for death independent from other clinical variables.[112] Also exercise related ventricular ectopy is related to mortality in this group of patients.[113]

Ventricular ectopy is more prominent at lower left ventricular ejection fractions and thus it has been controversial whether premature ventricular complexes constitute an independent risk factor for sudden death in patients with a low ejection fraction. Data from four post myocardial infarction studies, however, indicate that premature ventricular

ectopy is such a risk factor.[112,114-116] These observations point to it that premature ventricular complexes can trigger serious ventricular arrhythmias in a vulnerable substrate.

AIMS OF THE PRESENT STUDY

Many single causes of sudden death are known, yet most often more than one single cause is necessary to provoke a life threatening arrhythmia. Many pieces of the jigsaw puzzle of causes of sudden death have been presented in the previous sections. A complex interplay between myocardial injury, coronary vascular events, variation in autonomic tone and electrolyte state of the myocardium determine the occurrence of life threatening arrhythmias.

The theory underlying the hypothesis in this study is that in a large number of cases sudden death was induced by a destabilizing event in a heart already in a high risk state. This lethal destabilizing event is not an isolated incident, but is preceded by several minor destabilizing events which, if detected, characterize patients with an elevated risk for sudden death. Our study is aimed at the detection of destabilizing events which present at 24-hour and standard 12 lead electrocardiography. The electrocardiographic signs of a destabilizing event are most often, in our belief, an expression of (sudden) changes in the homeostasis of the autonomic nervous system.

On the basis of above considerations a study was designed in which the relation between several parameters from the standard 12 lead electrocardiogram and the 24-hour electrocardiogram and the occurrence of sudden death was investigated in patients who underwent 24-hour electrocardiography. The general design of the study is described in chapter 3. The risk implications of QTc prolongation as measured at a standard 12 lead electrocardiogram are analysed in chapter four and those of QTc and RR interval duration and variation as derived from 24-hour electrocardiography in chapter five. The prognostic value of parameters from standard 12 lead and 24-hour electrocardiography taken together with other clinical characteristics with regard to the occurrence of sudden death is investigated in chapter six.

APPENDIX 2A:
Basic anatomy and physiology of the autonomic nervous system of the heart.

The function of the heart is under direct control of the autonomic nervous system (next to the indirect control by the humoral system). The two antagonist parts of the autonomic system, the sympathetic and parasympathetic system, balance the action of the heart (homeostasis).

Efferent parts of the parasympathetic system terminate at the heart passing through the vagal nerve and innervate mainly the atria and especially the sinus node (figure 2.4). The efferents of the sympathetic system are bilaterally located along the vertebral column, synapse in the stellate ganglia and innervate predominantly the ventricles with a fine network of nerves. Afferent fibers run back to the central nervous system both through the

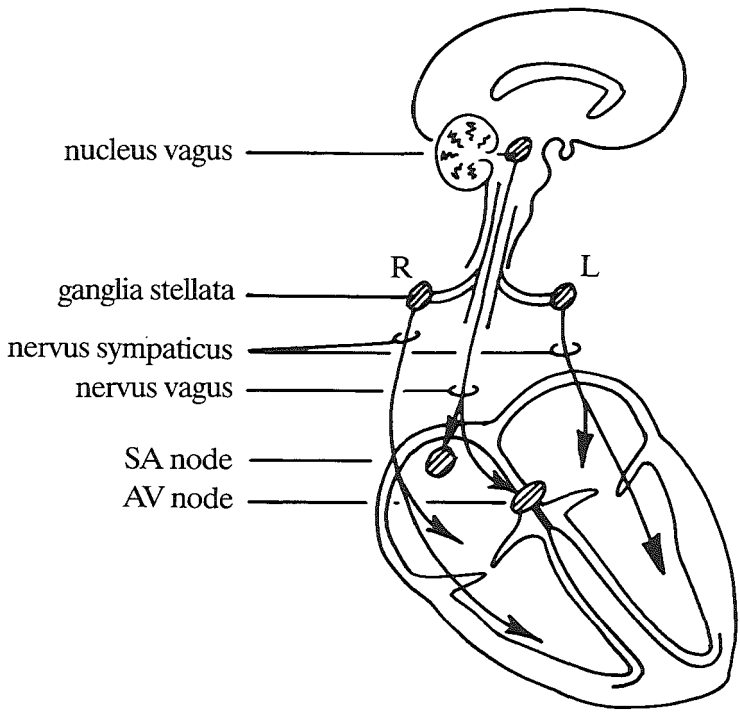

Figure 2.4: Schematic anatomy of the sympathetic and parasympathetic nervous system of the heart.

vagal nerve and the sympathetic trunk. For a detailed description of the anatomy the reader is referred to a publication by Janes et al.[117]

The function of the sympathetic system is to alert, to elicit the so called "fright, fight and flight reaction". On stimulation it increases heart rate (effect on the sinus node), conductivity (effect on the atrio-ventricular node) and contractility (effect on the ventricular myocardium); as a result blood pressure rises. The effects of the left and right sympathetic system are not identical; heart rate acceleration is mainly mediated through the right system (see also the section "Autonomic nervous system and QT interval").[118] The parasympathetic system antagonizes these effects: it decreases heart rate, conductivity and contractility. Afferent fibers of both systems carry feedback information to the central nervous system.[119]

APPENDIX 2B:
QT interval: definition and influence of heart rate.

Definition and measurement.

The QT interval is defined as the time interval between the beginning of the QRS complex and the end of the T wave in the surface electrocardiogram. Its duration represents the sum of the duration of both depolarization and repolarization of the cardiac muscle. In synchronous ECG leads QT interval duration will vary from lead to lead, depending on the

projection of the three dimensional vector of electrical activity on the specific leads. To approximate as close as possible the true duration of electrical activity, the first begin of the QRS complex and the last end of the T wave in any lead should be taken.[120] For nonsynchronous ECG leads the longest QT interval found is regarded as the most correct. For a reliable measurement it is also necessary to select those leads in which the T wave can be seen clearly (usually leads V2 - V4), and that no U wave interferes with the end of T.[120]

Influence of heart rate. In 1920 Bazett described the relation between QT interval and heart rate as follows: the QT interval divided by the square root of the RR interval is constant.[121] This quotient in which both QT and RR are expressed in seconds, is the so called corrected QT interval (QTc). Values up to 440 msec for QTc are considered to be normal.[122] Several other formulae have been proposed[123] but Bazett's formula, however, is the most commonly used today.

QT interval not always varies with the heart rate as described above.[124] In healthy individuals the familiar QT-RR relation was observed during exercise, while at considerable heart rate changes in the same individuals caused by Vasalva maneuver, dive reflex, hyperventilation, cold pressor test and breath holding the QT interval was hardly influenced. Correcting QT for heart rate in these maneuvers could lead to erroneous interpretations. The conclusion is drawn that there is very little, if any, direct effect of heart rate on QT duration and it is suggested that different sympathetic pathways control these two entities. Similar conclusions are drawn from pacing experiments.[125,126]

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3. Study design

INTRODUCTION

The present study was designed to assess the relation between parameters derived from standard twelve lead or twenty four hour ambulatory electrocardiography and the occurrence of sudden death. The archives of a central laboratory for the analysis of 24 hour electrocardiograms were chosen as starting point for the formation of the study population, because of the vast number of 24 hour electrocardiograms available. Specifically, Cardiolab, Rotterdam, an institution which analyses 24 hour electrocardiograms from approximately 70 hospitals from all over the Netherlands was chosen.

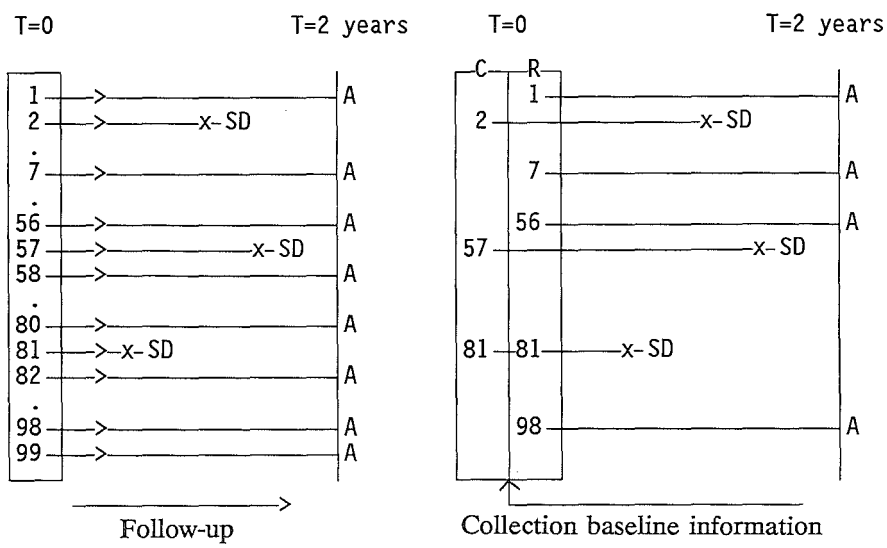

Figure 3.1: Nested case-referent study design. In the follow-up part of the study (left panel) all patients in the study cohort (patients 1-99) are followed for the occurrence of sudden death (2, 57, and 81). Parameters of study at the onset of follow-up (T=0), e.g. QT interval, are determined for all cases of sudden death and a random sample of all study patients (1, 7, 56, 81 and 98) (right panel); one case of sudden death (81) is included in the random sample!
A, Alive; C, Case of sudden death; R, patient selected in the random sample; SD, sudden death; T=0, start of follow-up; T=2 years, end of follow-up after two years.

The study population was composed of a consecutive series of 6693 patients who had 24 hours electrocardiography for a variety of reasons. All patients were followed for the occurrence of sudden death for a period of two years. In this respect, the study conforms with the conventional cohort follow-up design. The standard design of such a study would require collection of the electrocardiographic parameters at the start of follow-up for all study patients. This approach, however, is inefficient in the current situation. As the overall incidence of sudden death (cases) is low, the electrocardiographic parameters have to be determined in a disproportionate large number of patients who did not die suddenly (non-cases). A more efficient approach would be to measure the electrocardiographic baseline parameters in all cases of sudden death and in a *random sample* twice or three times as large from the complete source population. This design is known as a nested case-referent study (figure 3.1). Although measurements of the electrocardiographic parameters are performed only in a small subset of patients the evidence sought can be obtained with a comparable level of precision as in the conventional follow-up study.[1,2] In view of the above considerations it was highly attractive to choose the nested case-referent approach for the present study.

PATIENTS

Definition of the study cohort

Patients who had 24 hours electrocardiography in any of four Rotterdam client hospitals of Cardiolab (University Hospital "Dijkzigt", Bergweg Ziekenhuis, Sint Franciscus Gasthuis and Zuiderziekenhuis) form the source population for this study. These four Rotterdam hospitals were selected out of all client hospitals of Cardiolab because of their proximity to the Clinical Epidemiology Unit of the Department of Cardiology of the University Hospital where the study was carried out. Tapes of consecutive patients recorded between 15 February 1983 and 31 December 1984 were accepted; for the University Hospital tape accrual started at 15 August 1980. Thus, 9106 24 hour electrocardiograms were collected (table 3.1). If a patient had 24 hours electrocardiography more than once in the study period, only the last recording was used. Twenty two percent (2038) of all recordings were repeat tapes, which leaves 7068 patients. From these, 375 were excluded either because they had a pacemaker (365) or because they were under ten years of

Table 3.1: Origin of the 24 hour electrocardiograms

Hospital	nr	%
University Hospital Dijkzigt	4922	54%
Bergweg Ziekenhuis	528	6%
Sint Franciscus Gasthuis	2103	23%
Zuiderziekenhuis	1553	17%
Total	9106	100%

Table 3.2: Age and sex distribution of the study cohort

age (yrs)	men	%	women	%
≤ 50	1043	27%	747	27%
50-60	978	25%	479	17%
60-70	1129	29%	729	26%
> 70	779	20%	809	29%
total	3929	100%	2764	100%

age (10). The remaining 6693 patients form the study cohort. Their age and sex distribution are presented in table 3.2.

Mortality

Survival status at two years after 24 hours electrocardiography was ascertained for all patients via municipality registers. During follow-up, 716 patients (10.7%) were identified who died within two years after 24 hours electrocardiography. In 35 patients follow-up was incomplete, mainly because patients had moved abroad. The Kaplan-Meier[3] survival curve for the 6693 study patients is given in figure 3.2. The one and two-year cumulative mortality was 6.4% and 10.7% respectively.

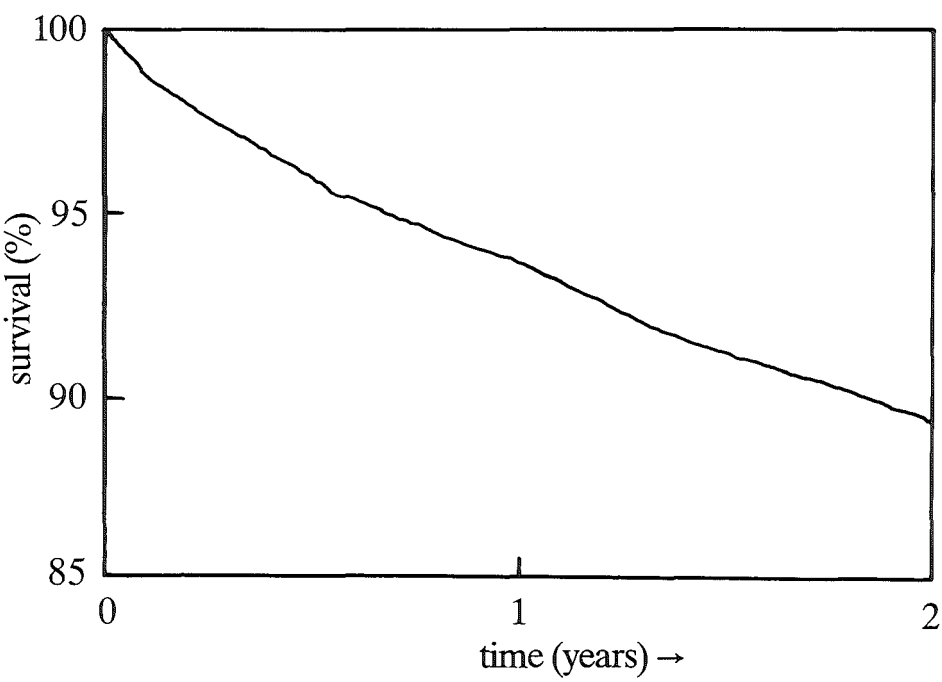

Figure 3.2: Survival in the study cohort

Cases of sudden death

To assess circumstances and causes of death records of general physicians and hospitals were retrospectively reviewed. In 30 patients (4.2%) no or insufficient information could be obtained, mainly due to the fact that the patient died more than four years before. Patients were accepted as case of sudden death if death was observed and occurred within one hour after new or more serious complaints, and its likely cause was cardiovascular. Also accepted were patients who unexpectedly died during sleep and those who died while unobserved provided that circumstantial evidence pointed to sudden death. Acceptance of cases of sudden death was independently verified by two senior cardiologists.

Table 3.3 shows the causes of death according to mode of death. Of the 716 study cohort patients who died within two years after 24 hours electrocardiography 459 (64%) of deaths were of cardiovascular origin; the 245 of these patients who died suddenly were selected as cases for this study. Data on 136 of the 716 deceased patients were evaluated in detail by the two senior cardiologists; 85 of these patients (63%) were classified as sudden death case. Table 3.4 shows details on the timing, observation and circumstances of death. Seventy five percent of all deaths was observed by a witness. Of the 245 cases 182 died within one hour and 63 within 24 hours of whom 32 during sleep. Autopsy was done in 96 patients (13.4%).

Reference patients

Reference patients in this study are 467 patients randomly selected from the source population of 6693 patients. Because this reference group was drawn from the complete study cohort – and not from the non-sudden death patients only – some cases of sudden death

Table 3.3: Distribution of main causes of death according to mode of death in 716 patients who died within two years after 24 hours electrocardiography

Cause of death	Nr		%
Sudden cardiac (cases)*	245		34%
Other cardiovascular	214		30%
myocardial infarction+		43	
terminal heart failure		91	
stroke		54	
other		26	
Non-cardiovascular	227		32%
malignancy		122	
infection (a.o. pneumonia, sepsis)		48	
non-natural		8	
other		49	
No or insufficient data available	30		4%
Total	716		100%

* For definition of sudden death see text; + death due to pump failure ≥ one hour after onset of symptoms.

Table 3.4: Timing, observation and circumstances of death in 716 patients who died within two years after 24 hours electrocardiography.

	All deaths		Cases*	
	Nr	%	Nr	%
Number of patients	716	100%	245	100%
Time interval				
instantaneous	164	23%	146	60%
< 1 hour	46	6%	36	15%
1 - 24 hours	114	16%	63	26%
> 1 day	359	50%	-	-
unknown	33	5%	-	-
Observation				
yes	540	75%	185	76%
no	64	9%	41	17%
unknown	112	16%	19	8%
Place of death				
home	229	32%	127	52%
hospital	340	48%	66	27%
nursing home	72	10%	9	4%
street	14	2%	13	5%
elsewhere	38	5%	30	12%
unknown	23	4%	-	-
Circumstances				
ill at bed	462	65%	65	27%
sleeping	37	5%	32	13%
working	7	1%	7	3%
other	133	19%	113	46%
unknown	77	11%	28	11%

* Cases, sudden deaths, see text for definition.

also were member of the reference group. In the nested case referent design the *random sample* replaces the total *study population* in the estimation of absolute risks for sudden death (see data analysis). It further serves as a description of all study patients (table 3.5).

COLLECTION OF BASELINE DATA

Baseline data (i.e. at the time of 24 hours electrocardiography) were retrospectively collected for all cases of sudden death and for all reference patients. Routine clinical patient characteristics and data on twelve lead electrocardiograms were directly obtained from the patient records in the four participating hospitals. Data pertaining to the routine-analysis of the 24 hour electrocardiograms were retrieved from the Cardiolab computer

Table 3.5: Distribution of patient characteristics at the time of 24 hours electrocardiography in all 467 reference patients.

Males	58%
Age > 60 years	49%
History of	
angina ever	33%
myocardial infarction	32%
congestive heart failure*	16%
any supraventricular arrhythmias	41%
any ventricular arrhythmias	39%
atrio-ventricular conduction defects	8%
palpitations	50%
dizziness	45%
syncope	18%
coronary bypass surgery	8%
transient ischemic attack or stroke	16%
intermittent claudication	7%
diabetes mellitus	8%
smoking ever	35%
Drug use	
none	21%
digitalis	23%
beta blockers	25%
nitrate	23%
diuretics	23%
antiarrhythmic drugs	22%
oral anticoagulants	28%

* Not in the acute phase of myocardial infarction

database. Special electrocardiographic parameters were obtained during re-analysis of the original 24 hour electrocardiograms with the use of a research computer system.

Routine clinical patient characteristics

Information on the following patient characteristics was collected: demographic data, cardiovascular risk indicators (cholesterol, blood pressure and smoking), cardiovascular history (angina, myocardial infarction, cardiac dysfunction, surgery), cardiovascular function tests if available, routine laboratory studies and current drug use.

Twelve lead electrocardiogram

Of each patient the last twelve lead electrocardiogram recorded prior to 24 hours electrocardiography was obtained. Three channel recorders at a paper speed of 25 mm/s had been used. The electrocardiogram was coded using the Cardiac Infarction Injury Score[4] and the Minnesota Code[5]. RR and QT intervals were measured in the combined leads I, II and III, V2 and V5. These latter leads were selected for comparison with their analogues on the 24 hour electrocardiogram. In the three synchronous standard leads I, II and III the QT interval was taken as the interval between the first onset of the QRS complex and the last

end of the T wave and was corrected for heart rate according to Bazett's formula: QTc = QT / $\sqrt{RR}$.[6] Finally information concerning the Q wave distribution was coded. Twelve lead electrocardiograms were not available in 24 patients. Further details are provided in chapter 4.

Twenty four hour electrocardiogram

All 24 hour electrocardiograms had been recorded and analysed in a standardized way (appendix 3A). During *routine analysis* the presence of arrhythmias was categorized as: 1) supraventricular premature or escape complexes or rhythms, 2) ventricular premature or escape complexes or rhythms, 3) atrio-ventricular conduction defects, and 4) impulse formation defects. Their occurrence was recorded as: absent, rarely present (>0-30% of recording time), frequently present (31-90%), or continuously present (>90%). For premature ventricular complexes and ventricular doublets hourly frequencies were given. Reports with these findings were sent to the referring physicians who could use them to adjust treatment strategies.

For the purpose of this study a computer-aided re-analysis was performed of the 24 hour electrocardiograms of cases and reference patients.[7,8] During the computer-aided analysis a stream of approximately 100,000 RR and and 200,000 QT intervals was obtained, as well as detailed information on the frequency and repetitiveness of ventricular arrhythmias. The procedure of computer-aided analysis is described in detail in appendices 5A and 5B. An analysis of parameters concerning QTc and RR interval duration and variability derived from the interval streams is presented in chapter 5.

Quality control

To obtain consistent clinical data during the two-year period of retrospective data collection in the four participating hospitals general instructions and short definitions on the patient characteristics to be obtained were printed on a data collection form. A manual containing details on the coding procedure was written and this was used as a reference to guarantee standardization of the procedure during the whole period of data collection. To eliminate coding errors ranges of variables and mutual consistencies between variables (for example within the Minnesota Code) were checked during input in the computer database.

STATISTICAL METHODS

Data analysis

The objective of this study was to investigate the relation between electrocardiographic parameters and the occurrence of sudden death. More specifically, the objective was to obtain reliable estimates of the strength of these relations and a description of their precision.[9] The strength of these relations is studied by a direct comparison of the risks for sudden death in different categories of the electrocardiographic parameter, for instance the risk in patients with QTc prolongation versus that in patients with a normal QTc. (QTc will be used as an example throughout this section).

Absolute risk. In the conventional follow-up study the absolute risk for sudden death (within two years) is estimated by the proportion patients who died suddenly (within two years) among those initially present in the study cohort. For instance, the risk for sudden death in patients with QTc prolongation is $r_1 = a/n_1$ (left 2x2 table in table 3.6). In the context of a nested case-referent design the number of patients at risk in a certain category is not directly available and must be estimated by multiplying the number of reference patients in that category with the inverse of the sampling fraction. In the middle and right 2x2 tables in table 3.6 the calculation of the absolute risk in a nested case-referent study is illustrated: $r_1 = a/\tilde{n}_1 = a/k.e$, with k the inverse of the sampling fraction. In the example the estimated number of patients at risk with QTc prolongation, $\tilde{n}_1$, is (6693/467)x86 = 1233 and the absolute risk for sudden death in patients with QTc prolongation, r_1, is 65/1233 = 0.053.

