Olli Anttonen

PREVALENCE, PROGNOSIS AND CHARACTERISTICS OF SUBJECTS WITH SHORT QT INTERVAL IN AN ELECTROCARDIOGRAM
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Academic dissertation to be presented, with the assent of the Faculty of Medicine of the University of Oulu, for public defence in the Main Auditorium of Päijät-Häme Central Hospital (Keskussairaankatu 7, 15850 Lahti) on February 6th, 2009, at 12 noon

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Faculty of Medicine, Institute of Clinical Medicine, Department of Internal Medicine, Division of Cardiology, University of Oulu, P.O.Box 5000, FI-90014 University of Oulu, Finland
Oulu, Finland

Abstract

Short QT syndrome is an inherited arrhythmia disorder characterized by a short QT interval, typical T-wave and ST-segment morphology and an increased risk of sudden cardiac death. The purpose of this thesis was to study the epidemiology and prognosis of the subjects with short QT intervals. Special attention was paid to the ECG changes that could illustrate the prognosis of subjects with short QT interval.

The first study comprised a group of patients with short QT syndrome. We report clinical presentation, ECG morphology, the prevalence of genetic mutations and the results of therapies in this group of patients.

The second study population consisted of 10,822 randomly selected middle-aged subjects followed up for 29 ± 10 years. QT intervals were measured using three correction methods for the heart rate in order to assess the prevalence and prognosis of those subjects with short QT intervals.

The third population consisted of three patients with short QT syndrome and nine controls. Holter recordings were analyzed to compare transmural dispersion of repolarization between patients and controls and also to study their capability to change repolarization indexes from baseline to maximal values.

In the fourth study ECGs from 10 patients with short QT syndrome were compared with ECGs of 12 asymptomatic subjects with short QT intervals. The aim was to find ECG abnormalities that would predict the outcome of the patients.

We found 62% of patients to be symptomatic, 34% had cardiac arrest. Atrial fibrillation was common. Most of the patients received an ICD or were placed on hydroquinidine.

The prevalence of QTc < 320ms was 0.10% and QTc < 340ms was 0.4%, respectively. Mortality or other serious symptoms did not differ between subjects and controls. We also found that the TPE/QT ratio as an index for abnormal transmural dispersion of repolarization was high compared to controls. Short QT syndrome patients had also lesser capacity to change the QT interval, indicating blunted autonomic response in SQTS.

Ten SQTS patients had significantly shorter Jpoint–Tpeak interval and higher TPE/QT ratio compared to controls.

In conclusion, shorter than normal QT interval might represent a novel short QT syndrome. However, in the general community short QT interval can reflect only the extreme end of the normal Gaussian distribution of QT intervals and these subjects carry a good prognosis. TPE/QT ratio and Jpoint–Tend intervals can be used as risk stratifiers in subjects with short QT intervals.

Keywords: Arrhythmia, ECG, short QT syndrome, sudden cardiac death
Acknowledgements

This study was carried out between 2004–2008 in Päijät-Häme Central Hospital, Lahti, Finland and in the Department of Internal Medicine, Division of Cardiology, University of Oulu, Finland.

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I wish express my warmest thanks to my co-authors Harri Rissanen MSc, Professor Antti Reunanen, Heikki Väänänen MSc and also to my foreign colleagues around the world who have joined me in this project.

A special foreign colleague needs to be mentioned. I spent one year at St’Georges Hospital, London, UK in the early 90’s. During that time I had a privilege to work with Edward Rowland MD, a gentleman and great electrophysiologist who introduced me in to the world of invasive diagnosis and treatment of cardiac arrhythmias.

I wish to thank my friends and colleagues in other Finnish hospitals. It has been a real privilege to work with such a great bunch of doctors throughout my working years. Please, do not be offended if you are not mentioned here. I am just lucky to have so many good friends and colleagues! I also owe my warmest thanks to the whole personnel of the department of Medicine in Lahti; sincere thanks go especially to my colleagues in cardiology, Seppo Voutilainen, Juppe Heikkilä and Liisa Kokkonen. I wish to thank our nurses in