Table 3.6: Calculation of absolute and relative risks in the conventional cohort follow-up and nested case-referent designs illustrated with an example for the nested case-referent design.

	Follow-up (general)		N-Case-Ref (general)		N-Case-Ref (example)	
	QTc		QTc		QTc	
	>440	≤440	>440	≤440	>440	≤440
Sudden death	a	b	a	b	65	111
Non-(sudden death)	c	d	?	?	?	?
Observed total	n_1	n_0	?	?	?	?
Sample			e	f	86	304
Estimated total			$\tilde{n}_1$=k.e	$\tilde{n}_0$=k.f	1233	4357
Absolute risk	r_1= a/n_1	r_0= b/n_0	r_1= $a/\tilde{n}_1$	r_0= $b/\tilde{n}_0$	r_1= 0.053	r_0= 0.025
Relative risk	r_1/r_0		r_1/r_0		2.1	

N-Case-Ref, Nested Case-Referent design; k, inverse of sampling fraction (6693/467 in the example).

In the follow-up design the absolute risk for sudden death in patients with QTc prolongation is $r_1 = a/n_1$. In the context of a nested case-referent design the number of patients at risk with QTc prolongation is not directly available and must be estimated as $\tilde{n}_1 = k.e$, with k the inverse of the sampling fraction and e the number of patients in the sample with QTc prolongation. In the example this number of patients is estimated as (6693/467)x86 = 1233 and thus the absolute risk for sudden death in patients with QTc prolongation, r_1, is 65/1233 = 0.053. The relative risk is in both study designs estimated by the ratio of the risk for sudden death in patients with QTc prolongation (r1) to that in patients with a normal QTc (r0). In the example this yields a relative risk of 0.053/0.025 = 2.1, which means that patients with QTc prolongation carry a risk twice as high as those with a normal QTc. Note that the relative risk does not depend on the sampling fraction since this factor cancels in the calculation: $r_1/r_0 = (a/k.e)/(b/k.f) = (a/e)/(b/f)$.

Relative risk. The effect of QTc prolongation on sudden death can be quantified by the relative risk which is obtained by dividing the absolute risk for sudden death in patients with QTc prolongation by that in patients with a normal QTc: i.e. $r_1/r_0 = 0.053/0.025 = 2.1$. This means that patients with QTc prolongation carry a risk twice as high as those with a normal QTc. Note that the relative risk does not depend on the sampling fraction since this factor cancels in the calculation: $r_1/r_0 = (a/k.e)/(b/k.f) = (a/e)/(b/f)$.

Precision. The 95%-confidence interval was used to describe the precision of the estimate of the relative risk. The 95%-confidence interval has a width such that it contains the true relative risk in 95% of the applications. The width of the confidence interval depends on the size of the study and the confidence level, which conventionally is set at 95%. It is noted that when the 95%-confidence interval does not contain 1 the relation of the electrocardiographic parameter with the risk for sudden death is statistically significant at the 5% level.

Several methods are available to calculate the 95%-confidence interval in the conventional follow-up study.[9] However, in the nested case-referent design the standard deviation of the relative risk which is needed for the estimation of the confidence interval cannot be calculated. For this reason the 95%-confidence interval of the odds ratio[10] was used, i.e. using all cases versus the non-cases from the referent group, which is a good approximation.

Multivariate analysis. Stratified analysis and logistic regression were used to assess the influences of independent risk factors of sudden death on the occurrence of sudden death and to identify baseline characteristics which modify the effect of the parameters under investigation.[1,2]

Size of the study

Sample size calculations using methods by Fleiss[11] and based on the assumption that the risk indicator would be present in 30% of the patients of the non-cases, an odds ratio of 1.5, a significance level of α=0.05 (one-sided), a power of 1-β=0.20 and a proportion of cases to non-cases of 2:1 indicated that approximately 250 cases would be necessary. The study of Velema[12] from the same institution reported a 5.5% two year mortality in a similar cohort of patients who had 24 hours electrocardiography. Sixty three percent of the deaths were cardiac. Thus it could be calculated that 250/(0.055x0.63) = 7200 patients had to be followed to accrue sufficient cases of cardiac death. A random sample of seven percent of this cohort, 500 patients, would form the reference group, twice as large as the index group.

DISCUSSION

The study population consisted of a heterogeneous group of patients accumulated in the years 1980-1984 from an urban area in whom an indication for 24 hours electrocardiography was present. There was a variety of indications to record such an electrocardiogram:

to evaluate complaints (palpitations, dizziness, syncope, angina) (54%), the effect of therapy (7%), the risk after myocardial infarction (14%), or a cardiac cause in transient ischemic attack or stroke (11%). Patients with a pacemaker were excluded because of technical problems to be expected during computer-aided analysis of the 24 hour electrocardiogram (see appendix 5A) and patients younger than ten years were also excluded, because of a dominance of congenital heart disease in this group.

The occurrence of sudden death in the cohort was conditional on the interventions which took place since 24 hours electrocardiography. Therefore the findings during routine analysis of the 24 hour electrocardiograms may have influenced intervention strategies. This would jeopardize the validity of the estimation of the effect of the electrocardiographic parameters on sudden death. However, in clinical practice only extreme QTc prolongation would lead to specific intervention; the other electrocardiographic parameters (heart rate variability and QT interval variability) are not generally used in clinical practice. Thus, it is unlikely that the validity of the estimation of the effect of the electrocardiographic parameters on sudden death is influenced by the findings on the 24 hour electrocardiograms. However, the effect is conditional on treatment administered since 24 hours electrocardiography. Consider for example the situation in which QTc prolongation increases the risk for sudden death when no interventions take place between the moment of QTc measurement and the end of follow-up. Assume further the existence of a hypothetical drug which prevents sudden death related to QTc prolongation and which has no side effects in patients with a normal QTc. This drug administered after 24 hours electrocardiography would yield an equal incidence of sudden death in patients with and without QTc prolongation, and thus, no association between QTc prolongation and sudden death would be found. The existence of a distortion of the QTc - sudden death relation as extreme as in this example is improbable however. Nevertheless, when interpreting the results of this study one should always realize that the findings are conditional on therapy given since 24 hours electrocardiography, which per se possibly induced certain therapeutic regimens.

Mortality in the study cohort was almost twice as high as expected on the basis of Velema's study (two-year mortality 10.7% versus 5.5%).[12] The series of Velema also originated from the archives of Cardiolab (1976-1978). As no major changes took place in the organizational structure of Cardiolab and as age and sex distributions of both study populations were virtually equal, it is tempting to ascribe the higher mortality in the present study to a more restrictive policy to record 24 hours electrocardiograms in more recent years. The high mortality made it possible to utilize cases of *sudden* cardiac death rather than cases of cardiac death for which the original study was planned (see "size of the study").

The criteria used for classification of the cases of sudden death were pragmatic because information on cause and circumstances of death had to be obtained one to four years after death. More strict criteria actually only can be used with concurrent case ascertainment (see also chapter 2: definition of sudden cardiac death). The ascertainment of the 74% of the cases who died within one hour after onset of complaints was fairly straightforward. Of the remaining 63 cases who died with 24 hours after onset of complaints, 32 did so during sleep and thus also fulfilled a clear criterion. In the remaining 31 patients

case ascertainment was more judgmental. These cases predominantly had large myocardial infarctions complicated by pump failure and arrhythmias. Cases who died within 24 hours and those on whom only scanty information was available were only accepted after independent review by two senior cardiologists.

For the current study a nested case-referent design was chosen because of efficiency considerations. Only for cases and a random sample of the study cohort parameters of study were determined, rather than for the complete study population. In our situation this meant the retrieval of the data of 691 patients in stead of those of the 6693 patients in the complete cohort. The decision to draw a reference group from the complete study population (and not from the non-cases) was mainly determined by the fact that it allowed the calculation of absolute risks (table 3.6), and the estimation of the relative risk rather than the odds ratio, which in its turn simplifies the presentation of the results of the study. The use of the odds ratio for the calculation of confidence limits is less elegant in this view, but several arguments defend this approach. Firstly, calculation of confidence limits for the odds ratio is possible, in contrary to that of the relative risk. Secondly, the relative risk equals the odds ratio as long as the fraction of cases among reference patients with and without QTc prolongation are equal. Because the incidence of sudden death is low (245/6693 = 0.037) the fraction of cases among reference patients is low too and thus no important differences between relative risk and odds ratio occur in this study. Finally, during multivariate analysis logistic regression is employed which is based on an odds ratio model.

In spite of the heterogeneity of the study population we are convinced that the study cohort provides an excellent basis to study the risk implications of various electrocardiographic parameters.

APPENDIX 3A:
Standard recording and analysis of 24 hour electrocardiograms at Cardiolab.

Recording technique
Twenty four electrocardiograms were obtained as follows. The skin was prepared for electrode attachment by removing hairs and rubbing with a tissue steeped in alcohol. Two bipolar leads, corresponding with the precordial leads V2 and V5, were acquired by placing the electrodes as shown in figure 3.3. The V2 analogue (lead 1) was derived from electrodes one and three, the V5 analogue (lead 5) from electrodes two and four. These locations were selected such that a clear P wave could be detected in lead one and a minimum of muscle artifacts would occur. A fifth electrode was placed on the right side of the chest, approximately above the sixth rib and was used as a reference to reduce base line shift in the electrocardiographic signal. Next a test electrocardiogram was made to check the quality of the signals. P wave and T wave amplitudes were required to be 80% of the R amplitude at most. If the R wave was (relatively) too small or if signal quality was poor the electrodes had to be moved until a satisfactory signal was obtained. To avoid tear on the electrodes and thus electrocardiogram artifacts, the electrode wires were taped to the patient. The electrocardiographic signals were recorded with the use of Oxford Medi-

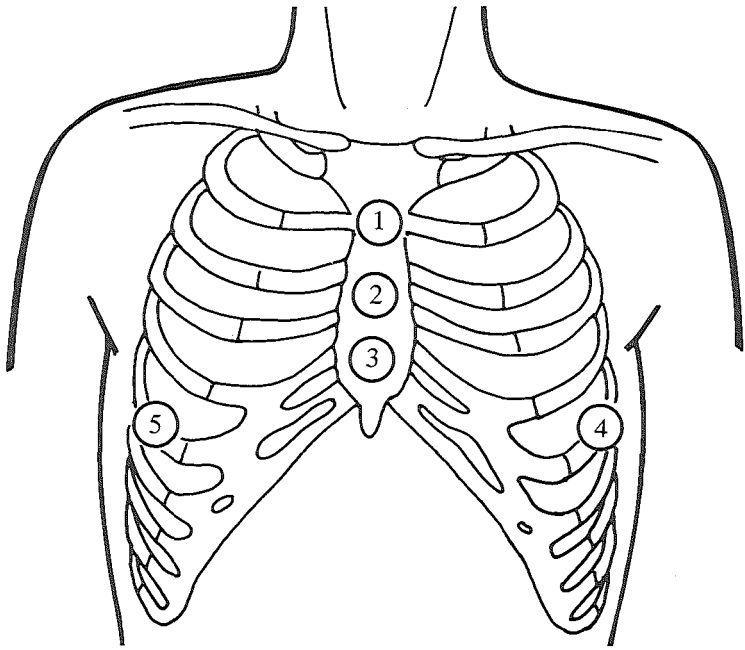

Figure 3.3: Electrode placement for 24-hour electrocardiography

cal Instruments recorders both of the AM and FM recording type. The patient was asked to denote activities, complaints and medication with their corresponding times of occurrence in a diary.

Analysis of 24 hour electrocardiograms

The 24 hour electrocardiograms were replayed on Oxford Medical Instruments analysers (initially the replay units PB-2 and PB-4 with the Medilog analyser, consequently with the Medilog 2 and MA-14 analysers) with a speed of 60 or 120 times real time. QRS complexes are shown superimposed on each other on a monitor. During normal sinus rhythm a regular quiet picture of superimposed QRS complexes is seen, during arrhythmias however, fast changes pass the screen. A premature ventricular complex presents with a QRS complex of aberrant morphology and thus contrasts with the dominant supraventricular QRS morphology. The electrocardiographic signal also is presented acoustically; the passage of a premature ventricular complex can be heard as a little tick in a low frequent background hum. Supraventricular premature complexes are detected because the shortening of the interval preceding the supraventricular premature complex produces flickering at the monitor and a little disturbance in the acoustic signal. Runs of premature complexes of both supraventricular or ventricular origin are detected because the frequency of the acoustic signal suddenly increases. During replay also attention is paid to the morphologies of the P-, QRS-, and T complexes and their time relations. Emphasis is given to PQ interval changes in order to detect atrio-ventricular conduction defects.

At a visual or acoustical event replay of the tape can be stopped and the last 40 seconds of real time electrocardiogram are recalled on the monitor enabling detailed investigation of the rhythm. If an arrhythmia is present the electrocardiogram can be written out on a two-channel strip chart recorder for report preparation. All types of arrhythmias occurring in the tape are documented by the electrocardiogram strips and the keeping of notes.

In the final report hourly bar diagrams are reported for premature ventricular complexes, irrespective of multiformity, and ventricular doublets. For the other arrhythmias a semi-quantitative scoring is used. The four categories on the scale are absent, rarely present, frequently present and continuously present corresponding to the percentage of recording time, respectively 0%, >0-30%, >30-90% and >90%.

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4. Standard 12 Lead Electrocardiogram

INTRODUCTION

There exists a controversy over the significance of QTc prolongation as a risk factor in patients after myocardial infarction: Surawicz concluded that "QTc has little, if any, predictive value after myocardial infarction",[1] while Locati stated that "QTc represents a simple and valid method of identifying patients at high risk of sudden death.[2] In this chapter the risk implications of QTc prolongation as measured at standard 12 lead electrocardiography for the occurrence of sudden death are analysed.

METHODS

Patients

Study patients were 6693 patients who had 24-hour electrocardiography. During two years of follow-up 245 cases of sudden death occurred. From all 6693 study patients 467 patients were randomly selected who served as reference group. A more detailed description of the study design, study patients, cases and the selection of reference patients is provided in chapter 3.

Standard 12 lead electrocardiogram

For all cases and reference patients a resting twelve lead electrocardiogram recorded at the time of 24-hour ambulatory electrocardiography was obtained. Three channel recorders at a paper speed of 25 mm/s had been used. Standard 12 lead electrocardiograms were not available in 24 patients. The QT interval was taken as the interval between the first onset of the QRS complex and the last end of the T wave in the three synchronous standard leads I, II and III and was corrected for heart rate according to Bazett's formula: $QTc = QT / \sqrt{RR}$.[3] No QTc measurement was done in the 100 patients with an intraventricular conduction defect (Minnesota code 7) and in the 18 patients with atrial fibrillation or frequent premature ventricular complexes. Hence, QTc measurement was available in 176 cases of sudden death and 390 reference patients. All measurements were done by the project manager without knowledge about the survival status of the patient. A QTc interval ≥440 ms was considered to be prolonged.

Routine clinical patient characteristics

Information on patient characteristics at time of 24-hour electrocardiography was obtained as described in chapter 3. Evidence of cardiac dysfunction was considered to be present if there had been a history of symptoms of pump failure or an ejection fraction < 40% at cineangiographic or radionuclide ventriculography ever.

RESULTS

The distribution of baseline characteristics in relation to QTc duration in the reference patients is shown in table 4.1. Female sex, advanced age and evidence of cardiac dysfunction were more frequently present among the patients with QTc prolongation than among those with a normal QTc.

In table 4.2 the occurrence of sudden death for patients with prolonged QTc and those with normal QTc is shown. It appeared that QTc prolongation doubled the risk for sudden death. There was a marked difference between patients with and without evidence of cardiac dysfunction: in the presence of evidence of cardiac dysfunction QTc prolongation

Table 4.1: Distribution of patient characteristics at the time of 24-hour electrocardiography in relation to QTc duration in the reference patients

	QTc interval	
	<440	≥440
All patients	304	86
Males	59%	47%
Age > 60 years	44%	59%
Evidence of cardiac dysfunction[1]	12%	26%
History of		
angina ever	32%	33%
myocardial infarction	29%	36%
any supraventricular arrhythmias	38%	50%
any ventricular arrhythmias	34%	48%
atrio-ventricular conduction defects	6%	10%
palpitations	50%	51%
dizziness	44%	44%
syncope	19%	10%
coronary bypass surgery	7%	7%
transient ischemic attack or stroke	15%	20%
intermittent claudication	7%	10%
diabetes mellitus	7%	14%
smoking ever	36%	29%
Drug use		
none	22%	13%
digitalis	21%	27%
beta blockers	28%	24%
nitrate	22%	24%
diuretics	18%	31%
antiarrhythmic drugs	18%	38%
oral anticoagulants	24%	38%

[1] Defined as a history of symptoms of pump failure or an ejection fraction < 40% at cineangiographic or radionuclide ventriculography ever.

Table 4.2: The occurrence of sudden death in relation to QTc prolongation and the evidence of cardiac dysfunction, age, sex and history of myocardial infarction.

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
QTc, all patients					
<440	111	4357	2.5%	-	-
≥440	65	1233	5.3%	2.1	(1.4, 3.1)
QTc, patients with evidence of cardiac dysfunction					
<440	47	516	9.1%	-	-
≥440	30	315	9.5%	1.0	(0.5, 1.9)
QTc, patients without evidence of cardiac dysfunction					
<440	64	3841	1.7%	-	-
≥440	35	917	3.8%	2.3	(1.4, 3.9)
QTc, patients without evidence of cardiac dysfunction, age ≤ 60 years					
<440	16	2307	0.7%	-	-
≥440	7	416	1.7%	2.4	(1.0, 6.9)
QTc, patients without evidence of cardiac dysfunction, age > 60 years					
<440	48	1534	3.1%	-	-
≥440	28	502	5.6%	1.8	(1.0, 3.3)
QTc, patients without evidence of cardiac dysfunction, females					
<440	17	1548	1.1%	-	-
≥440	10	545	1.8%	1.7	(0.7, 4.0)
QTc, patients without evidence of cardiac dysfunction, males					
<440	47	2293	2.0%	-	-
≥440	25	373	6.7%	3.3	(1.9, 6.9)
QTc, patients without evidence of cardiac dysfunction, with history of MI					
<440	34	975	3.5%	-	-
≥440	19	272	7.0%	2.0	(1.0, 4.7)
QTc, patients without evidence of cardiac dysfunction nor history of MI					
<440	30	2866	1.1%	-	-
≥440	16	645	2.5%	2.4	(1.2, 4.8)

SD, sudden death; Est.Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval; MI, myocardial infarction.
[1] Estimated as the number of reference patients multiplied with the inverse of the sampling fraction, 6693/467;
[2] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;
[3] Calculated as the 95%-CI for the odds ratio.

carried no increased risk for sudden death, in its absence the relative risk was 2.3. Because of the clinical significance of this difference, both groups were analysed separately, and also because the relative risks were statistically significantly different (p=0.038).

The lower part of table 4.2 shows the occurrence of sudden death for patients without evidence of cardiac dysfunction subdivided according to age, sex and history of myocardial infarction respectively. QTc prolongation carried a higher risk for sudden death in males as compared to females; this difference was not statistically different (p=0.17). The relative risk for sudden death of QTc prolongation was independent of age, previous

myocardial infarction (as shown in table 4.2) and of the history of angina, arrhythmias and the use of drugs.

Relative risk estimates obtained via stratified analysis and logistic regression (so-called adjusted estimates) were essentially the same as the ones described in table 4.2 (so-called crude estimates), both in patients with and without evidence of cardiac dysfunction.

DISCUSSION

Present study

Our study was primarily designed for the investigation of the relation between QTc variability and heart rate variability as measured in the 24-hour electrocardiogram and the risk for sudden death. The setting of this project, however, provided an opportunity to study the relation between the standard 12 lead electrocardiogram QTc and sudden death.

The relative risk of QTc prolongation for sudden death was 2.3 in the patients without evidence of cardiac dysfunction and 1.0 in those with dysfunction (table 4.2). Because of this substantial difference, which was statistically significant, we considered the two groups as two different entities. Possibly the electrophysiologic properties of hearts in patients with cardiac dysfunction could be different from those in patients without cardiac dysfunction. It has to be noticed that the patients with evidence of cardiac dysfunction had a higher risk for sudden death than the patients without dysfunction (the relative risk of 4.5 of cardiac dysfunction for sudden death can be calculated from the data in table 4.2); QTc prolongation did not further increase the risk for sudden death in patients with cardiac dysfunction. Neural compensating mechanisms active during cardiac dysfunction possibly preclude the expression of QTc prolongation in the form of ventricular fibrillation. In patients without evidence of cardiac dysfunction the relative risk was independent of a history of myocardial infarction, the use of any drug or any other important clinical variable except sex. We are not aware of any (patho)physiologic explanation for the intriguing difference between females and males. Also, heart rate did not influence the relative risk, although Bazett's calculation of QTc at low heart rates may not always be adequate.

The presence of incomparabilities of patient characteristics did not form a problem in obtaining a valid estimate of the relative risk – for the estimates obtained via stratified analysis or logistic regression (adjusted estimate) and via the simple analysis (crude estimate) were essentially the same.

We conclude that in patients without intraventricular conduction defects and cardiac dysfunction QTc prolongation measured in a standard 12 lead electrocardiogram doubles the risk for sudden death as compared to a normal QTc. Age, history of myocardial infarction, heart rate, and drug use do not affect the strength of the association. In patients with cardiac dysfunction QTc prolongation does not increase the risk for sudden death. Because of the stability of the relative risk over many subgroups our results apply to a broad population of patients.

Comparison with other studies

The results of earlier studies on the relation between QTc prolongation and sudden death are summarized in table 4.3.[4-15] (The data from the original papers were rearranged to allow a uniform presentation.) The upper part of the table shows death rates in patients with and without QTc prolongation with corresponding relative risks and 95%-confidence intervals; the lower part mean QTc values and standard deviations for deaths and survivors together with the corresponding differences and 95%-confidence intervals. Because in the last four studies no data on the number of patients with a prolonged and a normal QTc were published, relative risks as presented in the upper part of the table could not be calculated. All studies were confined to post myocardial infarction patients with the exception of that of Puddu, who used patients with angiographically proved coronary artery disease[10] (table 4.3).

Some authors have reported on death from all causes, some on cardiac death, and Ahnve on major cardiac events (sudden death, circulatory standstill and reinfarction).[13] Some studies were not primarily designed to assess the relation between QTc prolongation and sudden death, and hence sudden death rates were not reported in all instances. The use of death from all causes as outcome dilutes the relation between QTc prolongation and outcome as is illustrated by the Beta Blocker Heart Attack Trial, in which the relative risk of 1.8 (1.3, 2.5) for sudden death attenuated to 1.6 (1.3, 2.0) when death from all causes was used,[7] and the weak associations reported in the studies by Pohjola-Sintonen and Ahnve.[9,12]

Several authors of the studies performed after Schwartz's original paper[4] was published, have concluded that their studies did not confirm his observations.[5,9,12,14,15] However, in all studies (Ahnve's excepted[12]) the observed relative risk or QTc difference points to an increased risk for (sudden) death with QTc prolongation. The confidence intervals in these studies all include the null value (1 for the relative risk, 0 for the QTc difference), or in the terminology of the original papers: the relation of QTc with the risk for (sudden) death was not statistically significant at the 5% level. Several of the smaller studies were inconclusive when considered separately. However, taken together these studies corroborate Schwartz' observations, a phenomenon often observed in meta-analyses. The relative risk found in our patients without cardiac dysfunction compares well with those summarized in table 4.3[4-11] and especially with those from the large Beta Blocker Heart Attack Trial.[7]

Variability of the QTc interval

Repeated measurements of QTc allow investigators to identify temporary prolongation of QTc intervals, which is an indication for a (temporarily) increased risk for sudden death. Schwartz measured QTc every two months during follow-up. Patients with a high variability of QTc were more likely to die suddenly than those with low QTc variability.[4] This hypothesis is further investigated in chapter 5 by analysis of the variability in QTc and heart rate in the 24-hour electrocardiograms that led to entry of our patients into our study.

Conclusions

The data from our study indicate that in the absence of evidence of cardiac dysfunction

Table 4.3 Comparison of studies reported in the literature (4-15) and this study.

Author	Source	Nr at risk	Follow-up (yrs)	Type of case[1]	(sudden) death rates QTc≥440		QTc<440		RR[2]	95%-CI	Remarks
Schwartz[4]	post MI	55	7	sudden death	76%	(16/21)	35%	(12/34)	2.2	1.3, 3.6	
Boudoulas[5]	post MI	100	3.6	cardiac death	31%	(4/13)	18%	(16/87)	1.7	0.7, 4.2	
Ahnve[6]	post MI	214	1	cardiac death	23%	(10/43)	2%	(3/171)	13.3	3.8, 46.1	
Peters[7]	post MI	3692	2.1	sudden death	6.6%[3] 4.9%[3]	(41/619) (32/650)	3.7% 2.6%	(46/1230) (31/1193)	1.8 1.9	1.2, 2.7 1.2, 3.1	Placebo Propranolol
Juul-Möller[8]	post MI	96	1	cardiac death	50%[4]	(9/18)	9%[5]	(7/78)	5.6	2.4, 13.0	
Pohjola-Sintonen[9]	post MI	457	4	all death	30%	(31/104)	22%	(79/353)	1.3	0.9, 1.9	
Puddu[10]	proven CAD at angio	1157	3.8	sudden death	12%	(29/233)[6]	7%	(69/924)[6]	1.7	1.0, 2.9	
Fioretti[11]	post MI	474	1	all death	13.8%	(20/125)	7.6%	(25/304)	1.8	1.0, 3.2	
Algra (this study)	24h ECG candidates	5589	2	sudden death	3.8% 9.5%	(35/917) (30/315)	1.7% 9.1%	(64/3841) (47/516)	2.3 1.0	1.4, 3.9 0.5, 1.9	CD absent CD present

					deaths N	deaths QTc (sd)	survivors N	survivors QTc (sd)	DQTc	95%-CI	
Ahnve[12]	post MI	210	3-6	all death	46	430 (42)[7]	164	431 (34)[7]	-1	-13, 11	
Ahnve[13]	post MI	160	1	major cardiac events	31	434 (35)	129	417 (42)	17	1, 33	
Møller[14]	post MI	89	2	sudden death	11	435 (25)	78	419 (30)	16	-4, 36	
Wheelan[15]	post MI	518	1.5	sudden death	28	458 (31)	490	451 (36)	7	-7, 21	

The upper part of the table shows death rates in patients with and without QTc prolongation, the corresponding relative risks and 95%- confidence intervals; the lower part shows mean QTc values and standard deviations (ms) for deaths and survivors along with the corresponding difference and 95%-confidence intervals. RR, relative risk; CI, confidence interval; MI, myocardial infarction; CAD, coronary artery disease; CD, cardiac dysfunction; sd, standard deviation; DQTc, QTc in deaths - QTc in survivors.

[1] death within a maximum of 24 hours after onset of complaints; [2] relative risks are calculated from the actual numbers on which the authors based their conclusions; [3] QTc≥450;[4] QTc>480; [5] QTc<480; [6] denominators estimated from sample of survivors; [7] estimated from standard deviations presented.

QTc prolongation may double the risk for sudden death. The findings from our study accord with those in the literature when taken together. Furthermore, our study indicates that in patients with cardiac dysfunction the high risk for sudden death is independent of QTc prolongation.

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5. 24 Hour electrocardiogram

INTRODUCTION

In this chapter data pertaining to the relation between QTc and RR duration and variation as derived from 24-hour electrocardiography and the occurrence of sudden death is presented. In addition the correspondence between parameters from 24-hour electrocardiography and standard 12 lead electrocardiography is investigated.

METHODS

Patients

Study patients were 6693 patients who had 24-hour electrocardiography. During two years of follow-up 245 cases of sudden death occurred. Reference patients are 467 patients randomly selected from all 6693 study patients. A detailed description of the study design in particular of study patients, cases and the selection of reference patients is provided in chapter 3.

Poor signal quality of the 24-hour electrocardiograms of four patients precluded the calculation of the parameters concerning QTc and RR duration and variability. These patients were excluded from the present analyses; thus 241 cases remained for analysis. From the original 467 reference patients only a randomly selected subset of 268 patients was used in the present analysis, because the computer-aided re-analysis of the 24-hour electrocardiograms appeared to be very time consuming. We thus decided to involve the smaller subset of reference patients gaining time, but losing some precision of the relative risk estimates.

QTc interval duration and variation

The parameters of QTc interval duration and variation shown in the upper panel of table 5.1 were obtained. Mean, maximum and minimum QTc were taken as duration parameters, while QTc >440 ms, short-term variation, long-term variation and the day-night mean QTc difference were taken as variability parameters. These parameters were derived from a stream of approximately 100,000 RR and QT intervals obtained during computer-aided re-analysis of 24-hour electrocardiograms of all cases and reference patients (appendix 5A and 5B).[1,2] During computer-aided analysis QT measurements in three episodes of 30 minutes of the 24-hour electrocardiogram were reviewed and manually corrected. The selection of the three 30 minutes episodes was based on 1) maximum RR interval variability, 2) maximum QT interval variability, and 3) minimum mean TQ duration (appendix 5A). QT measurements which were not reviewed were adjusted with the mean difference of QT measurements before and after review in the three 30 minutes episodes in that 24-hour electrocardiogram. All QT data analyses were performed with the

Table 5.1: Parameters of QTc and RR duration and variability during 24-hour electrocardiography and their definition.

Parameter	Definition
QTc interval	
Mean QTc	mean over 24 hours of per minute QTc means
Maximum QTc	maximum of per minute QTc means
Minimum QTc	minimum of per minute QTc means
QTc >440 ms	mean over 24 hours of per minute percentages of QTc intervals >440 ms
Short-term variation QTc	mean over 24 hours of per minute standard deviations of QTc intervals
Long-term variation QTc	standard deviation over 24 hours of per minute means of QTc intervals
Day-night mean QTc difference	difference of mean QTc between 7.30 - 21.30 and 0.00 - 5.00
RR interval / heart rate	
Mean heart rate	mean over 24 hours of per minute heart rate means
Maximum heart rate	maximum of per minute heart rate means
Minimum heart rate	minimum of per minute heart rate means
Interval differences >50 ms	mean over 24 hours of per minute percentages of consecutive intervals with an absolute difference >50 ms
Short-term variation RR	mean over 24 hours of per minute standard deviations of RR intervals
Long-term variation RR	standard deviation over 24 hours of per minute means of RR intervals
Day-night mean heart rate difference	difference of mean heart rate between 7.30 - 21.30 and 0.00 - 5.00

Note: all parameters were calculated over 24 hours unless indicated otherwise.

use of heart rate corrected QT (QTc) intervals.[3] QTc was calculated only if the current and previous QRS complex were of supraventricular origin while a running RR average with 1/8 update was used in the computation.

For comparison with their analogues on the 24-hour electrocardiogram QTc intervals were determined in leads V2 and V5 of standard 12 lead electrocardiograms recorded at the time of 24-hour electrocardiography for all cases and reference patients. In patients with an intraventricular conduction defect (Minnesota code 7) or rhythm disturbances no QTc measurement was performed.

Patients with an intraventricular conduction defect (Minnesota code 7) at the standard 12 lead electrocardiogram recorded at the time of 24-hour electrocardiography were excluded from the QTc analyses. Also patients with evidence of cardiac dysfunction* were excluded because analyses of the standard 12 lead electrocardiogram QTc revealed no

* conform definition in chapter 4: history of symptoms of pump failure or an ejection fraction < 40% at cineangiographic or radionuclide ventriculography ever.

relation between QTc prolongation and sudden death in these patients (chapter 4). Thus, 104 cases and 201 reference patients were available for the QTc analyses.

RR interval duration and variability

For the analyses of heart rate variability only RR intervals between QRS complexes of supraventricular origin were used. Intervals which duration was <80% or >120% of that of the running RR average were excluded to eliminate premature supraventricular complex related intervals and ventricular arrests. Also excluded were the intervals following a short interval (presumably related to a premature supraventricular complex) because these intervals tend to be prolonged as partially compensatory pause. In the lower panel of table 5.1 the summary parameters of RR duration and variation are defined.

In the RR data analyses patients with supraventricular rhythms (other than sinus rhythm) as reported during routine analysis of the 24-hour electrocardiogram were excluded. Thus, 193 cases and 230 reference patients remained for the RR interval analyses.

Data analysis

Statistical data analysis approaches were the same as those described in chapter 3 apart from the use of a correction factor of 241/245 in the calculation of absolute risks to compensate for the exclusion of four cases. In the initial analyses all parameters mentioned in table 5.1 were divided into thirds. If the absolute risks for sudden death in two adjacent categories were essentially the same, these categories were joined into one category in later analyses.

RESULTS

The distribution of baseline characteristics of all 268 reference patients and those in the subsets for the QTc and RR analyses are shown in table 5.2. The exclusions of patients for the QTc and RR data analyses are indicated.

In table 5.3 the occurrence of sudden death for patients in several categories of QTc parameters is shown. Both patients with shortening and those with prolongation of mean QTc had a more than double risk for sudden death in comparison to patients with mean QTc values between 400 and 440 ms. The same pattern was found for the other parameters of QTc duration: maximum and minimum QTc and the percentage QTc >440 ms. Increased risks of QTc shortening were found to be independent of heart rate (table 5.4). For short-term and long-term QTc variability an elevated risk was found in both high and low extremes, also if the analysis was restricted to the three 30 minutes episodes in which QT measurements were reviewed and corrected and hence variation was determined most accurately. The day-night QTc difference was not related to the occurrence of sudden death.

Because of the unexpected observation that QTc shortening was related to an increased risk for sudden death, we scrutinized the risk implications of QTc in the three 30 minutes episodes with manually edited QT measurements. The results are presented in table 5.5. Again, an elevated risk of QTc shortening was found; this increase of risk did

Table 5.2: Distribution of patient characteristics at the time of 24-hour electrocardiography in all reference patients and those selected for the QTc and RR data analyses.

		In data analyses of	
	All (n=268)	QTc (n=201)	RR (n=230)
Outpatient	82%	81%	81%
Males	61%	58%	64%
Age >60 years	52%	49%	49%
Evidence of cardiac dysfunction[1]	18%	excluded	17%
History of			
angina ever	35%	29%	37%
myocardial infarction	33%	26%	34%
any supraventricular arrhythmias	40%	36%	33%
any ventricular arrhythmias	37%	30%	35%
atrio-ventricular conduction defects	8%	6%	6%
palpitations	50%	51%	48%
dizziness	45%	45%	47%
syncope	17%	17%	17%
coronary bypass surgery	8%	5%	8%
transient ischemic attack or stroke	13%	15%	13%
intermittent claudication	8%	8%	9%
diabetes mellitus	9%	8%	8%
smoking ever	34%	38%	35%
Drug use			
none	22%	25%	24%
digitalis	21%	12%	17%
beta blockers	26%	28%	26%
nitrate	28%	23%	29%
diuretics	24%	17%	22%
antiarrhythmic drugs	22%	19%	20%
oral anticoagulants	23%	19%	21%
Standard 12 lead electrocardiogram			
Minnesota code 7	13%	excluded	13%
24-hour electrocardiogram, routine analysis			
supraventricular rhythms[2]	14%	13%	excluded
premature ventricular complex	84%	82%	83%
ventricular bigeminy	18%	13%	18%
ventricular doublet	34%	24%	32%
ventricular tachycardia	12%	7%	12%

[1] Defined as a history of symptoms of pump failure or an ejection fraction <40% at cineangiographic or radionuclide ventriculography ever;

[2] including: atrial fibrillation, atrial flutter, supraventricular tachycardias and supraventricular escape rhythms.

Table 5.3: The occurrence of sudden death in relation to several parameters of QTc duration in the 24-hour electrocardiogram in patients without intraventricular conduction defects or evidence of cardiac dysfunction.

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
Mean QTc (ms)					
<400	36	1130	3.2%	2.4	(1.4, 4.3)
400-440	36	2678	1.3%	-	-
≥440	29	934	3.1%	2.3	(1.3, 4.5)
Maximum QTc (ms)					
<440	25	688	3.6%	2.8	(1.5, 5.5)
440-480	40	3046	1.3%	-	-
≥480	39	1204	3.2%	2.5	(1.4, 4.4)
Minimum QTc (ms)					
<370	46	1818	2.5%	1.7	(1.0, 3.1)
370-400	32	2186	1.5%	-	-
≥400	26	934	2.8%	1.9	(1.1, 3.9)
Percentage QTc >440 ms					
<10	40	1327	3.0%	1.8	(1.0, 3.5)
10-30	29	1769	1.6%	-	-
≥30	32	1646	1.9%	1.2	(0.7, 2.2)
Short-term variation QTc (ms)					
<20	56	2678	2.1%	1.4	(0.7, 2.8)
20-25	16	1056	1.5%	-	-
≥25	29	1007	2.9%	1.9	(1.0, 4.4)
Long-term variation QTc (ms)					
<10	28	958	2.9%	2.2	(1.2, 4.2)
10-15	37	2727	1.4%	-	-
≥15	39	1253	3.1%	2.3	(1.4, 4.2)
Difference daytime - nighttime QTc (ms)					
<-5	28	1400	2.0%	1.1	(0.6, 2.1)
-5-+5	44	1695	2.6%	1.4	(0.8, 2.8)
≥+5	26	1425	1.8%	-	-

SD, sudden death; Est.Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval.

[1] Estimated as the number of reference patients multiplied with the inverse of the sampling fraction, 6693/268 and corrected by 241/245 because of the exclusion of four cases;

[2] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;

[3] Calculated as the 95%-CI for the odds ratio.

not depend on heart rate. A subdivision of the risk implications of mean QTc over 24 hours and the three 30 minutes episodes by Holter channel is shown in table 5.6. For all QTc duration parameters the elevation of risk for sudden death by QTc shortening is most outspoken in channel 1, the V2 analogue.

In figures 5.1 and 5.2 the relation between QTc measurements from 24-hour electrocardiography and standard 12 lead electrocardiography is shown for the corresponding

Table 5.4: The occurrence of sudden death in relation to mean QTc duration over 24 hours in the 24-hour electrocardiogram and mean heart rate over 24 hours in patients without intraventricular defects or evidence of cardiac dysfunction.

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
Mean QTc over 24 hours (ms), mean heart rate <70 bpm					
<400	17	344	4.9%	3.2	(1.1, 8.0)
400-440	12	786	1.5%	-	-
≥440	8	123	6.5%	4.3	(1.3,19.8)
Mean QTc over 24 hours (ms), mean heart rate 70-85 bpm					
<400	10	540	1.9%	1.2	(0.5, 3.1)
400-440	18	1130	1.6%	-	-
≥440	10	516	1.9%	1.2	(0.5, 3.1)
Mean QTc over 24 hours (ms), mean heart rate ≥85 bpm					
<400	9	221	4.1%	5.2	(1.6,21.2)
400-440	6	762	0.8%	-	-
≥440	11	295	3.7%	4.7	(1.5,17.3)

SD, sudden death; Est.Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval.

[1] Estimated as the number of reference patients multiplied with the inverse of the sampling fraction, 6693/268 and corrected by 241/245 because of the exclusion of four cases;

[2] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;

[3] Calculated as the 95%-CI for the odds ratio.

Table 5.5: The occurrence of sudden death in relation to mean QTc duration in the three 30 minutes episodes of the 24-hour electrocardiogram selected for QT review in patients without intraventricular conduction defects or evidence of cardiac dysfunction.

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
Mean QTc over episode 1[4] (mean heart rate: 76.8 bpm)					
<400	37	1179	3.1%	1.9	(1.1, 3.3)
400-440	44	2604	1.7%	-	-
≥440	20	1081	1.9%	1.1	(0.6, 2.1)
Mean QTc over episode 2[4] (mean heart rate: 80.7 bpm)					
<400	41	1499	2.7%	1.7	(1.0, 3.1)
400-440	38	2358	1.6%	-	-
≥440	23	983	2.3%	1.5	(0.8, 2.9)
Mean QTc over episode 3[4] (mean heart rate: 96.2 bpm)					
<400	24	1032	2.3%	1.3	(0.7, 2.4)
400-440	43	2358	1.8%	-	-
≥440	29	1474	2.0%	1.1	(0.6, 2.0)

SD, sudden death; Est.Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval; bpm, beats per minute.

[1] Estimated as the number of reference patients multiplied with the inverse of the sampling fraction, 6693/268 and corrected by 241/245 because of the exclusion of four cases;

[2] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;

[3] Calculated as the 95%-CI for the odds ratio.

[4] For selection criteria of the three 30 minutes episodes see appendix 5A.

Table 5.6: The occurrence of sudden death in relation to mean QTc duration over 24 hours and three selected 30 minutes episodes subdivided by Holter channel in patients without intraventricular conduction defects or evidence of cardiac dysfunction.

	Holter channel 1			Holter channel 2		
	%SD	RR[1]	(95%-CI[2])	%SD	RR[1]	(95%-CI[2])
Mean QTc						
<400	3.1%	3.0	(1.3, 7.0)	3.3%	2.0	(0.9, 4.8)
400-440	1.1%	-	-	1.6%	-	-
≥440	4.7%	4.5	(1.8,12.4)	2.3%	1.4	(0.6, 3.2)
Mean QTc over episode 1[3]						
<400	3.3%	2.5	(1.1, 5.2)	2.9%	1.5	(0.7, 3.7)
400-440	1.3%	-	-	2.0%	-	-
≥440	2.3%	1.7	(0.6, 4.2)	1.6%	0.8	(0.3, 1.9)
Mean QTc over episode 2[3]						
<400	2.5%	2.0	(0.9, 4.5)	3.1%	1.6	(0.9, 4.5)
400-440	1.3%	-	-	1.9%	-	-
≥440	4.1%	3.2	(1.2,10.0)	1.7%	0.9	(0.4, 2.1)
Mean QTc over episode 3[3]						
<400	2.3%	1.3	(0.6, 2.9)	2.3%	1.2	(0.5, 3.8)
400-440	1.7%	-	-	1.9%	-	-
≥440	2.0%	1.2	(0.5, 3.1)	1.9%	1.0	(0.5, 2.2)

%SD, two year sudden death rate; RR, relative risk; CI, confidence interval.

[1] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;

[2] Calculated as the 95%-CI for the odds ratio.

[3] For selection criteria of the three 30 minutes episodes see appendix 5A.

lead pairs, Holter channel 1 with lead V2 and Holter channel 2 with lead V5 respectively. Both figures disclose a poor correspondence of the measurements. The findings on QTc duration at 24-hour electrocardiography were compared with those at the corresponding leads (V2,V5) from the standard 12 lead electrocardiogram. The results in table 5.7 show no increased risk for sudden death in patients with QTc shortening in the combined leads I, II and III and single lead V5, and a trend in single lead V2.

In table 5.8 the occurrence of sudden death in relation to several heart rate parameters is shown. Mean heart rates below 70 and over 80 beats per minute are related to a slightly increased risk for sudden death. Maximum heart rate has a clear inverse relation with the risk for sudden death, while the same applies for a minimum heart rate above 65 beats per minute.

A low percentage of intervals differences larger than 50 ms also exhibits an elevated risk. Both short-term and long-term variation of RR interval duration show a strong inverse relation with the risk for sudden death: patients with low short-term and long-term variation have a four times higher risk for sudden death as compared to patients with high variation. This finding is reflected in the risk implications of day-night mean heart rate

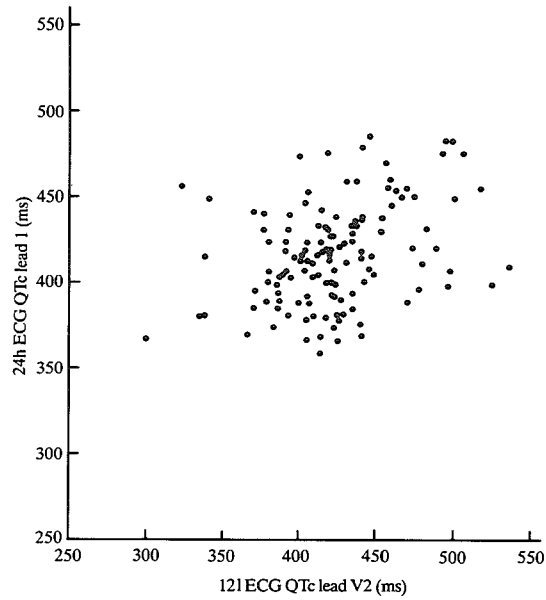


Figure 5.1: Relation between QTc measurements from 24-hour electrocardiography (channel 1) and standard 12 lead electrocardiography (lead V2).

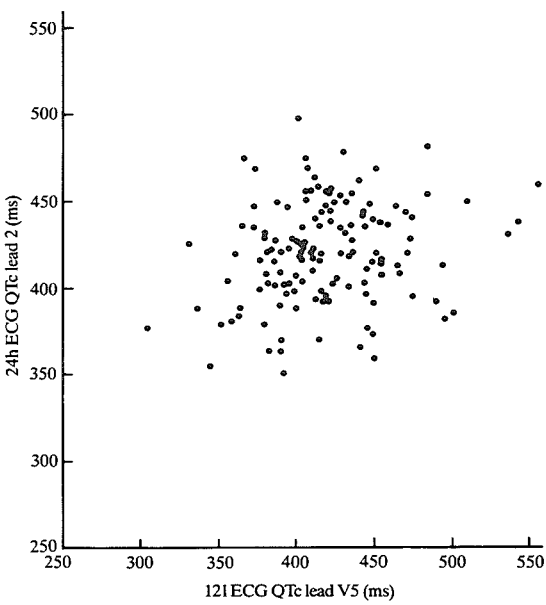


Figure 5.2: Relation between QTc measurements from 24-hour electrocardiography (channel 2) and standard 12 lead electrocardiography (lead V5).

Table 5.7: The occurrence of sudden death in relation to QTc duration in leads V2 and V5 of 12 lead resting electrocardiograms recorded at the time of 24-hour electrocardiography in patients without intraventricular conduction defects or evidence of cardiac dysfunction.

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
QTc lead V2 (ms)					
<400	26	1204	2.2%	1.3	(0.8, 2.4)
400-440	38	2365	1.6%	-	-
≥440	37	1218	3.0%	1.9	(1.2, 3.4)
QTc lead V5 (ms)					
<400	22	1276	1.7%	1.0	(0.6, 1.9)
400-440	36	2150	1.7%	-	-
≥440	36	1261	2.9%	1.7	(1.0, 3.0)
QTc leads I, II and III (ms)					
<400	25	1491	1.7%	1.0	(0.6, 1.8)
400-440	39	2350	1.7%	-	-
≥440	35	917	3.8%	2.3	(1.4, 4.1)

SD, sudden death; Est.Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval.

[1] Estimated as the number of reference patients multiplied with the inverse of the sampling fraction, 6693/268 and corrected by 241/245 because of the exclusion of four cases;

[2] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;

[3] Calculated as the 95%-CI for the odds ratio.

difference: differences below 15 beats per minute are related to two to three fold risks for sudden death. In figure 5.3 trends of per minute means of heart rate, per minute standard deviation of RR duration and the percentage interval differences >50 ms are shown both for a patient who suddenly died during two years follow-up (upper panel) and a patient who survived this period. Relative risk estimates obtained via stratification for beta blocker use were essentially the same as the ones described in table 5.8, while these estimates for patients on beta blockers did not differ notably from those for patients not using these drugs. Stratification for evidence of cardiac dysfunction showed no important additional information.

DISCUSSION

QTc interval duration

Risk implications of the QTc duration parameters at 24-hour electrocardiography were compared to those of QTc duration derived from standard 12 lead electrocardiography. Prolongation of the mean QTc duration over 24 hours >440 ms was related to a more than double risk for sudden death as compared to QTc durations between 400 and 440 ms.

Table 5.8: The occurrence of sudden death in relation to several parameters of heart rate in the 24-hour electrocardiogram in patients without supraventricular rhythms.

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
Mean heart rate (bpm)					
<70	66	1597	4.1%	1.6	(0.9, 2.6)
70-80	46	1769	2.6%	-	-
≥80	73	2113	3.5%	1.3	(0.8, 2.1)
Maximum heart rate (bpm)					
<100	59	1056	5.6%	2.5	(1.5, 4.3)
100-125	84	2383	3.5%	1.6	(1.0, 2.5)
≥125	50	2211	2.3%	-	-
Minimum heart rate (bpm)					
<65	124	4545	2.7%	-	-
≥65	69	1105	6.2%	2.3	(1.5, 3.8)
Interval differences >50 ms (%)					
<3	81	1670	4.8%	1.8	(1.2, 2.8)
≥3	104	3832	2.7%	-	-
Short-term variation RR interval (ms)					
<25	86	1228	7.0%	4.1	(2.6, 8.1)
25-40	72	2653	2.7%	1.6	(1.0, 2.9)
≥40	27	1597	1.7%	-	-
Long-term variation RR interval (ms)					
<8	88	1376	6.4%	4.4	(2.6, 7.7)
8-12	71	2088	3.4%	2.3	(1.5, 4.2)
≥12	32	2186	1.5%	-	-
Difference daytime - nighttime heart rate (bpm)					
<10	87	1621	5.4%	2.8	(1.8, 4.6)
10-15	45	1155	3.9%	2.0	(1.2, 3.4)
≥15	48	2506	1.9%	-	-

SD, sudden death; Est.Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval.

[1] Estimated as the number of reference patients multiplied with the inverse of the sampling fraction, 6693/268 and corrected by 241/245 because of the exclusion of four cases;

[2] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;

[3] Calculated as the 95%-CI for the odds ratio.

Prolongation of minimum and maximum QTc duration showed comparable increases of risk. These findings accord with those from the standard 12 lead electrocardiogram (chapter 4). However, a striking new finding was that patients with a mean QTc duration <400 ms also had a more than double risk for sudden death in comparison to patients with intermediate QTc durations (400-440 ms). This finding was unexpected because earlier studies on the risk implications of QTc duration, including our own study on the standard 12 lead electrocardiogram, did not indicate that QTc *shortening* had a relation with an increased risk for sudden death (chapter 4). The finding, furthermore, did not accord with the theory that QTc prolongation is an electrocardiographic equivalent of inhomogeneous

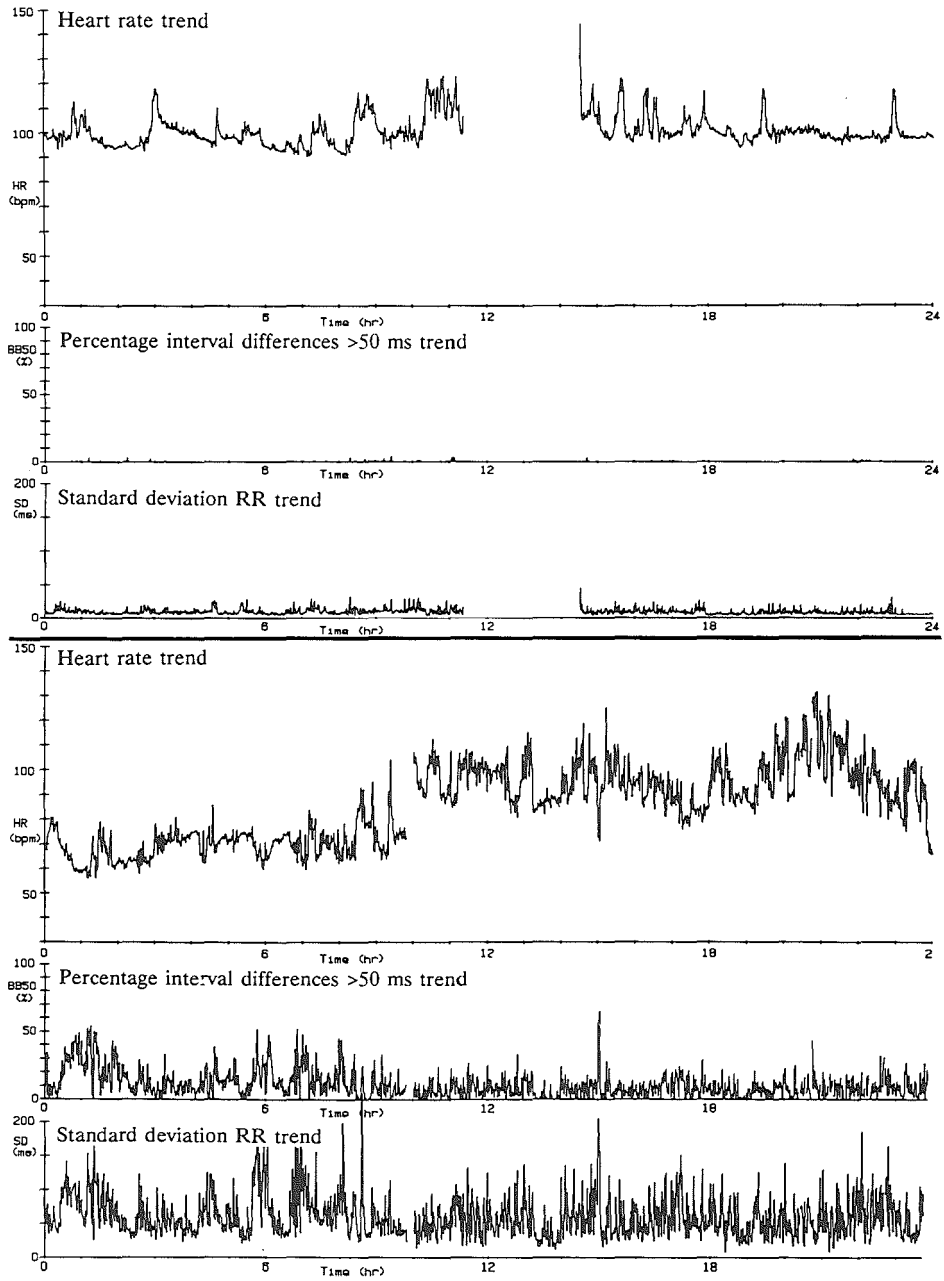


Figure 5.3 : Trends of per minute means of heart rate, standard deviation of RR duration and the percentage interval differences >50 ms. Upper panel: for a patient who died suddenly seven weeks after 24-hour electrocardiography. Lower panel: for a patient who was alive during follow-up two years after 24-hour electrocardiography.

prolongation of repolarization which per se predisposes for the occurrence of malignant ventricular arrhythmias and sudden death. In this theory QTc shortening would be related to decreased risks for sudden death. Explanations for the discrepancy between the findings from 24-hour and standard 12 lead electrocardiography must be sought in the differences between these electrocardiographic methods.

A first difference concerns the situation in which the electrocardiogram is recorded and its consequences for the application of the Bazett formula for the correction of QT duration for heart rate.[3] During standard 12 lead electrocardiography the patient is in a static situation, as opposed to that during *dynamic* 24-hour electrocardiography. It is not likely, however, that this difference explains our observation on QTc shortening because we found that QTc interval duration at resting hours during nighttime (0.00 - 5.00 h) had the same risk implications as during the complete 24 hours. A point of related concern is the validity of the Bazett formula under static circumstances. Many alternative formulae for the heart rate correction of the QT interval have been proposed[4] but QTc according to Bazett is most commonly used today and, for example, it is applied as one of the defining criteria of the Long QT Syndrome.[5] In our data the U-shaped risk curve of QTc interval duration also emerged in the subgroup with lowest mean heart rate (table 5.4). At these heart rates only minor differences exist between QT and QTc interval duration. Thus, we therefore concluded that it seems unlikely that our observation on QTc shortening is explained by the use of the Bazett formula.

A second difference pertains to the leads used. All studies on QTc duration derived from standard 12 lead electrocardiography, including ours, used standard leads I, II and III for the determination of QTc. During Holter electrocardiography, however, bipolar leads are used which correspond best with the unipolar leads V2 and V5 (appendix 3A). Thus, it is more appropriate to compare QTc measurements in leads V2 and V5 with their analogues from the Holter. Figures 5.1 and 5.2 showed a limited correspondence between QTc measurements from the two types of electrocardiographic registrations. However, a similar limited correspondence was found between different leads *within* a standard 12 lead electrocardiogram. QTc in lead V5 did not show an elevated risk for patients with QTc shortening while in lead V2 a trend (relative risk of 1.3) was observed. Theoretically it is possible that a long QT interval in one lead concurs with a short QT interval in another lead if the last part of repolarization takes place in a plane perpendicular to the axis of the lead in which the short QT interval is recorded. In our data, it were always anteriorly located leads in which QTc shortening was related to an increased risk for sudden death: at standard 12 lead electrocardiography such a trend was observed in V2, while the effect of QTc shortening in the Holter leads was most outspoken in channel 1, the most anteriorly located of the two. Thus, in some patients with prolonged repolarization the terminal part may take place in the frontal plane only, perpendicular to the lead axes of anteriorly located leads and hence "invisible" from there.

A third difference between Holter and standard electrocardiography pertains to the technical characteristics of the recording procedure: the frequency characteristics of Holter electrocardiography are limited.[6] This might lead to a distorted registration of repolarization and systematic under- or over-estimation of QT duration. However, this does not explain why a U-shaped risk curve for QTc duration would develop.

A fourth difference concerns fallacies in the process of determination of QTc duration parameters from the 24-hour electrocardiogram. Mean QTc over 24 hours is based on QTc computations in which computer measured QT intervals and a running RR average are used, a large range of heart rate is covered, and an average over 24 hours is determined, as opposed to the simple calculation of QTc at standard resting 12 lead electrocardiography in which one QT and one RR interval is used. Nevertheless it is not likely that these computational differences play a major role because QTc shortening in the three episodes which were reviewed and corrected had the same risk implications. Moreover the same trend was found for other parameters of QTc duration: initial QTc, maximum and minimum QTc, while the effect of QTc shortening did not depend on heart rate.

We may have observed a true pathophysiologic phenomenon. If reentry is considered to be the mechanism responsible for sudden death in our study patients, and reentry is more likely to occur during inhomogeneous repolarization and a short excitation wavelength (i.e. the product of refractory period and conduction velocity), then at least two explanations can be given for an increased risk for sudden death by QT interval shortening. Firstly, in inhomogeneous repolarization it might well be so that repolarization is "observed" to be complete from anteriorly located electrodes while this merely is an artifact because terminal repolarization occurs in a plane which can not be observed from this electrode. A discrepancy between QT duration from different leads may then be interpreted as evidence of inhomogeneous repolarization, one of the conditions for reentry arrhythmias. Secondly, short QT may be the result of a short refractory period which would yield a short excitation wavelength predisposing for reentry.[7]

QTc interval variability

The percentage QTc intervals >440 ms, that is the percentage of intervals generally considered to be prolonged, was taken as measure of the number of episodes during which the patient would be in a state of high risk for sudden death. Based on observations on QTc duration from the standard 12 lead electrocardiogram and data presented by the group of Bayès de Luna[8] it was expected that a high percentage QTc >440 ms would be related to a high sudden death rate. This, however, does not emerge from our data. This finding may be attributed to the limited relation of prolongation of mean QTc duration over 24 hours with sudden death. The parameters of QTc variation can be interpreted as a measure of the number and duration of episodes in which extreme QTc durations occur, hence the number and duration of high risk episodes. No clear relation of high variation with sudden death, however, emerges from our data, probably for the same reason as mentioned before: the lack of a strong relation of QTc prolongation with sudden death. Our observations are at variance with those by Schwartz who noted higher variation of QTc duration between bimonthly repeated standard 12 lead electrocardiograms in patients who died suddenly during a 7 year follow-up after myocardial infarction than in patients who survived this follow-up period.[9] However, in his study QTc prolongation was related to sudden death (see chapter 4, table 4.3). In conclusion: our data show that QTc variation has no strong relation with the occurrence of sudden death; both prolongation and shortening of QTc duration are related to an increased risk for sudden death as compared to intermediate QTc values (400-440 ms).

RR interval duration (heart rate)

Mean heart rate over 24 hours exhibits no clear relation with the occurrence of sudden death, neither does it in the patient groups off beta blockers and without evidence of cardiac dysfunction. Actually, the average of all mean heart rates over 24 hours in our study did not differ from that reported for a group of healthy male subjects (77 versus 74 beats per minute).[10] Probably, prognostic information with regard to sudden death is lost by taking the 24 hours average, because the other parameters of heart rate had prognostic implications and also because reports on heart rate as taken from standard 12 lead electrocardiograms showed that sudden death rates increased progressively with heart rate.[11,12] A maximum heart rate <100 beats per minute was related to an increased risk for sudden death, also if patients on beta blockers and those with evidence of cardiac dysfunction were excluded from the analysis. This finding may be compared to that from exercise testing in which inability to raise heart rate is related to a poor prognosis.[13] Reversely, in comparison to healthy subjects patients with angiographically proven coronary artery disease reached lower maximum heart rates.[14] Thus, low maximum heart rate may be interpreted as a correlate of low exercise capacity. A minimum heart rate over 65 beats per minute more than doubles the risk for sudden death. High minimum heart rate may be the reflection of many conditions some of which include impaired myocardial function, autonomic imbalance, poor physical fitness or any combination. The role of the first factor may be confirmed by our data: minimum heart rate was higher in patients with evidence of cardiac dysfunction than in those without (difference: 5.2 beats per minute, 95% confidence interval 2.9, 7.5).

RR interval variability (heart rate variability)

The percentage of successive intervals which differed more than 50 ms was taken as measure of parasympathetic activity.[15] This index is primarily sensitive to frequency components of the heart rate spectrum between 0.15 and 0.50 Hz,[16] and comprises the peak of variations around 0.25 Hz which corresponds to the respiratory frequency modulated by the parasympathetic nervous system.[17,18] Short-term variation, defined as the 24 hour mean of per minute standard deviations of RR intervals, is sensitive to spectral components between approximately 0.05 and 0.50 Hz,[16] containing not only respiratory frequencies but also those attributed to the baroreceptor reflex which is influenced by both the sympathetic and parasympathetic nervous system. Long-term variation, the standard deviation over 24 hours of per minute RR interval means, corresponds with low frequency components of the heart rate spectrum, around frequencies of 0.02 - 0.05 Hz,[16] enclosing the peak which probably originates from fluctuations in peripheral vasomotor tone associated with thermoregulation.[19]

Patients with low parasympathetic activity as expressed by 50 ms interval differences <3% had approximately a double risk for sudden death as those with high parasympathetic activity (intervals differences ≥3%). Patients with low levels of short-term variation (<25 ms) had a fourfold risk for sudden death as compared to patients with high levels (≥40 ms). This latter observation is probably in accordance with that on 50 ms interval differences because short-term variation of RR intervals at least partly is interpreted as a measure of parasympathetic activity. However, it is likely that a different explanation

must be sought for the finding that long-term RR interval variation also shows a strong reverse relation with the occurrence of sudden death, because long-term variation appears to be less dominated by the parasympathetic nervous system.

In a group of 808 survivors of acute myocardial infarction from the Multicenter Post-Infarction Project heart rate variability (taken as the standard deviation of all normal RR intervals in a 24-hour electrocardiogram) less than 50 ms was related to a 5.3 times higher risk for mortality from all causes within a median follow-up period of 31 months than heart rate variability over 100 ms.[20] These findings were confirmed in a more detailed study by this group.[21] In a comparison of heart rate variability parameters, similar to the ones we used, six survivors of documented ventricular fibrillation had clearly lower levels of variability as assessed by all parameters than a comparison group of six volunteers without evidence of heart disease.[16] Thus, our findings correspond well with those reported in the literature.

Implications

Given the elaborate procedure used in this study to obtain QTc parameters from 24-hour electrocardiography and the limited risk implications of these parameters with regard to the occurrence of sudden death QTc measurement from 24-hour electrocardiography may have limited value for clinical routine. The finding, however, that shortening of mean QTc derived from 24-hour electrocardiography is related to an increased risk for sudden death may stimulate new research on the effect of electrode localisation on QTc duration and its pathophysiologic mechanisms. Heart rate variability may be useful in clinical practice because this parameter is easily obtained from 24-hour electrocardiography and has a strong relation with the occurrence of sudden death, and moreover, since low variability is linked to low parasympathetic activity, heart rate variability may give direction to therapeutic interventions. Insofar as low parasympathetic activity is related to high sympathetic activity beta blockers may be efficacious drugs. This would be in agreement with pooled observations from long-term beta blocker trials which yield a 32% reduction of the incidence of sudden death.[22] Direct stimulation of parasympathetic activity by parasympathicomimetic drugs may be an alternative, however, their efficacy in man still has to be demonstrated.

Conclusions

The data from our study indicate that both prolongation and shortening of mean QTc derived from 24-hour electrocardiography are related to a doubled risk for sudden death as compared to intermediate QTc values (400 - 440 ms). QTc variability has no clear relation to sudden death, neither has mean heart rate. Maximum heart rate <100 beats per minute and minimum heart rate ≥65 beats per minute are related to a more than double risk for sudden death as compared to heart rates ≥125 and <65 beats per minute respectively. Patients with <3% RR interval differences >50 ms have a twofold risk for sudden death in comparison to those with ≥3% interval differences. Both short-term and long-term RR interval variation have a strong inverse relation with the risk for sudden death: patients with low short-term and long-term variation have a four times higher risk as compared to patients with high variation.

APPENDIX 5A:
Analysis of 24-hour electrocardiograms at ARGUS-TX-QT

Introduction

After publications of Lown appeared at the end of the sixties[23] the interest in the study of premature ventricular activity increased greatly. The need of reliable detection, in particular that of premature ventricular complexes, became apparent. Thus computer programs were developed for automatic detection of premature ventricular complexes. The ARGUS system was one of the first and originates from Washington University, St. Louis, USA.[24] In 1979 the ARGUS system was implemented at the Thoraxcenter.[1]

The analysis of 24-hour electrocardiograms at ARGUS-TX-QT was a ten step procedure which is summarized in table 5.9. Programs one through five and eight had been implemented at the start of the study. Programs six, seven, nine and ten were developed specially for the current study.[2]

QRS complex processing

Firstly, electrocardiographic signals of both channels were digitized at a replay speed of 120 times real time and a sampling frequency of 250 Hertz per real time second, i.e. a data acquisition frequency of 120x250x2 samples per second or 60K. For the complete 24-hour electrocardiogram this amounted to some 5000M samples, which were stored on computer disk in about 50 megabyte (MByte) space. Sample data of eight tapes could be stored simultaneously.

Secondly, QRS complexes were detected and classified into so-called QRS families.[25] A QRS family was described with a set of 4 parameters: duration, height, offset and area.[26] All members of a QRS family had similar characteristics within certain limits. Pacemaker spikes in the electrocardiographic signal disturbed QRS detection, hence 24-hour electrocardiograms of pacemaker patients could not be processed.

Machine edit phase one was the next step. The QRS families generated by ARGUS were classified into the categories shown in table 5.10. Thus a stream of QRS labels and

Table 5.9: The ten steps of ARGUS-TX-QT

1. DIG	(I)	Replay and digitization
2. ARG	(A)	ARGUS QRS detection and family generation
3. ME1	(A)	Machine edit phase 1: labeling of QRS families
4. ME2	(I)	Machine edit phase 2: labeling of QRS families
5. ED1	(I)	QRS edit: labeling of single QRS complexes
6. QTM	(A)	QT interval measurements
7. QTE	(I)	QT interval edit in selected ECG fragments
8. STR	(A)	Strip generation of selected ECG fragments
9. QTS	(A)	Data save for storage on magnetic tape
10. QTR	(A)	Report generation

(A), automatic; (I), interaction with technician; ECG, electrocardiogram

Table 5.10: ARGUS QRS labels

N	Normal, narrow, supraventricular
B	Borderline, slightly widened, probable supraventricular
A	Abnormal, wide, not premature with regard to the current rhythm
V	Ventricular, wide and premature
V?	Unedited ventricular, wide, possibly ventricular, to be edited
F	False ventricular, previously marked V?, not ventricular
Z	Noise, poor signal quality

measurements with accompanying RR intervals was created which was stored in the so-called CYCLE data stream.[26]

During the second phase of the machine edit interaction with a technician was needed. A QRS complex representative of a family of possible ventricular complexes was presented to determine whether the complex was of true ventricular origin. If the technician decided that the QRS complex was "true ventricular" all members of the family were given the V label, else the label was left V? for further editing during the next step.

During the interactive edit of single QRS complexes, step 5, several phases could be distinguished. All V? labelled QRS complexes were presented for a decision about the origin of the complex. The QRS complex was labeled V if the origin was ventricular, else it was labeled F, false ventricular complex. The next phases of the human QRS edit were directed towards error detection. Firstly, all intervals which were long in comparison to the current rhythm were presented in order to detect unlabeled QRS complexes which yielded erroneously long intervals. Secondly, all intervals shorter than a by the technician determined threshold were shown. Thus, incorrectly labeled premature beats of either supraventricular or ventricular origin could be detected. Thirdly, a set of special QRS sequences was presented to the technician, e.g. the shortest and longest NN, NV and VV intervals and the fastest and slowest heart rate. Finally, whenever the technician found premature ventricular complexes incorrectly labeled as A or B, a special A or B search could be done in which all A or B labeled QRS complexes were presented for editing.

QT interval processing

After completion of QRS editing measurement of QT intervals took place. With the use of the QRS onsets the end of the T waves was searched for within a heart rate dependent window. The end of T wave algorithm simulated as much as possible the human observer: it looked for the first horizontal segment in the electrocardiogram after the top of the T wave. A detailed description of the algorithm and its evaluation is given in appendix 5B.[2]

During the seventh step of ARGUS-TX-QT QT interval measurements were presented for review and correction. Because of the presence of approximately 100,000 QRS complexes in a 24-hour electrocardiogram and the measurement of QT intervals in two channels, approximately 200,000 QT intervals were available for editing. Since it was not feasible to edit all QT intervals a selection of three episodes of 30 minutes in one channel was made to limit editing time. The channel in which QT interval duration had the

strongest correlation with RR interval duration was selected for QT editing, because the quality of the QT measurements in this channel was considered to be best. Since RR- and QT interval variability were the main determinants of study, these were used in the criteria to select the three 30 minutes episodes. From the 48 30 minutes episodes available first the episode with maximum RR variability was selected. RR variability was defined as the standard deviation of the per minute averages of the RR intervals in a 30 minutes episode. This definition was adopted to try to avoid detection of high frequency variability due to sinus arrhythmia. Secondly the episode with maximum QT interval variability (the standard deviation of all QT intervals in a 30 minutes episode) was chosen and finally the episode with the shortest TQ intervals (average of all TQ intervals in a 30 minutes episode). This latter episode was selected because of the proximity of the end of repolarization and the start of the next depolarization, a high risk situation for the initiation of ventricular arrhythmias.

Data storage and reporting

The last three steps were completely automatically run. During step 8, the strip generation, a selection of arrhythmias from the 24-hour electrocardiogram was written out on a two-channel chart recorder. In step 9 the complete CYCLE data stream with accompanying QT intervals was stored to magnetic tape for detailed analysis later. An extract of these data, containing RR- and QT interval variability measures, was directly put in an on-line database. Finally in step 10 a concise report of the analysis results was generated and presented to the technician as feed-back.

Comparison of QT measurements before and after edit

For the three 30 minutes episodes in which QT measurements were reviewed and corrected measurements before and after edit were compared. In table 5.11 the mean differences and attending standard deviations are shown. QT measurements by the human editor were on average approximately 8 ms shorter than those by the computer.

Table 5.11: Mean differences of QT measurements after and before QT editing for three 30 minutes episodes of 24-hour electrocardiograms.

30 minutes episode	Mean difference (SD) after - before edit (ms)
Maximum RR variability[1]	-7.8 (15.6)
Maximum QT variability[2]	-9.5 (21.2)
Minimum mean TQ[3]	-7.4 (12.9)

[1] RR variability: standard deviation of per minute averages of RR intervals;
[2] QT variability: standard deviation of all QT intervals;
[3] mean TQ: mean of all TQ intervals.

APPENDIX 5B:
An algorithm for computer measurement of QT intervals in the 24-hour electrocardiogram

[Reproduced with permission from: Algra A, Le Brun H, Zeelenberg C. An algorithm for computer measurement of QT intervals in the 24-hour electrocardiogram. Proceedings Computers in Cardiology 1986; 117-9.]

Summary
It is hypothesized that (rapid) changes of QT interval duration can lead to life threatening situations. To study the dynamics of QT interval duration an algorithm was developed for its measurement in the 24-hour electrocardiogram. Computer QT measurements were compared with "hand" measurements using a test data base of 8 electrocardiogram episodes of each 130 seconds (total of 1587 QRST complexes).

It is concluded that the reproducibility of QT measurements by computer is comparable or better than the reproducibility in measurements done by human interpreters. The magnitude of measurements deviations is 10-15 ms.

Introduction
Prolongation of the heart rate corrected QT interval (QTc)[3] is associated with high rates of ventricular arrhythmias and sudden cardiac death. This relation was found both in patients with the idiopathic long QT syndrome[27] and in patients with QTc prolongation after a myocardial infarction.[9] An environmental trigger, probably mediated through the sympathetic nervous system, can lead to QTc prolongation and deterioration of an initially normal sinus rhythm into ventricular fibrillation[28]. Thus, it is hypothesized that (rapid) changes of QT interval duration also can lead to life threatening situations. Dynamic behavior of QT interval duration can be studied in the 24-hour electrocardiogram. To facilitate QT interval measurements a computer algorithm was developed.

Methods
The previously described ARGUS-TX system[1] forms the environment for the development and implementation of the new QT algorithm. After digitization at a frequency of 250 samples per second, eight 24-hour electrocardiograms can be stored on-line in the system. During machine edit onset and beat label are determined for each QRS complex. In the next step a human editor reviews the machine generated data. Thus a stream of QRS-onsets – QT interval starts – and RR sequences is obtained.

End of T algorithm. In a second pass the new algorithm determines the end of the T waves. In the development of the algorithm the human interpreter served as a model. First of all the end of the T wave is looked for within a narrow window after the QRS complex. Secondly, there must be a transition of the terminating sloping limb of the T wave to a flat segment. Thirdly, noise should not interfere with interpretation. Finally no end of T will be determined in premature ventricular complexes (PVC).

These three conditions are translated in the computer algorithm as follows. An "end of T measurement window" is calculated using the previous RR interval (figure 5.4) and is based on Bazett's formula[3]: $QT = QTc \times \sqrt{RR}$. The normal value of QTc is 440 ms and to

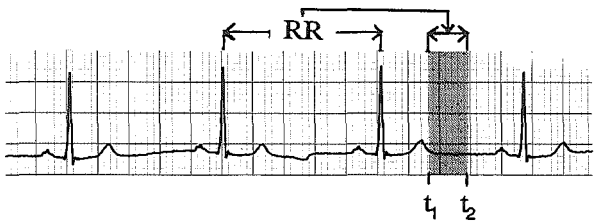


Figure 5.4: Determination of the end of T measurement window: $t_1 = 0.36 \times \sqrt{RR}$; $t_2 = 0.55 \times \sqrt{RR}$; t_1, t_2 and RR in seconds.

find a realistic end of the T wave a lower limit of 360 ms and an upper limit of 550 ms was chosen. If no suitable previous RR interval is present because the previous beat was labeled ventricular extrasystole or noisy, the running RR average is used.

Within the "end of T measurement window" a search is done for a flat segment of at least 40 ms duration. If such an interval is found its beginning is used to mark the end of the T wave. During noisy episodes with either baseline shift or high frequency noise no flat segment will be found. An end of T measurement is suppressed in this situation in accordance with condition three. QRS complexes labeled PVC or noisy will be skipped during end of T analysis.

Test database. In order to test the algorithm a QT measurement database was set up. Eight electrocardiogram episodes digitized at 250 samples per second with a duration of 130 seconds each, containing a total of 1587 QRST complexes were used. The size of the database was determined by a trade-off between the aim of representativeness of all possible QRST morphologies and feasibility of the number of hand measurements.

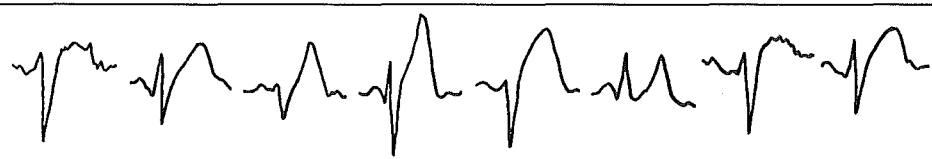
End of T measurements were obtained by "hand" with the use of a hairline on a Tektronix graphics terminal. Three series of "hand" measurements were done: two (A1 and A2) by the first author A, an experienced electrocardiogram reader, and one by the second author B, who has less experience with end of T determination.

To describe the comparison between the human observers and the computer three parameters were used. The mean difference (md) in milliseconds represents the systematic difference between two series of observations. The mean of the absolute values of the differences minus the mean difference (mean(ld-mdl)), the dispersion, abbreviated as DISP, is used as a measure of variation in the differences. DISP for all electrocardiogram episodes together is reported as a weighed average of the dispersion in each individual electrocardiogram segment. As an alternative measure for the variation in the differences the weighed average of the standard deviations (SD) in the electrocardiogram episodes is presented.

Results

For each of the eight electrocardiogram episodes included in the database a reference complex is displayed in table 5.12. The upper panel of the same table provides for each electrocardiogram episode the number of QRST complexes, the number of complexes in which an end of T was detected and the mean heart rate. From a total of 1587 QRST complexes, 836 QT measurements could be obtained.

Table 5.12 QT database description

ECG segment nr	1	2	3	4	5	6	7	8	ALL
reference complex									
nr QRST	176	231	250	243	126	203	171	187	1587
perct. QT	49%	46%	15%	23%	100%	54%	81%	94%	53%
mean HR	81	107	115	112	58	94	79	86	---
remarks	noisy signal	---	many PVC's	---	good quality	some PVC's	noisy signal	good quality	---
mean dif. A1-A2	-4.3	1.3	-4.8	-4.0	-0.9	1.0	1.1	-2.6	-1.1
mean dif. A1-B	-3.2	5.9	9.2	8.0	39.4	27.2	-2.7	9.2	12.3
mean dif. A1-C	-3.8	-0.3	2.1	-10.1	1.8	5.3	10.3	-2.3	1.2
DISP A1-A2	15.5	5.8	6.6	5.9	9.5	5.6	10.1	6.6	8.3
DISP A1-B	17.5	9.6	8.1	8.3	11.9	11.8	13.9	10.5	11.8
DISP A1-C	20.1	9.5	6.5	11.2	13.8	6.4	19.2	10.8	12.7

nr QRST, number of QRST complexes in ECG fragment; perct. QT, percentage QRST complexes in which QT measurement was done; HR, mean heart rate in ECG fragment; PVC, premature ventricular complex; dif., difference; DISP, mean(\|d-md\|), mean of absolute value of difference minus mean of difference between comparison groups specified by ECG segment; md, mean of difference;

Table 5.13: Comparison of QT interval measurements.

		md	DISP	SD
intra observer	A1 - A2	-1.1	8.3	14.5
inter observer	A1 - B	12.3	11.8	16.2
observer-computer	A1 - C	1.2	12.7	18.8

md, mean of difference; DISP, dispersion, mean(ld-mdl), mean of absolute value of difference minus mean of difference, weighed average of DISP's of individual ECG episodes; SD = standard deviation, weighed average of SD's of individual ECG episodes; all measurements are in milliseconds.

Overall results of the comparisons on the 836 QRST complexes in which the computer generated a measurement are shown in table 5.13. "Hand" measurements from the first author were obtained in duplex and the two series A1 and A2 were compared to determine variability within one observer (intra observer variability). Inter observer variability was studied by comparing "hand" measurements of the first and second author: A1 versus B. Computer performance finally was studied by the comparison of series A1 and C. The lower panel of table 5.12 gives the mean differences between the same three comparison series as presented in table 5.13 but specified by electrocardiogram segment.

Discussion

The upper panel of table 5.12 shows that the percentage of QT measurements obtained in each of the electrocardiogram segments ranges from 15 to 100%. At the lower bound of this range electrocardiogram segment three is found which contained many PVC's in which no end of T measurements are done. In electrocardiogram segment five QT measurement was possible in all QRST complexes because of good signal quality and a low heart rate. Though electrocardiogram segment four has a good signal quality the end of the T wave was detected only in 23% of the QRST complexes. This was due to the low amplitude of the terminal negative part of the T wave which made it impossible to detect a sufficiently long flat segment within the measurement window.

Since no gold standard is available for the duration of the QT intervals in the database, comparisons have to be made with the use of the next best: measurements obtained from the most experienced electrocardiogram reader A. Comparison of the two measurement series A1 and A2 yielded a small systematic difference of 1.1 ms. Comparison of the first and second author (A1 versus B) showed a larger but still small difference: 12.3 ms; B tends to detect the end of the T wave earlier than A. A more detailed analysis of these differences (lower part of table 5.11) demonstrates that electrocardiogram segments five and six contribute most to the overall difference. In these segments B's tendency to early end of T detection is probably reinforced by the presence of the low amplitude of the terminal negative part of the T wave. The likeness of measurement series A1 and C (computer) was great; the mean difference of the series was 1.2 ms. This correspondence might be expected since human observer A was also the writer of the computer algorithm and thus A was the model referred to in the methods section.

The mean of the absolute values of the differences minus the mean difference, the dis-

persion (DISP), is a measure of variation of the differences. This variation originates from random deviations from the true value made by the observer.

DISP was consistently high in electrocardiogram segment one (table 5.12 lower part) as compared with the other segments. The source of dispersion is the noise of the signal in this segment. The pooled data for DISP as well as the data for the individual electrocardiogram segments show consistently higher values for the A1-B comparisons as for the A1-A2 comparisons. Since QT intervals were measured from the same electrocardiogram segments DISP differences most likely arise from differences between the two observers. These differences probably are due to differences in experience between the electrocardiogram readers with end of T determination.

The magnitude of the systematic differences of the computer measurements ranges from almost zero to 10.1 ms (electrocardiogram segment four). Computer QT interval measurements thus will deviate at most 10 ms from values obtained by electrocardiogram reader A, the most experienced of the two. As changes of QT interval duration are a major topic of study in the ongoing project it is however at least as important to have the disposal of an algorithm in which random deviation from the true QT durations are small. QT duration changes of less than 10 ms might not be detected with the reported algorithm since the dispersion of in the differences was 13 ms. It should however be brought to attention that QT interval measurements in the ARGUS-TX system are accurate with a resolution of 4 ms, the duration of one electrocardiogram sample. Four ms changes are thus the smallest variations that can be observed.

It is concluded that the reproducibility of QT measurements by computer is comparable or better than the reproducibility in measurements done by human interpreters. The magnitude of measurements deviations is 10-15 ms.

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6. Prediction of sudden death

INTRODUCTION

In this chapter risk functions are described for the prediction of sudden death in patients who had 24-hour electrocardiography for a variety of clinical conditions and questions. Their efficiency in identifying patients most likely to die suddenly within two years after 24-hour electrocardiography is evaluated. Risk functions are developed in a stepwise approach following the order in which clinical information becomes available. The first risk function is based on the disease history only. Subsequent risk functions include standard 12 lead electrocardiography, blood tests, data from routine rhythm analysis of 24-hour electrocardiograms, exercise test, echocardiography, computer-aided analysis of 24-hour electrocardiograms and contrast ventriculography. In addition, risk functions based on electrocardiographic variables only are developed.

METHODS

Patients and baseline characteristics

A total of 6693 patients who had 24-hour electrocardiography were studied. During a two-year follow-up period 245 cases of sudden death occurred. From all 6693 study patients 467 were randomly selected and served as reference patients. The following baseline data (i.e. at the time the 24-hour electrocardiogram was recorded) were collected: patient history, routinely available tests, data on standard twelve lead electrocardiograms, data pertaining to routine rhythm analysis of the 24-hour electrocardiograms, and parameters derived from computer-aided analysis of the original 24-hour electrocardiograms. A detailed description of the study design is provided in chapter 3.

Risk function

The objective of the analysis was to find the combination of baseline variables that most closely predicted the occurrence of sudden death within two years after 24-hour electrocardiography. The most efficient and rational method of evaluating the risk for sudden death is to synthesize in a quantitative way the major risk factors for sudden death into a composite score. This can be accomplished by the use of a logistic regression function that estimates the conditional probability of sudden death given a set of variables x_1, x_2,...,x_j measured at the time of 24-hour electrocardiography. The function has the form $P=[1+\exp-(a_0+b_1x_1+b_2x_2+...+b_jx_j)]^{-1}$ where P is the probability for sudden death given x_1, x_2,...,x_j and a_0, b_1, b_2,...,b_j are coefficients to be estimated from the data. Estimation is by the maximum likelihood method of Walker-Duncan.[1] Constant a_0 needs to be adjusted by a correction a_1 because a_0 is estimated from the data of a subset of all 6693 study patients.[2]

Besides absolute risk estimates in each model relative risk estimates or odds ratios are obtained directly from the regression coefficients b_1, b_2,...,b_j. If indicator variables are

used, which have a value of 1 if the property considered is present and 0 if it is not, coefficient b_n of variable x_n can be interpreted as the logarithm of the relative risk for sudden death of the presence of variable x_n (value=1) as compared to the absence of variable x_n (value=0). This relative risk is independent of the other variables which are considered in the model. As an example, if the regression coefficient for previous myocardial infarction is 0.72, its antilogarithm ($e^{0.72}$) is 2.1. This means that the risk for sudden death within two years for patients with previous myocardial infarction is 2.1 times as high as it is for patients who had no myocardial infarction. This increase of risk is independent of the other risk factors retained in the model. It should be noted that this interpretation is conditional upon the data coding strategy.

Variables selected from univariate analysis were sequentially entered into the model until no remaining candidate variable met a significance level of 0.10. For this purpose the SAS procedure LOGIST[3] was used. For consecutive models groups of variables were presented for inclusion. Correction a_1 is the natural logarithm of $(N_D/N_C)/(n_D/n_C)$ in which N_D is the number of cases of sudden death among all study patients, N_C is the number of non-cases among all study patients, n_D is the number cases in the model and n_C is the number of non-cases in the model. The absolute risk for an individual patient is obtained by calculation of the sum of the patients coefficients b_1, b_2,...,b_j, the constant a_0 and a correction a_1 and transforming it into the absolute risk as follows:
$P=1/[1+\exp-(a_0+b_1x_1+b_2x_2+...+b_jx_j)]$.

Risk function assessment

For each model risk estimates were calculated for each patient in order to check whether predicted risk was in agreement with observed risk. In order to do this patients were grouped into five subgroups according to estimated risk: low, medium low, medium, medium high, and high risk, each subgroup containing an approximately equal number of cases. For each subgroup the mean of the individual risk estimates was compared to the observed risk.[4] The information content of the models was compared by use of receiver-operator characteristic (ROC) curves.[5] In these curves sensitivity (true-positive rate) at different cutoffs points of risk predicted by the risk function is graphed as a function of 1-specificity (false-positive rate) for the corresponding cutoff points. The more a ROC curve is located in the upper left corner of the graph the higher the information content of the risk function is, i.e. the higher both sensitivity and specificity for the prediction of sudden death are.

RESULTS

Univariate analysis

Table 6.1 shows the occurrence of sudden death in relation to disease history at the time of 24-hour electrocardiography. Age ≥ 60 years, male sex, history of angina, myocardial infarction, congestive heart failure and a ventricular aneurysm clearly increased the risk for sudden death with relative risk estimates varying from 2.4 to 4.5. Patients complaining about palpitations had half the risk for sudden death as compared to those without these

Table 6.1: The occurrence of sudden death in relation to several clinical characteristics at the time of 24-hour electrocardiography.

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
Sex					
female	58	2795	2.1%	-	-
male	186	3812	4.9%	2.4	(1.7, 3.4)
Age					
<60	66	3282	2.0%	-	-
≥60	178	3325	5.4%	2.7	(2.0, 4.0)
History of angina					
no	104	4400	2.4%	-	-
yes	140	2207	6.3%	2.7	(2.0, 3.9)
History of myocardial infarction					
no	93	4515	2.1%	-	-
yes	151	2092	7.2%	3.5	(2.6, 5.0)
History of congestive heart failure					
no	143	5561	2.6%	-	-
yes	101	1046	9.7%	3.8	(2.8, 5.9)
History of ventricular aneurysm					
no	224	6478	3.5%	-	-
yes	20	129	15.5%	4.5	(1.9, 9.5)
History of arrhythmias					
no	64	2852	2.2%	-	-
SV only	37	1204	3.1%	1.4	(0.9, 2.3)
V ± SV	143	2551	5.6%	2.5	(1.8, 3.7)
History of atrio-ventricular conduction defects					
no	206	6062	3.4%	-	-
yes	38	545	7.0%	2.1	(1.3, 3.4)
History of palpitations					
no	162	3296	4.9%	-	-
yes	82	3311	2.5%	0.5	(0.4, 0.7)
History of dizziness					
no	138	3669	3.8%	-	-
yes	106	2938	3.6%	1.0	(0.7, 1.3)
History of syncope					
no	186	5446	3.4%	-	-
yes	58	1161	5.0%	1.5	(1.0, 2.2)
Functional class					
1	73	3669	2.0%	-	-
2	117	2078	5.6%	2.8	(2.1, 4.3)
>2	33	344	9.6%	4.8	(2.6, 8.4)
History of stroke					
no	203	5905	3.4%	-	-
yes	41	702	5.8%	1.7	(1.1, 2.7)
History of intermittent claudication					
no	214	6120	3.5%	-	-
yes	30	487	6.2%	1.8	(1.1, 3.3)

continued...

Table 6.1 ...continued

	SD	Est.Total[1]	%SD	RR[2]	95%CI[3]
History of diabetes mellitus					
no	204	6077	3.4%	-	-
yes	40	530	7.5%	2.2	(1.4, 3.8)
Family history of myocardial infarction or death before age of 60					
no	211	5632	3.7%	-	-
yes	33	975	3.4%	0.9	(0.6, 1.4)
Current cigarette smoking					
no	161	4328	3.7%	-	-
yes	83	2279	3.6%	1.0	(0.7, 1.4)
Current alcohol use >6 units/day					
no	226	6349	3.6%	-	-
yes	18	258	7.0%	2.0	(1.0, 3.7)
Current digitalis use					
no	123	5059	2.4%	-	-
yes	121	1548	7.8%	3.2	(2.4, 4.7)
Current beta blocker use					
no	174	4973	3.5%	-	-
yes	70	1634	4.3%	1.2	(0.9, 1.8)
Current nitrate use					
no	138	5059	2.7%	-	-
yes	106	1548	6.8%	2.5	(2.0, 4.0)
Current class 1 and 3 anti arrhythmic drug use					
no	187	5632	3.3%	-	-
yes	57	975	5.8%	1.8	(1.2, 2.7)
Current calcium antagonist use					
no	204	5632	3.6%	-	-
yes	40	975	4.1%	1.1	(0.8, 1.9)
Current diuretic use					
no	101	5073	2.0%	-	-
yes	143	1534	9.3%	4.7	(3.4, 6.8)
Current antihypertensive drug use					
no	197	6019	3.3%	-	-
yes	47	588	8.0%	2.4	(1.6, 4.1)
Current oral anticoagulant drug use					
no	143	4773	3.0%	-	-
yes	101	1834	5.5%	1.8	(1.3, 2.5)
Number of drugs currently used					
none	6	1362	0.4%	-	-
1 or 2	54	2623	2.1%	4.7	(2.0,11.5)
>2	184	2623	7.0%	15.9	(7.5,41.1)

SD, sudden death; Est.Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval; SV, supraventricular; V ± SV ventricular and/or supraventricular; n.a., not available.

[1] Estimated from the number of reference patients multiplied with the inverse of the sampling fraction, 6693/467;

[2] Calculated from the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;

[3] Calculated as the 95%-CI for the odds ratio.

complaints. Patients with a history of stroke, intermittent claudication or diabetes mellitus had an approximately two-fold risk for sudden death as compared to those without such a history. Family history and cigarette smoking had no risk implications with regard to sudden death. The more drugs a patient used the higher his risk for sudden death was. Also, if each group of drugs was considered separately, patients on that drug had a higher risk for sudden death than those not using that drug, except for those on beta blockers and calcium antagonists. This relation was most pronounced for digitalis and diuretics with relative risks of 3.2 and 4.7 respectively.

Of the common laboratory tests investigated only the blood tests shown in table 6.2 had a relation with sudden death; no such relation was found for high or low potassium levels. The strength of the relation of an increased cardiothoracic ratio and sudden death

Table 6.2: The occurrence of sudden death in relation to parameters derived from several tests.

	SD	Est.Total[1]	%SD	RR[2]	95%-CI3
Serum creatinine (μmol/l)					
<110 or n.a.	181	5761	3.1%	-	-
≥110	63	846	7.5%	2.4	(1.8, 4.0)
Serum bilirubin (μmol/l)					
<12 or n.a.	204	5890	3.5%	-	-
≥12	40	717	5.6%	1.6	(1.1, 2.7)
Serum albumin (g/l)					
≥40 or n.a.	206	6105	3.4%	-	-
<40	38	502	7.6%	2.2	(1.3, 3.5)
Hematocrit (%)					
<50 or n.a.	227	6335	3.6%	-	-
≥50	17	272	6.2%	1.7	(1.0, 4.0)
CT ratio chest X-ray (%)					
<50 or n.a.	173	5303	3.3%	-	-
≥50	71	1304	5.4%	1.7	(1.2, 2.5)
Left ventricular dilatation at echocardiography					
no or n.a.	135	5360	2.5%	-	-
yes	109	1247	8.7%	3.5	(2.6, 5.3)
Maximal load exercise test (% of age/sex adjusted norm)					
≥70	56	2594	2.2%	-	-
n.a.	143	3569	4.0%	1.9	(1.3, 2.7)
<70	45	444	10.1%	4.7	(2.9, 8.8)
Ejection fraction (%)					
≥40 or n.a.	196	6392	3.1%	-	-
<40	48	215	22.3%	7.3	(4.0,13.8)

SD, sudden death; Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval; n.a., not available.

[1] Estimated from the number of reference patients multiplied with the inverse of the sampling fraction, 6693/467;

[2] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;

[3] Calculated as the 95%-CI for the odds ratio.

Table 6.3: The occurrence of sudden death in relation to parameters derived from standard 12 lead electrocardiography.

	SD	Est.Total[1]	%SD	RR[2]	95%-CI3
Heart rate ≥90 bpm					
no	154	4672	3.3%	-	-
yes	87	1734	5.0%	1.5	(1.1, 2.2)
Q waves (Minnesota code 1)					
no	110	4414	2.5%	-	-
minor[4]	57	1118	5.1%	2.0	(1.4, 3.2)
major[4]	74	874	8.5%	3.4	(2.4, 5.5)
Left ventricular hypertrophy (Minnesota code 3.3)					
no	226	6148	3.7%	-	-
yes	15	258	5.8%	1.6	(0.9, 3.8)
ST depression (Minnesota code 4)					
no	122	4472	2.7%	-	-
minor[5]	41	889	4.6%	1.7	(1.1, 2.8)
major[5]	78	1046	7.5%	2.7	(2.1, 4.5)
Negative or flat T wave (Minnesota code 5)					
no	87	3741	2.3%	-	-
yes	154	2666	5.8%	2.5	(1.9, 3.7)
A-V conduction defect (Minnesota code 6.1-6.3)					
no	219	5991	3.7%	-	-
yes	22	416	5.3%	1.4	(0.8, 2.7)
Ventricular conduction defect (Minnesota code 7)					
no or 7.3[6]	186	5747	3.2%	-	-
7.2 or 7.7[6]	12	272	4.4%	1.4	(0.6, 2.9)
7.1, 4 or 8[6]	43	387	11.1%	3.4	(2.2, 6.3)
Premature atrial complex (Minnesota code 8.1.1)					
no	228	6148	3.7%	-	-
yes	13	258	5.0%	1.4	(0.7, 3.3)
Premature ventricular complex (Minnesota code 8.1.2 or 8.1.3)					
no	194	5747	3.4%	-	-
yes	47	659	7.1%	2.1	(1.4, 3.4)
Atrial fibrillation (Minnesota code 8.3.1)					
no	216	5962	3.6%	-	-
yes	25	444	5.6%	1.6	(0.9, 2.7)
ST elevation (Minnesota code 9.2)					
no	224	6292	3.6%	-	-
yes	17	115	14.8%	4.2	(1.9,11.1)
Left atrial overload (Minnesota code 9.3.2)					
no	162	5002	3.2%	-	-
yes	79	1405	5.6%	1.7	(1.2, 2.5)
Axis in horizontal plane (Minnesota code 9.4)					
right[7]	63	2336	2.7%	-	-
neutral	126	3096	4.1%	1.5	(1.0, 2.1)
left[7]	52	975	5.3%	2.0	(1.2, 3.0)
Cardiac infarction injury score[8]					
<10	42	3210	1.3%	-	-
10-30	112	2150	5.2%	4.0	(2.8, 6.4)
≥30	87	1046	8.3%	6.4	(4.4,11.0)

continued...

Table 6.3 ...continued

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
QTc leads I, II, III (ms)					
<440	111	4357	2.5%	-	-
≥440	65	1233	5.3%	2.1	(1.4, 3.1)
n.a.	65	817	8.0%	3.1	(2.1, 4.9)

SD, sudden death; Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval; bpm, beats per minute; A-V, atrio-ventricular.

[1] Estimated from the number of reference patients multiplied with the inverse of the sampling fraction, 6693/467;

[2] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;

[3] Calculated as the 95%-CI for the odds ratio.

[4] major, Minnesota code 1.1; minor, Minnesota code 1.2 and 1.3.

[5] major, Minnesota code 4.1 and 4.2; minor, Minnesota code 4.3 and 4.4.

[6] 7.1, left bundle branch block; 7.2, right bundle branch block; 7.3, incomplete right bundle branch block; 7.4, intraventricular block; 7.7, left anterior fascicular block; 7.8, 7.2 and 7.7.

[7] right, Minnesota code 9.4.1, QRS transition zone at or right of V3; left, Minnesota code 9.4.2, QRS transition zone at or left of V4.

[8] See reference 8 by Rautaharju et al.

was limited. Parameters of poor left ventricular function as expressed by left ventricular dilatation at echocardiography (end diastolic diameter ≥55 mm[6]), a low maximum work load at bicycle exercise testing or an ejection fraction <40% had clear risk implications with regard to sudden death.

Table 6.3 shows the relation of parameters derived from standard 12 lead electrocardiography with sudden death in the 667 patients in whom a standard 12 lead electrocardiogram was available. Virtually all classification items of the Minnesota code,[7] except code 2, were related to sudden death. Patients with a normal Cardiac Infarction Injury Score (CIIS),[8] i.e. <10, had a low risk for sudden death (1.3%), while patients with scores between 10 and 30 had a four-fold and those with a score >30 had a six-fold risk for sudden death.

Table 6.4 shows the occurrence of sudden death in relation to the parameters derived from routine rhythm analysis of the 24-hour electrocardiograms. 17% of all patients had no premature ventricular complexes, ventricular doublets or ventricular tachycardia and they were at low risk for sudden death (1.0%). Those with premature ventricular complexes or ventricular doublets had a three times higher risk and those with ventricular tachycardia had a more than ten-fold risk. Patients with frequent premature atrial complexes, i.e. occurring during 30% - 90% of the recording time, and those with atrial fibrillation had a two times higher risk for sudden death as compared to those without these supraventricular arrhythmias. Patients with sinus arrhythmia, sinus bradycardia (<50 bpm), or sinus tachycardia (>150 bpm, detected in episodes in which heart rate gradually increased and decreased, and P waves could be detected) had lower risks for sudden death than those without.

Table 6.4: The occurrence of sudden death in relation to parameters derived from routine rhythm analysis of 24-hour electrocardiograms.

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
Ventricular arrhythmias					
No PVC/D/VT	12	1161	1.0%	-	-
PVC ± D	153	4859	3.1%	3.0	(1.7, 5.9)
VT ± PVC/D	80	674	11.9%	11.5	(6.5,27.3)
Ventricular bigeminy					
no	159	5432	2.9%	-	-
yes	86	1261	6.8%	2.3	(1.8, 3.7)
Ventricular fusion complex					
no	231	6378	3.6%	-	-
yes	14	315	4.4%	1.2	(0.6, 2.6)
Accelerated ventricular rhythm (40-100 bpm)					
no	223	6492	3.4%	-	-
yes	22	201	11.0%	3.2	(2.0, 9.2)
Ventricular escape complex or rhythm (<40 bpm)					
no	233	6607	3.5%	-	-
yes	12	86	14.0%	4.0	(1.4,10.2)
Frequent premature atrial complexes (>30%)					
no	205	6220	3.3%	-	-
yes	40	473	8.5%	2.6	(1.7, 4.7)
Blocked premature atrial complex					
no	217	6062	3.6%	-	-
yes	28	631	4.4%	1.2	(0.8, 2.2)
Supraventricular tachycardia (>100 bpm)					
no	153	4959	3.1%	-	-
yes	92	1734	5.3%	1.7	(1.3, 2.5)
Accelerated atrial rhythm (50-100 bpm)					
no	213	5862	3.6%	-	-
yes	32	831	3.8%	1.1	(0.7, 1.8)
Paroxysmal atrial tachycardia with block					
no	227	6349	3.6%	-	-
yes	18	344	5.2%	1.5	(0.8, 2.9)
Atrial escape complex or rhythm (<50 bpm)					
no	238	6435	3.7%	-	-
yes	7	258	2.7%	0.7	(0.3, 1.9)
Atrial fibrillation					
no	213	6263	3.4%	-	-
yes	32	430	7.4%	2.2	(1.3, 3.7)
Atrial flutter (>250 bpm)					
no	240	6564	3.7%	-	-
yes	5	129	3.9%	1.1	(0.4, 3.5)
Premature junction complex					
no	236	6521	3.6%	-	-
yes	9	172	5.2%	1.4	(0.6, 3.7)
Accelerated junction rhythm or junction tachycardia[4]					
no	236	6392	3.7%	-	-
yes	9	301	3.0%	0.8	(0.4, 1.8)

continued...

Table 6.4 ...continued

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
Junction escape complex or rhythm[4]					
no	226	6363	3.6%	-	-
yes	19	330	5.8%	1.6	(0.9, 3.1)
Sinus arrhythmia					
no	193	4185	4.6%	-	-
yes	52	2508	2.1%	0.4	(0.3, 0.6)
Sinus bradycardia (<50 bpm)					
no	203	4945	4.1%	-	-
yes	42	1748	2.4%	0.6	(0.4, 0.9)
Sinus tachycardia (>150 bpm)					
no	241	6048	4.0%	-	-
yes	4	645	0.6%	0.2	(0.1, 0.4)
Sinus arrest					
no	237	6292	3.8%	-	-
yes	8	401	2.0%	0.5	(0.2, 1.1)
Sino-auricular block					
no	244	6607	3.7%	-	-
yes	1	86	1.2%	0.3	(0.0, 2.5)
Atrio-ventricular block, first degree					
no	224	6306	3.6%	-	-
yes	21	387	5.4%	1.5	(0.8, 2.6)
Atrio-ventricular block, second or third degree					
no	241	6650	3.6%	-	-
yes	4	43	9.3%	2.6	(0.5,11.0)
Ventricular arrest					
no	228	6335	3.6%	-	-
yes	17	358	4.7%	1.3	(0.7, 2.5)

SD, sudden death; Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval; PVC, premature ventricular complex; D, ventricular doublet; VT, ventricular tachycardia.

[1] Estimated from the number of reference patients multiplied with the inverse of the sampling fraction, 6693/467;

[2] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference;

[3] Calculated as the 95%-CI for the odds ratio.

[4] Frequency limits as for the atrial rhythms.

Table 6.5 shows the occurrence of sudden death in relation to QTc interval parameters derived from computer-aided analysis of 24-hour electrocardiograms in patients without intraventricular conduction defects. This table is an extended version of table 5.3 which was based on patients without intraventricular conduction defects and without evidence of cardiac dysfunction. The univariate relation between RR interval parameters derived from the computer-aided analysis and sudden death was presented in table 5.8. Patients with high ventricular ectopy rates (≥30/hr) had a four times higher risk for sudden death as compared to those with rates below 1/hr (table 6.5).

Table 6.5: The occurrence of sudden death in relation to QTc parameters[1] and ventricular ectopy at 24-hour electrocardiography (computer-aided analysis data).

	SD	Est.Total[1]	%SD	RR[2]	95%-CI[3]
Mean QTc (ms)					
<400	55	1376	4.0%	1.6	(1.0, 2.7)
400-440	75	3022	2.5%	-	-
≥440	47	1130	4.2%	1.7	(1.0, 2.9)
Maximum QTc (ms)					
<440	41	786	5.2%	2.3	(1.4, 4.2)
440-480	77	3464	2.2%	-	-
≥480	67	1523	4.4%	2.0	(1.3, 3.2)
Minimum QTc (ms)					
<370	76	2211	3.4%	1.3	(0.8, 2.0)
370-400	66	2481	2.7%	-	-
≥400	43	1081	4.0%	1.5	(0.9, 2.6)
Percentage QTc >440 ms					
<10	50	1572	3.2%	0.9	(0.6, 1.6)
10-30	66	1965	3.4%	-	-
≥30	61	1990	3.1%	0.9	(0.6, 1.5)
Short-term variation QTc (ms)					
<20	82	2997	2.7%	1.1	(0.6, 1.9)
20-25	31	1253	2.5%	-	-
≥25	64	1277	5.0%	2.0	(1.2, 3.9)
Long-term variation QTc (ms)					
<10	43	1105	3.9%	1.7	(1.1, 3.0)
10-15	68	3022	2.3%	-	-
≥15	72	1646	4.4%	1.9	(1.3, 3.3)
Ventricular ectopy rate (beat/hr)					
<1	45	2653	1.7%	-	-
1-30	86	2260	3.8%	2.2	(1.5, 3.7)
≥30	109	1670	6.5%	3.8	(2.8, 7.1)

SD, sudden death; Total, estimated total number of patients; %SD, two year sudden death rate; RR, relative risk; CI, confidence interval.

[1] In patients without intraventricular conduction defects.

[2] Estimated from the number of reference patients multiplied with the inverse of the sampling fraction, 6693/268 and corrected by 241/245 because of the exclusion of four cases.

[3] Calculated as the ratio of sudden death rates in which the rate of the category indicated by a missing RR was taken as reference.

[4] Calculated as the 95%-CI for the odds ratio.

Multivariate risk functions

Table 6.6 summarizes eight logistic regression models based on the stepwise approach following the order in which clinical information becomes available. Model 1 was developed with the use of history only; in model 2 data from standard 12 lead electrocardiography were added. Common laboratory tests and the cardiothoracic ratio did not reach the significance level for inclusion when added to model 2. In the models 3 and 4 data from 24-hour electrocardiography were entered, in model 3 only those obtained by routine rhythm analysis, in model 4 also those derived from computer-aided analysis. In model 5 exercise test and echocardiography were added to model 3, the model was extended with contrast ventriculography in model 6, and once more with the parameters derived from computer-aided analysis of 24-hour electrocardiograms in model 8. Model 7 was based on model 4 plus the data from the computer-aided analysis.

Model 1 was based on 684 patients. The models in which data on standard 12 lead electrocardiography were entered were based on a maximum of 667 patients because standard 12 lead electrocardiograms were not available in 17 patients. Models 4, 7 and 8, including parameters derived from the computer-aided analysis of 24-hour electrocardiograms, were based on 480 patients because not all 24-hour electrocardiograms had been subjected to computer-aided analysis (see chapter 5). For each of the models 1-8 predicted and observed risks for sudden death are shown in table 6.7 as well as the limits of the risk categories and the number of patients in each of the categories. ROC curves based on models 1-8 are shown in figure 6.1.

Table 6.8 summarizes four logistic models based on electrocardiographic data only. Model 9 is based on standard 12 lead electrocardiography only, model 10 on routine rhythm analysis of 24-hour electrocardiograms only, model 11 on all parameters derived from 24-hour electrocardiography and model 12 is based on the combination of all electrocardiographic data. Table 6.9 shows predicted and observed risks for sudden death for models 9-12. In figure 6.2 ROC curves for the electrocardiographic models are shown.

DISCUSSION

Stepwise approach

The risk functions were developed according to a stepwise approach in which we followed clinical decision making in practice. Disease history and a standard 12 lead electrocardiogram always are at disposal of the cardiologist and therefore were used for the basic models 1 and 2. Since our study population was defined by 24-hour electrocardiography we judged that the order of the next steps had to be 24-hour electrocardiography, bicycle exercise testing and echocardiography rather than ending with 24-hour electrocardiography (models 3, 4 and 5). This latter strategy applies, for example, to patients referred for ischemic heart disease. In the last step information from contrast ventriculography was entered (models 6 and 8). The new information derived from the computer-aided analysis of the 24-hour electrocardiograms was entered at two different places in the stepwise process. This enabled us to compare early and late availability of these data (models 4 and 7).

Table 6.6 Indicator variates (with coefficients and standard errors) retained in the logistic regression models to predict the occurrence of sudden death on the basis of history, 12 lead electrocardiography, routine rhythm and study analysis of 24 hour electrocardiography, exercise test, echocardiography, and ventriculography.

Indicator	M1 (N=684) Coeff.	SE	M2 (N=667) Coeff.	SE	M3 (N=667) Coeff.	SE	M4 (N=480) Coeff.	SE	M5 (N=667) Coeff.	SE	M6 (N=667) Coeff.	SE	M7 (N=480) Coeff.	SE	M8 (N=480) Coeff.	SE
History																
Age ≥60 years	0.75	0.21	0.54	0.21	0.35	0.22	0.31	0.26	0.41	0.23	0.55	0.23	0.52	0.26	0.63	0.27
Male gender	0.78	0.22	0.85	0.22	0.86	0.23	0.77	0.27	0.92	0.24	0.81	0.24	0.83	0.27	0.77	0.27
Myocardial infarction	0.74	0.20	0.55	0.21	0.63	0.22	0.73	0.26	0.59	0.24	0.56	0.23	0.58	0.27	0.45	0.27
Congestive heart failure	0.70	0.23	0.57	0.24	0.49	0.24	0.65	0.30	--	--	--	--	--	--	--	--
Palpitations	-0.47	0.20	-0.44	0.20	-0.59	0.21	-0.63	0.25	-0.64	0.22	-0.69	0.22	-0.61	0.25	-0.62	0.25
Syncope	0.65	0.23	0.67	0.24	0.70	0.25	0.93	0.30	0.74	0.26	0.72	0.26	0.83	0.30	0.82	0.30
Stroke	0.48	0.27	0.52	0.29	--	--	--	--	--	--	--	--	--	--	--	--
Alcohol use > 6 units/day	0.69	0.41	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Current drug use																
Diuretics	1.03	0.21	0.82	0.22	0.78	0.22	0.75	0.27	0.67	0.22	0.66	0.22	0.79	0.26	0.76	0.26
Nitrates	0.50	0.21	0.48	0.21	0.48	0.22	0.52	0.26	0.43	0.23	0.48	0.23	--	--	--	--
Anti hypertensive drugs	0.49	0.28	--	--	--	--	--	--	--	--	--	--	--	--	--	--
12 lead electrocardiography																
Major IVCD[1]			1.17	0.37	1.22	0.36	1.14	0.41	1.12	0.36	0.82	0.34	0.96	0.42	0.91	0.42
Flat or negative T wave[2]			0.67	0.26	0.47	0.27	--	--	0.50	0.27	--	--	0.75	0.28	0.69	0.28
ST depression ≥0.05mV[3]			0.51	0.26	0.51	0.26	0.68	0.29	0.44	0.27	0.67	0.24	--	--	--	--
QTc ≥440ms or n.a.[4]			0.42	0.22	--	--	--	--	--	--	--	--	--	--	--	--
24 hour electrocardiography, routine rhythm analysis																
Ventricular tachycardia					0.87	0.26	0.80	0.31	0.99	0.26	0.96	0.27	1.01	0.31	0.96	0.32
Frequent PAC (>30%)					1.23	0.32	1.28	0.38	1.24	0.33	1.29	0.33	1.14	0.38	1.13	0.38
Sinus tachycardia (>150 bpm)					-1.03	0.62	-1.26	0.69	-1.08	0.65	-1.26	0.69	--	--	--	--
Atrial fibrillation					0.61	0.34	--	--	0.57	0.34	0.58	0.34	--	--	--	--
Supraventricular rhythms[5]							0.94	0.35					--	--	--	--
Exercise test																
Max load <70% norm or n.a.									0.85	0.24	0.83	0.24	1.15	0.27	1.12	0.28
Echocardiography																
Dilatation of left ventricle (EDD ≥50mm)									0.95	0.24	0.86	0.24	1.19	0.28	1.14	0.28
24 hour electrocardiography, study analysis																
Maximum heart rate <100 bpm							1.02	0.31					0.70	0.28	0.70	0.28
Minimum heart rate ≥65bpm							0.95	0.33					--	--	--	--
Long-term variation $\overline{QTc}$ <10 or ≥15ms							0.49	0.25					--	--	--	--
Maximum QTc <440 or ≥480ms							0.47	0.25					0.52	0.25	0.52	0.25
Ventriculography																
Ejection fraction <40%											1.15	0.38			1.05	0.46
Constant[6]	-5.49		-5.90		-5.72		-6.48		-6.45		-6.25		-7.06		-7.02	

M1, history only; M2, M1 + 12 lead electrocardiography; M3, M2 + routine rhythm analysis of 24 hour electrocardiography; M4, M3 + study analysis of 24 hour electrocardiography; M5, M3 + exercise test and echocardiography; M6, M5 + ventriculography; M7, M5 + study analysis 24 hour electrocardiography; M8, M7 + ventriculography; M, model; Coeff, coefficient; SE, standard error; IVCD, intraventricular conduction defect; n.a., not available; --, variable did not meet significance level for entry; EDD, end diastolic diameter.

[1]left bundle branch block or intraventricular block or right bundle branch block with left anterior fascicular block (Minnesota codes 7.1, 7.4 and 7.8); [2]Minnesota code 5; [3]Minnesota code 4.1 or 4.2; [4]not assessable mainly due to intraventricular block; [5]only entered into models with study analysis parameters, see chapter 5: exclusion in RR interval analysis; [6]corrected to enable the calculation of absolute risks, see methods.

Table 6.7 Risk for sudden death within two years after 24 hour electrocardiography predicted by logistic models 1-8 and observed risk.

	M1 (N=684)		M2 (N=667)		M3 (N=667)		M4 (N=480)		M5 (N=667)		M6 (N=667)		M7 (N=480)		M8 (N=480)	
Risk score	u.l.	nr.	u.l.	nr.	u.l.	nr.	u.l.	nr.	u.l.	nr.	u.l.	nr.	u.l.	nr.	u.l.	nr.
Low risk	2.5	317	3.0	331	3.0	336	3.0	223	3.3	359	3.0	363	3.3	219	3.4	228
Medium low risk	5.9	145	5.6	113	7.2	134	7.1	84	7.0	111	7.3	112	7.8	91	7.6	82
Medium risk	9.9	88	11.1	97	11.9	77	13.5	63	12.6	82	13.0	75	13.6	65	14.2	62
Medium high risk	18.0	76	18.5	62	22.0	61	24.3	57	25.1	61	29.0	62	23.1	55	27.0	59
High risk		58		64		59		53		54		55		50		49
Risk score	pred.	obs.	pred.	obs.	pred.	obs.	pred.	obs.	pred.	obs.	pred.	obs.	pred.	obs.	pred.	obs.
Low risk	1.1	1.2	1.1	1.2	1.0	1.2	1.2	1.1	1.1	1.1	1.1	1.0	1.1	1.1	1.2	1.0
Medium low risk	3.8	3.4	4.2	4.4	4.7	3.6	4.8	4.9	5.2	4.8	5.0	4.8	5.0	4.1	5.2	5.1
Medium risk	7.6	7.3	7.9	6.3	9.2	10.5	9.7	10.9	9.7	9.3	9.9	11.6	10.5	9.3	10.6	10.9
Medium high risk	13.7	12.5	14.7	22.8	15.6	19.7	18.3	14.0	18.0	22.3	19.0	18.6	18.7	21.7	19.1	14.0
High risk	26.0	31.1	26.8	20.1	35.4	28.5	42.0	27.9	42.8	38.0	47.9	42.7	43.5	39.1	47.9	65.1

All risks are expressed as percentages.
u.l., upper limit of risk of a risk category; nr., number of patients in a risk category; pred., mean of predicted risks for the patients within a risk category; obs., observed risk for the patients within a risk category.

Table 6.8 Indicator variates (with coefficients and standard errors) retained in the logistic regression models to predict the occurrence of sudden death on the basis of 12 lead electrocardiography and 24 hour electrocardiography.

Indicator	M9 (N=667) Coeff.	SE	M10 (N=691) Coeff.	SE	M11 (N=488) Coeff.	SE	M12 (N=480) Coeff.	SE
12 lead electrocardiography								
Cardiac Infarction Injury Score >10	0.89	0.23					1.14	0.25
Major Q waves[1]	0.56	0.22					0.60	0.29
Major IVCD[2]	1.34	0.35					--	--
Flat or negative T wave[3]	0.72	0.25					--	--
ST depression $\geq$0.05mV[4]	0.65	0.24					0.80	0.27
QTc $\geq$440ms or n.a.[5]	0.49	0.20					0.78	0.23
Premature ventricular complex	0.44	0.26					--	--
24 hour electrocardiography, routine rhythm analysis								
Ventricular tachycardia			1.41	0.23	1.01	0.29	1.01	0.29
Frequent PAC (>30%)			0.82	0.29	1.06	0.35	1.09	0.36
Sinus tachycardia (>150 bpm)			-1.50	0.55	-1.19	0.64	-1.14	0.67
PVC and/or ventricular doublet			1.00	0.33	--	--	--	--
Sinus arrhythmia			-0.45	0.20	--	--	--	--
Supraventricular tachycardia			0.41	0.20	--	--	--	--
Atrial fibrillation			0.59	0.30	0.90	0.50	--	--
Supraventricular rhythms[6]					1.23	0.52	1.03	0.38
24 hour electrocardiography, study analysis								
Ventricular ectopic complex rate >1/hr					0.75	0.25	--	--
Long-term variation RR interval <12 ms					0.80	0.30	0.65	0.32
Minimum heart rate $\geq$65bpm					0.97	0.29	0.93	0.30
Maximum heart rate $\leq$100 bpm					0.86	0.30	0.73	0.31
Short-term variation RR interval <40 ms					0.65	0.32	--	--
Maximum QTc <440 or $\geq$480ms					0.73	0.23	0.45	0.23
QTc measurements not available[5]					1.20	0.34	--	--
Long-term variation QTc <10 or $\geq$15ms					0.54	0.23	--	--
Constant[7]	-4.96		-4.51		-6.42		-6.06	

M9, 12 lead electrocardiography only; M10, routine rhythm analysis of 24 hour electrocardiography only; M11, M10 + study analysis of 24 hour electrocardiography; M12, M11 + 12 lead electrocardiography; M, model; Coeff, coefficient; SE, standard error; n.a., not available; PAC, premature atrial complex; PVC, premature ventricular complex; --, variable did not meet significance level for entry.

[1]Minnesota code 1.1; [2]left bundle branch block or intraventricular block or right bundle branch block with left anterior fascicular block (Minnesota codes 7.1, 7.4 and 7.8); [3]Minnesota code 5; [4]Minnesota code 4.1 or 4.2; [5]not assessable mainly due to intraventricular block; [6]only entered into models with study analysis parameters, see chapter 5: exclusion in RR interval analysis; [7]corrected to enable the calculation of absolute risks, see methods.

Table 6.9 Risk for sudden death within two years after 24 hour electrocardiography predicted by logistic models 9-12 and observed risk.

	M9 (N=667)		M10 (N=691)		M11 (N=488)		M12 (N=480)	
Risk score	u.l.	nr.	u.l.	nr.	u.l.	nr.	u.l.	nr.
Low risk	2.8	299	2.8	245	3.0	210	3.1	210
Medium low risk	5.5	126	3.7	173	5.0	81	5.9	77
Medium risk	9.0	86	6.0	112	8.8	73	10.5	77
Medium high risk	9.7	62	10.9	63	15.0	66	17.7	60
High risk		94		98		58		56
Risk score	pred.	obs.	pred.	obs.	pred.	obs.	pred.	obs.
Low risk	1.3	1.3	1.5	1.4	1.4	1.2	1.2	1.1
Medium low risk	4.2	4.3	2.9	3.2	4.0	4.9	4.4	4.8
Medium risk	6.6	7.0	4.6	4.6	6.4	7.1	7.6	8.0
Medium high risk	9.5	15.0	8.3	5.9	11.4	9.1	13.3	11.5
High risk	13.3	8.7	15.3	15.5	24.3	16.6	30.5	15.0

All risks are expressed as percentages.
u.l., upper limit of risk of a risk category; nr., number of patients in a risk category; pred., mean of predicted risks for the patients within a risk category; obs., observed risk for the patients within a risk category.

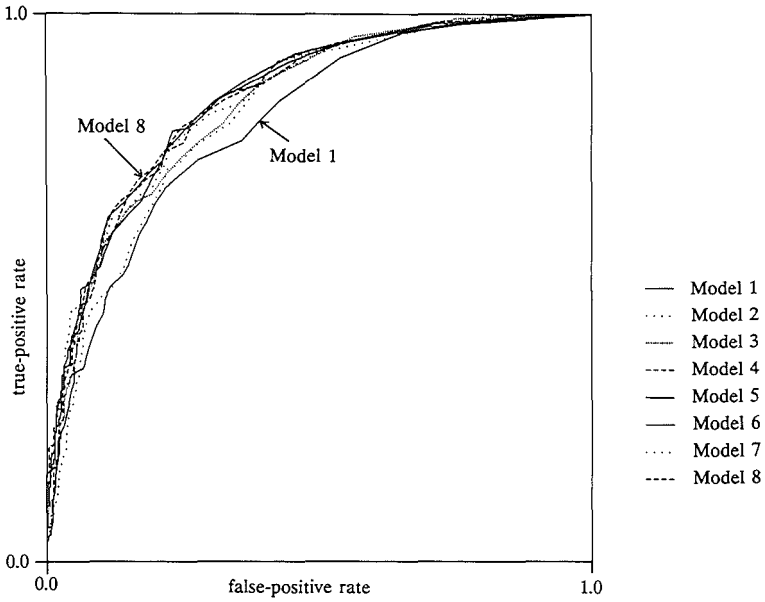

Figure 6.1: Receiver-operator characteristic curves for predicition models 1-8.

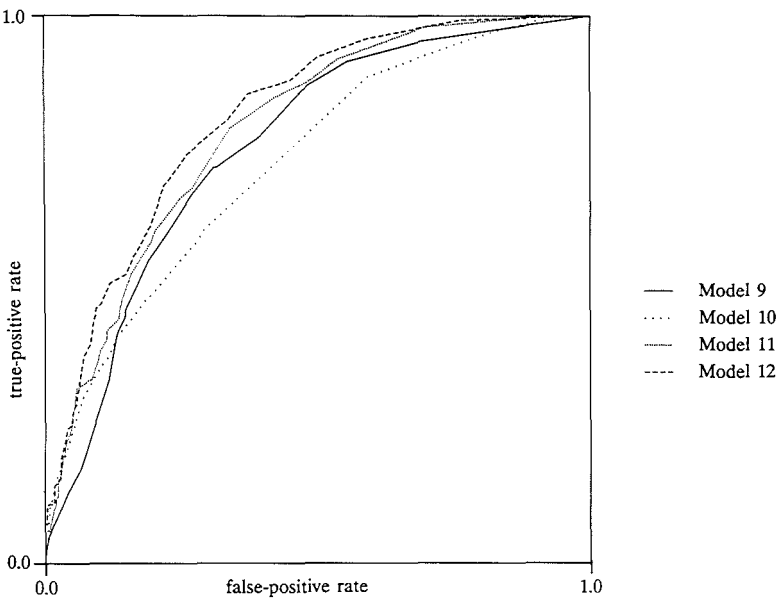

Figure 6.2: Receiver-operator characteristic curves for prediction models 9-12.

Prediction model based on history only

In model 1 age ≥60 years and male sex each independently doubled the risk for sudden death within two years after 24-hour electrocardiography by a factor two. These data correspond well with those from the Framingham study which showed in univariate analysis that males had approximately a 2.5 higher risk for sudden death than females, irrespective of the presence of coronary heart disease (see table 2.1).[9] Risk in both sexes increased with age (table 2.1). These relations may be explained by a higher prevalence of atherosclerotic heart disease in males and older persons. The known risk factors for cardiovascular disease cigarette smoking, hypertension, hypercholesterolemia, diabetes mellitus and family history did not enter the model. The presence of overt heart disease in a large part of the study population probably prevailed over these risk factors. A history of myocardial infarction, stroke and nitrate use all were included in model 1 and may be interpreted as indicators of advanced atherosclerotic heart disease. Use of diuretics had the strongest independent relation with sudden death in this model (relative risk 2.8). The use of diuretics and the presence of a history of congestive heart failure were both retained in the model, which may be due to the application of diuretics as antihypertensive drugs, but it also may be attributed to potassium depleting effects of the thiazide diuretics which may predispose to lethal arrhythmias.[10] No firm conclusions on the effects of class 1 and 3 anti arrhythmic drugs on the occurrence of sudden death can be drawn from the data in this study because only 15% of the study population were using these drugs. It may be speculated that this low percentage is a reflection of changing patterns of prescribing these drugs. Although in univariate analysis the use of these drugs was associated with the occurrence of sudden death, no such relation was observed after adjustment for clinical variables in model 1. It should be stressed here that our study does not provide a valid basis to draw conclusions on the relation between drug use and sudden death because of the preference of the treating physician to prescribe drugs to patients with a high risk for sudden death ("confounding by indication").

A history of palpitations had a negative relation with sudden death, an observation similar to that reported by Velema.[11] A pathophysiologic explanation of this finding may be as follows. After a ventricular extrasystole the filling phase of the left ventricle is prolonged, hence more blood is contained in the ventricle at the end of diastole than usual, while arterial pressure has dropped more than usual. During next systole in a healthy heart all extra blood is removed at once resulting in a high pulse pressure. This sudden increase of blood pressure, which can be followed by a change in heart rate induced by the baroreceptor reflex, may cause the sensation of a palpitation. Patients with cardiac dysfunction are not able to generate such a high pulse pressure and accordingly have no palpitations. Thus, patients complaining about palpitations may be reassured as to their prognosis with regard to sudden death. A history of syncope, however, must be taken seriously; patients with such a history have an approximately double risk for sudden death, independent from other variables taken into account. Thus, this variable was retained in all models. A possible explanation may be that syncope was caused by a nonlethal arrhythmia. Dizziness had no relation with sudden death, it probably represents a too nonspecific characteristic to be of any predictive value.

Prediction models based on history and electrocardiographic data

Model 2 showed that left bundle branch block, right bundle branch block combined with a left anterior fascicular block, and intraventricular block (QRS duration ≥120 ms) had a strong independent relation with sudden death (relative risk 3.2). These findings are in accordance with findings from other studies. These conduction defects are considered a manifestation of more advanced atherosclerotic heart disease.[12,13] Taking into account all other factors in the model QTc prolongation ≥440 ms had only limited independent value as a predictor for sudden death; its relative risk was 1.5.

When ventricular tachycardia was entered into model 3 it showed a strong independent relation with sudden death. This relation has been reported frequently in post myocardial infarction patients[14-19] and also in another study on patients who had 24-hour electrocardiography.[11,20] Ventricular tachycardia may be viewed as an indicator of a heart which is in a high risk state, both because of impaired myocardium (substrate) or the presence of modulating factors (see figure 2.1). Frequent premature atrial complexes showed to be an even stronger independent predictor of sudden death. To the best of our knowledge this finding has never been reported before. A direct relation between premature atrial complexes and the occurrence of sudden death is difficult to explain. It is known, however, that an increased diastolic pressure as a result of ischemic heart disease may cause supraventricular ectopic activity and atrial fibrillation. Our data do not support this hypothesis since frequent premature atrial complexes had predictive value independent of parameters of left ventricular dysfunction. Patients with sinus tachycardia (>150 bpm) have lower risks for sudden death than those without; probably it concerns patients with a good physical condition without overt heart disease, who are able to do heavy exercise, and do! When model 3 was extended with parameters from computer-aided analysis of 24-hour electrocardiograms four new parameters entered: maximum heart rate <100 bpm, minimum heart rate ≥65 bpm, long-term variation of QTc <10 or ≥15 ms and maximum QTc <440 or ≥480 ms.

Extended prediction models

When model 3 was expanded with variables from exercise testing and echocardiography both a low maximum exercise load and left ventricular dilatation at echocardiography were retained in the model. These variables superseded the importance of a history of congestive heart failure; both variables indicate impairment of cardiac function. Upon entry of left ventricular ejection fraction into model 5 in model 6 maximum exercise load and left ventricular dilatation at echocardiography retained in the model. This may indicate that they all carry some independent prognostic information. If model 5 was extended with the computer-aided analysis parameters instead of ejection fraction (model 7) several variables dropped from the model because they just failed to reach statistical significance (p=0.104-0.189): nitrates, ST depression, sinus tachycardia (>150 bpm), atrial fibrillation, minimum heart rate <100 bpm and extreme long-term QTc variation. However, this is largely due to the fact that model 7 was based on less patients than model 5 (480 versus 667 patients). In final model 8 all information available was used. No major changes of the coefficients of the variables already present were observed.

Prediction models based on electrocardiographic information only

To obtain a better insight in the contribution of each of the electrocardiographic techniques used, risk functions based solely on these data were developed. Model 9 is based on the standard 12 lead electrocardiogram only and contained all variables already retained in model 2 (history and standard 12 lead electrocardiogram) plus major Q waves (Minnesota code 1.1) and a CIIS score >10. These latter two variables replaced history of myocardial infarction in model 2. In model 10 (routine rhythm analysis of 24-hour electrocardiograms only) the same variables included in model 3 were present supplemented with premature ventricular complexes with or without ventricular doublets, sinus arrhythmia and supraventricular tachycardia. When computer-aided analysis parameters were added (model 11) eight new parameters entered the model. Some information in this model actually was derived from the standard 12 lead electrocardiogram: the variable "QTc measurements not available" which should be interpreted as the presence of intraventricular block based on standard 12 lead electrocardiography was used to suppress QTc measurements in these patients.

When all electrocardiographic information was taken together each of the electrocardiographic techniques contributed to the prediction of sudden death. This is also illustrated by the ROC curves shown in figure 6.2: the models containing information from one electrocardiographic procedure only (models 9-11) contain less predictive information than model 12 which combines all electrocardiographic information available. This may be no surprise since the different techniques harvest different types of information. In fact, information on the three main component causes of sudden death, i.e. substrate, modulators and trigger is derived (see chapter 2). Standard twelve lead electrocardiography contains information on the *substrate* (Q waves, intraventricular conduction defects, ST segment and T wave abnormalities) as well as on the *modulator* autonomous nervous system (ST segment, T wave and QT interval). Routine rhythm analysis of 24-hour electrocardiograms supplies information on supraventricular and ventricular arrhythmias (*trigger*), atrio-ventricular conduction defects and impulse formation disturbances, while from the computer-aided analysis information on the autonomic nervous system (*modulator*) comes forward.

Information content of the risk functions and assessment of fit

In this chapter risk functions for the prediction of sudden death within two years after routine 24-hour electrocardiography for various clinical questions were developed. First, risk functions were constructed based on routine available clinical parameter. In subsequent models variables from more advanced (and more expensive!) tests were added. The increasing information content of the models was evaluated by use of the ROC curves shown in figure 6.1. Going from model 1 to 3 the information content of the models clearly increased, more extended models (4-8), however, hardly showed a higher information content than model 3 which was based on history, standard 12 lead electrocardiogram and routine rhythm analysis of 24-hour electrocardiograms. Thus, with relatively simple clinical parameters sudden death is predicted as well as when information of more advanced tests is added.

The models we developed showed in general a good correspondence between pre-

dicted and observed risk for sudden death (table 6.7). However, it should be noted that this good correspondence partly can be attributed to the fact that the assessment of fit was studied in the same patients on which the models were developed. With model 8 the 13% of the all study patients could be identified in which 60% of all sudden death occurred; for model 1 these numbers were 18% and 60% respectively. However, model 3 also showed a good performance: it identified the 14% of all study patients in which 60% of all sudden death occurred. With model 3 and more extended models one can predict sudden death over an approximately 40-fold range from the lowest to highest quintile of risk.

Applicability of the risk functions

All functions were derived from the data of patients who entered the study because they had 24-hour electrocardiography for a variety of reasons. Thus, models not containing data from this electrocardiographic procedure actually are at fault in so far that they suggest to be generally applicable. These models only can be interpreted conditional on the fact that 24-hour electrocardiography was performed, i.e. the model on history only (model 1) only is valid in patients who had an indication for 24-hour electrocardiography. Since this information is already available it is reasonable to consider model 3 (history, standard 12 lead electrocardiogram and routine analysis of 24-hour electrocardiogram) as the basic model. Thus, it is fair to conclude that only limited additional information is gained with regard to the prediction of sudden if more tests are added to the model. This may have cost-benefit implications for risk stratification after acute myocardial infarction. Information acquired with one of the prediction models may provide a guideline for clinical decision-making in individual patients.

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7. General discussion

INTRODUCTION

In this chapter comments are given on the design of the study, implications of the causal research on the relation between QTc and RR interval duration and variability and sudden death and the implications of the risk functions for the prediction of sudden death. These comments reflect the personal opinion of the author on the design and findings from the study.

STUDY DESIGN

The nested case-referent study design is an efficient approach to assess the relation between parameters derived from standard 12 lead or 24-hour electrocardiography and the occurrence of sudden death. Parameters of study had to be determined only for sudden deaths and a random sample of all study patients rather than for the total study population. The design combines advantages from a follow-up study and a case-control study: absolute risks can be calculated because the denominators are known while a rare outcome is studied. The results of such a study can be presented in the format of a follow-up study, which is easy to comprehend. The lack of exact methods for the calculation of the precision of relative risk estimates remains a problem however (see chapter three).

In causal research comparability of patient groups and of information collected is a major issue in order to obtain a valid estimate of the relative risk. When studying the relation between QTc duration and sudden death by comparison of the absolute risks for sudden death in patients with a normal QTc and those with QTc prolongation, these two study groups ideally should have an identical prognosis with regard to sudden death if the QTc duration of both groups was equal. In intervention research comparability of prognoses is pursued (but not guaranteed) by random allocation of treatment. In the context of this study the patient groups not necessarily had an equal prognosis. However, there appeared to be no major incomparabilities of known risk factors for the relative risk estimates obtained via stratified analysis or logistic regression (adjusted estimate) and via the simple analysis (crude estimate) were essentially the same.

Information regarding patient characteristics at the time of 24-hour electrocardiography must be obtained in a way that is identical for sudden deaths and patients in the random sample. Ideally therefore the investigator should be blinded as to the outcome when collecting baseline data. For the computer-aided analysis of the 24-hour electrocardiograms this could be achieved by use of a coding scheme; for the retrieval of data from the patient records this was not feasible. Nevertheless, the investigators refrained as much as possible from looking at the outcome when retrieving the information from the patient records. In conclusion, we believe that a valid estimate of the relative risk was obtained

with regard to the standard 12 lead electrocardiogram QTc, and QT and RR interval duration and variability from the 24-hour electrocardiogram as well.

To which patients are the findings of this study applicable? Our study population consisted of patients who had 24-hour electrocardiography for a variety of reasons and received treatment guided by the findings during routine rhythm analysis of the 24-hour electrocardiograms. The parameters of study, QT and RR interval duration and variability were not available to the treating physician and, hence, could not have directly influenced treatment strategies, but an indirect influence via other related parameters cannot be excluded. Results must therefore be interpreted conditional on routine treatment given in the years 1980-1986 (see also chapter 3). Nevertheless, we believe that the results on QTc duration as measured at a standard 12 lead electrocardiogram apply to a broad population of patients because of the stability of the relative risk over many subgroups of patients and the accordance with the literature. We also feel confident that our findings on heart rate variability are valid because they are consonant with those reported by others. Probably more caution is warranted when interpreting the findings on QTc duration and variability from 24-hour electrocardiography since no corroborating literature yet exists.

QTC DURATION AND VARIABILITY

Prolongation of the heart rate corrected QT interval ≥440 ms when measured in standard leads I, II, and III of a standard 12 lead electrocardiogram more than doubled the risk for sudden death as compared to normal QTc in patients without signs of cardiac dysfunction. In patients with cardiac dysfunction the by itself high risk for sudden death was independent of QTc prolongation. We are not aware of studies in which a similar difference between patients with and without cardiac dysfunction was found. This finding may be attributed to different electrophysiologic properties of the myocardium whether or not accompanied by an altered homeostasis of the autonomic nervous system.

Shortening of QTc <400 ms as compared to normal QTc (400-440 ms) did not imply a higher risk when measured from the standard leads I, II, and III of the standard 12 lead electrocardiogram. However, QTc shortening determined from anterior lead V2 showed a trend for higher risks. QTc measurements from the anteriorly located leads at 24-hour electrocardiography clearly exhibited additional risk for patients with shortened QTc and for those with prolonged QTc as well. We did not anticipate the finding on QTc shortening because it did not agree with the hypothesis that inhomogeneous prolongation of repolarization, of which QTc prolongation is an electrocardiographic sign, predisposes for the occurrence of ventricular arrhythmias and sudden death. Also, we were not aware of literature describing such a relation (apart from that induced by a high dose of digitalis for example).

Although we realize that the Bazett formula to correct QT duration for heart rate may not be optimal in all circumstances (see appendix 2A) we nevertheless decided to use this formula. One important reason is that the major part of the existing literature employs the same correction. Furthermore, it is applied in the definition of the Long QT Syndrome.[1] An additional reason is the observation (in retrospect) that our findings on the relation

between QTc duration and sudden death did not depend on heart rate. This probably would have been the case if the Bazett formula had been of no use at all.

One of the assumptions underlying our hypothesis that patients with unstable QTc duration have an elevated risk for sudden death was based on reports that QTc prolongation was related to an increased risk for sudden death.[2] Since both patients with QTc prolongation *and shortening* had an elevated risk for sudden death in our study the interpretation of the findings on QTc interval variability is complex. We observed that both patients with low and high QTc variation had higher risks than those with intermediate levels of QTc variation, an observation which is at odds with the hypothesis that high variation would be an indicator of a frequent unstable electrical state of the heart. Given the difficulties to draw clear-cut conclusions on the effects of QTc interval variability and the time consuming process to obtain this parameter from 24-hour electrocardiography, there seems for the time being to be no or little clinical relevance to measure QTc interval variability.

HEART RATE AND ITS VARIABILITY

RR interval duration and the parameters derived form it can easily be acquired from 24-hour electrocardiograms. The different parameters deepen the understanding in the activity of the sympathetic and parasympathetic nervous system of the heart and, hence, may guide in the choice of treatment strategies. For example, patients with low short-term heart rate variability and few RR interval differences >50 ms have low parasympathetic activity. Insofar as low parasympathetic activity is related to high sympathetic activity beta blockers may be efficacious drugs.

PREDICTION OF SUDDEN DEATH

The risk functions derived in chapter six may be applied to assess a patient's risk for sudden death after 24-hour electrocardiography. A high risk for sudden death may constitute an indicator for treatment. Furthermore, the choice of treatment can be guided by insights in the threatening pathophysiologic mechanisms derived form those factors contributing most to the elevated risk. Thus, it may be attempted to prevent sudden death in these patients. Also, the risk functions may be applied in the selection of high risk patients for intervention studies.

From our observations it is obvious that the sophisticated parameters derived from 24-hour electrocardiography do not substantially contribute to the prediction of sudden death. However, in individual patients a skilled physician may selectively use these methods to answer specific questions. These results indicate that as regards the risk for sudden death it is sufficient to collect data on history, standard 12 lead electrocardiography and the routine rhythm analysis of 24-hour electrocardiograms (see chapter 6, model 3). The additional information from other tests, e.g. in the context of protocolized medicine, will not yield better prediction while it will increase the costs.

INDICATIONS FOR FUTURE RESEARCH

In this study we sought to increase our understanding of the mechanisms behind one of the major challenges of cardiology: sudden cardiac death. A multitude of questions and problems was brought out. Inherent to all research, this led to new questions and problems, and thus to goals for future research.[3]

The finding on the risk implications of QTc shortening remains puzzling. Further research may be indicated to clarify its precise relation with sudden death. A first step would be to compare QTc measurements obtained simultaneously from different leads, including those routinely used in 24-hour electrocardiography, and furthermore to determine their risk implications. Short-term experiments with drugs which modify either sympathetic or parasympathetic nervous system activity may clarify the contribution of each of the systems to (regional) QT duration.

The parameters chosen for heart rate variability were based on the calculation of simple statistics and were somewhat loosely related to the better defined peaks obtained from power spectral analysis. Given the availability of RR interval sequences on some 500 patients including 250 sudden deaths, of extensive baseline characteristics on these patients, and of computer packages for power spectral analysis, a detailed study of the risk implications of heart rate variability as defined by the peaks from power spectral analysis may be obtained at low additional cost.

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8. Summary

Sudden cardiac death, commonly defined as death occurring unexpectedly due to a cardiac cause within one hour of the onset of symptoms is a major cause of death in the industrialized world. Its incidence is estimated to be 1-2 per 1000 person-years, which yields an annual toll of approximately 20,000 in the Netherlands. In 85% of sudden deaths the final mechanism is ventricular fibrillation.

The underlying factors leading to the evolution of sudden cardiac death can be categorized into three groups: the substrate, modulators and triggers. *Substrate* refers to those factors that relate to the (damaged) structure of the myocardium. The major factor in this group is myocardial infarction. *Modulators* are those factors that temporarily increase the risk for sudden death. Important modulators are acute ischemia, electrolyte disturbances and influences from the autonomic nervous system. A *trigger* is a factor which initiates a fatal ventricular arrhythmia in a sufficiently high risk state created by substrate and modulators. The trigger is often the ubiquitous premature ventricular complex.

The objective of this study was to investigate the relation between QT and RR interval duration and variation and the occurrence of sudden death. The QT interval is an electrocardiographic parameter of the total duration of depolarization and repolarization of the myocardium. Its duration not only depends on heart rate (with increasing heart rate the QT interval shortens) but also depends on the balance of the activity of the left and right sympathetic nervous system. Prolongation of repolarization, hence of QT duration, is related to an increased incidence of malignant ventricular arrhythmias and sudden death. RR interval duration, a correlate of heart rate, is influenced by the parasympathetic and sympathetic nervous system. We hypothesized that sudden death may be induced by destabilization of autonomous nervous system activity and investigated this hypothesis by means of parameters derived from 24-hour electrocardiography. (*Chapter 2*)

We followed 6693 consecutive patients who had had 24-hour ambulatory electrocardiography for a variety of clinical questions for two years. In this period 245 patients died suddenly, 182 within one hour of the onset of their symptoms and 63 during sleep or otherwise unobserved. A reference group of 467 patients was randomly drawn from the total group of 6693 patients. Baseline data at the time of 24-hour electrocardiography on routine clinical patient characteristics, standard 12 lead electrocardiography and 24-hour electrocardiography were retrospectively obtained for the 245 sudden death patients and the 467 reference patients. This so-called *nested case-referent study design* allowed us to estimate absolute risks for sudden death while collection of baseline data was restricted to a limited number of patients. (*Chapter 3*)

In all patients without an intraventricular conduction disturbance QT interval duration was measured in leads I, II, and III of the standard 12 lead electrocardiogram and corrected for heart rate with use of Bazett's formula ($QTc=QT/\sqrt{RR}$). In patients without evidence of cardiac dysfunction (history of congestive heart failure and/or ejection fraction <40%), QTc ≥440 ms bore a 2.3 times higher risk for sudden death in comparison to

QTc <440 ms (95%-confidence interval: 1.4, 3.9). In contrast, patients with evidence of cardiac dysfunction had a relative risk of 1.0 (0.5, 1.9). These relative risks did not change when other patient characteristics were considered. Adjustment for age, sex, history of myocardial infarction, heart rate and the use of drugs did not alter these relative risks. We concluded that the data from our study indicate that in the absence of evidence of cardiac dysfunction QTc prolongation may double the risk for sudden death. Our findings accord with those in the literature provided that these are taken together. Furthermore, our study indicates that in patients with cardiac dysfunction the high risk for sudden death is independent of QTc prolongation. (*Chapter 4*)

During computer-aided re-analysis of the 24-hour electrocardiograms consecutive measurements of RR and QT intervals were obtained from which parameters indicating RR and QT interval duration and variation were derived. These parameters were related to the occurrence of sudden death. Prolongation of the mean QTc interval over 24 hours ≥440 ms was associated with a more than double risk for sudden death as compared to a mean QTc between 400 and 440 ms. Furthermore, *shortening* of the mean QTc <400 ms was attended by more than twice as high a risk for sudden death as compared to mean QTc values between 400 and 440 ms. Analysis of QTc from anterior lead V2 of the standard 12 lead electrocardiogram showed a slightly increased risk of QTc shortening in lead V2, however, this does not fully account for and explain the effect of QTc shortening at the 24-hour electrocardiogram. Both short and long-term QTc variability had no distinct relation with the risk for sudden death. This partly is attributed to the finding of the U-shaped risk curve of QTc duration derived from 24-hour electrocardiography. Both short and long-term heart rate (RR) variability showed a clear relation with the occurrence of sudden death: the higher heart rate variability was, the lower the risk for sudden death. Short-term heart rate variability is related to parasympathetic activity, hence our data indicate that low parasympathetic activity concurs with a high risk for sudden death. (*Chapter 5*)

In chapter six we identified the combination of variables that most closely predicted the occurrence of sudden death within two years after 24-hour electrocardiography. This was accomplished by the calculation of risk functions based on the logistic regression model. First, risk functions were constructed based on routinely available clinical information. Subsequently, information from more advanced tests was added. The information content of the risk functions was evaluated by use of receiver operator characteristic (ROC) curves. The risk function based on history, standard 12 lead electrocardiogram and routine analysis of 24-hour electrocardiograms had almost the same information content as the most extended function which also included exercise test, echocardiography, computer-aided analysis of 24-hour electrocardiography and ventriculography. Risk functions based on electrocardiographic data only showed that 12 lead electrocardiograms, routine rhythm analysis and computer-aided analysis of 24-hour electrocardiograms each had an independent contribution to the prediction of sudden death. This reflects the different type of information obtained by each of the techniques. (*Chapter 6*)

9. Samenvatting

Plotselinge hartdood wordt vaak gedefinieerd als niet verwachte dood binnen een uur na klachten door een cardiale oorzaak. Het is een van de belangrijkste doodsoorzaken in de geïndustrialiseerde wereld. De incidentie wordt geschat op 1 à 2 gevallen per 1000 persoon-jaren. Voor Nederland komt dat neer op ongeveer 20.000 gevallen per jaar. In 85% van de gevallen is de oorzaak ventrikelfibrilleren.

De factoren, die tot het optreden van plotselinge dood leiden, kunnen in drie groepen worden ingedeeld: substraat, modulatoren en triggers. Onder *substraat* vallen die factoren die tot beschadiging van de hartspier leiden. De belangrijkste factor in deze groep is het hartinfarct. *Modulatoren* zijn die factoren die het risico voor plotselinge hartdood tijdelijk verhogen. Belangrijke modulatoren zijn acute ischaemie, elektrolytstoornissen en invloeden vanuit het autonome zenuwstelsel. Een *trigger* is een factor, die een fatale ventriculaire ritmestoornis op gang kan brengen indien substraat en modulatoren voor een toestand van voldoende hoog risico hebben gezorgd. De trigger is vaak het veel voorkomende premature ventriculaire complex.

De vraagstelling van dit onderzoek betrof de relatie tussen de duur en variatie van het QT en RR interval en het optreden van plotselinge dood. Het QT interval is een electrocardiografische parameter van de totale duur van de depolarisatie en repolarisatie van de hartspier. De duur van het QT interval hangt niet alleen af van de hartfrekwentie (met het toenemen van de hartfrekwentie neemt de duur van het QT interval af), maar ook van de balans tussen de aktiviteit van het linker en rechter sympatische zenuwstelsel. Bij verlenging van de repolarisatie – en daarmee van het QT interval – treden maligne ventriculaire ritmestoornissen en plotselinge hartdood vaker op. De duur van het RR interval (de tijd tussen twee hartslagen, dus omgekeerd evenredig met de hartfrekwentie) wordt beïnvloed door zowel het parasympatische als het sympatische zenuwstelsel. Onze hypothese is dat plotselinge hartdood veroorzaakt kan worden door een verstoring van de aktiviteit van het autonome zenuwstelsel. We onderzochten deze hypothese door gebruik te maken van 24 uurs electrocardiogrammen. (*Hoofdstuk 2*)

In het onderzoek vervolgden we gedurende twee jaar 6693 patiënten, bij wie een 24 uurs electrocardiogram werd gemaakt om uiteenlopende redenen. In deze periode van twee jaar overleden 245 patiënten plotseling, 182 binnen een uur na het ontstaan van klachten en 63 in de slaap of anderszins niet geobserveerd. Er werd een referentiegroep van 467 patiënten gevormd door uit de hele groep van 6693 patiënten een steekproef te nemen. Retrospectief verzamelden we gegevens zoals die waren ten tijde van het maken van het 24 uurs electrocardiogram van de 245 patiënten, die plotseling overleden en de 467 referentie-patiënten. Deze gegevens betroffen routine klinische patiëntengegevens, standaard 12 afleidingen electrocardiogrammen en 24 uurs electrocardiogrammen. Een dergelijke onderzoeksopzet wordt in de angelsaksische literatuur een *nested case-referent* onderzoek genoemd. Het stelde ons in staat absolute risico's voor plotselinge dood te

schatten, terwijl we slechts de gegevens van een deel van de patiënten behoefden te verzamelen (i.t.t. die van alle 6693 patiënten). (*Hoofdstuk 3*)

Bij alle patiënten zonder intraventriculaire geleidingsstoornis werd het QT interval in de afdelingen I, II en III van het standaard 12 afleidingen electrocardiogram gemeten. De QT intervallen werden aangepast aan de hartfrekwentie volgens de formule van Bazett: $QTc = QT/\sqrt{RR}$. Bij patiënten bij wie geen aanwijzingen waren voor een gestoorde hartspierfunctie (anamnese van decompensatio cordis en/of een ejectiefractie <40%) ging verlenging van het QTc interval (≥440 ms) gepaard met een 2,3 maal zo hoog risico voor plotselinge dood in vergelijking tot een QTc interval <440 ms (95% betrouwbaarheidsinterval: 1,4 ; 3,9). Daarentegen hadden patiënten met een gestoorde hartspierfunctie een relatief risico van 1,0 (0,5; 1,9). Deze relatieve risico's veranderden niet na adjustering voor leeftijd, geslacht, voorgeschiedenis van een hartinfarct, hartfrekwentie en het gebruik van geneesmiddelen. Wij kwamen tot de conclusie dat verlenging van het QTc interval het risico voor plotselinge dood kan verdubbelen bij afwezigheid van hartspierfunctiestoornissen. Deze bevindingen komen overeen met die in de literatuur. Verder concludeerden we dat het hoge risico voor plotselinge dood bij patiënten met hartspierfunctiestoornissen niet afhangt van de duur van het QT interval. (*Hoofdstuk 4*)

Tijdens heranalyse van de 24 uurs electrocardiogrammen met behulp van een computer werden metingen van alle RR en QT intervallen verkregen. Hieruit werden parameters over de duur en variabiliteit van deze intervallen berekend en gerelateerd aan het optreden van plotselinge dood. Verlenging van het gemiddelde QTc interval over 24 uur (≥440 ms) ging gepaard met een meer dan twee keer zo hoog risico voor plotselinge dood in vergelijking tot een gemiddelde QTc duur tussen 400 en 440 ms. Verder ging ook verkorting van het QTc interval (<400 ms) gepaard met een meer dan twee keer zo hoog risico voor plotselinge dood in vergelijking tot een gemiddelde QTc duur tussen 400 en 440 ms. Analyse van de QTc duur van de anterior gelegen afleiding V2 van het standaard 12 afleidingen electrocardiogram toonde een enigszins verhoogd risico van QTc verkorting in deze afleiding. Hiermee wordt echter het effect van QTc verkorting zoals gemeten op het 24 uurs electrocardiogram niet volledig verklaard. Kortdurende en langdurende variaties van de QTc duur vertoonden geen duidelijke relatie met het risico van plotselinge dood. Dit wordt toegeschreven aan de U-vormige risicocurve van de QTc duur in het 24 uurs electrocardiogram.

Zowel kortdurende als langdurende variaties van de hartfrekwentie toonden een duidelijke relatie met het optreden van plotselinge dood: hoe meer hartritme variabiliteit, hoe lager het risico voor plotselinge dood. Kortdurende hartritmevariaties zijn gerelateerd aan de aktiviteit van het parasympatische zenuwstelsel. Onze gegevens wijzen er dus op dat lage aktiviteit van het parasympatische zenuwstelsel gepaard gaat met een hoog risico voor plotselinge dood. (*Hoofdstuk 5*)

In hoofdstuk 6 stelden we de combinatie van variabelen vast die het meest precies het optreden van plotselinge dood voorspelden binnen twee jaar na 24 uurs electrocardiografie. Daarbij werd gebruik gemaakt van risicofuncties gebaseerd op het logistische regressiemodel. Eerst werden risicofuncties bepaald op basis van routine klinische gegevens; later werd informatie van meer geavanceerde onderzoekingen toegevoegd. De hoeveelheid informatie aanwezig in de risicofuncties werd beoordeeld met behulp van zogenaam-

de "receiver operator characteristic" (ROC) curves. De risicofunctie gebaseerd op anamnese, standaard 12 afleidingen electrocardiogram en de routine analyse van het 24 uurs electrocardiogram bevatte nagenoeg dezelfde informatie als de meest uitgebreide functie waarin ook de inspanningstest, het electrocardiogram, de computer re-analyse van het 24 uurs electrocardiogram en het ventriculogram waren opgenomen. Risicofuncties die alleen op electrocardiografische gegevens gebaseerd waren lieten zien dat het standaard 12 afleidingen electrocardiogram, de routine analyse van het 24 uurs electrocardiogram en de computer re-analyse van het 24 uurs electrocardiogram elk een onafhankelijke bijdrage hadden aan de voorspelling van de plotselinge dood. Dit weerspiegelt de verschillende aard van de informatie die met elk van deze technieken wordt verkregen. (*Hoofdstuk 6*)

10. Dankwoord

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Curriculum vitae

Ale Algra werd op 6 juli 1953 te Nieuw-Amsterdam geboren. Hij bezocht het Christelijk Lyceum te Emmen waar hij in 1971 het eindexamen HBS-B behaalde. Van 1971 tot 1974 studeerde hij natuurkunde aan de Rijksuniversiteit te Utrecht en deed in 1975 kandidaatsexamen. Met als doel uiteindelijk biomedical engineer te worden deed hij vanaf 1974 de studie geneeskunde aan de Erasmus Universiteit te Rotterdam en legde in 1981 het artsexamen af. Tijdens de geneeskunde studie was hij werkzaam als student-assistent op de afdeling cardiologie van het Thoraxcentrum. Vanaf mei 1981 was hij als wetenschappelijk medewerker aan deze afdeling verbonden, waar hij methoden ontwikkelde voor het automatisch analyseren van 24 uurs electrocardiogrammen, betrokken was bij een reorganisatie van de centrale ECG dienst en ECG onderwijs gaf. Sedert januari 1984 werkte hij aan het onderzoek waarop dit proefschrift gebaseerd is. Dit onderzoek werd onderbroken door een opleiding aan de Harvard School of Public Health van september 1984 tot juni 1985 waar hij de graad van Master of Science in Epidemiology behaalde. Met ingang van 1 maart 1990 zal hij worden aangesteld bij de Rijksuniversiteit Utrecht als wetenschappelijk projectleider van het Nederlands TIA onderzoek.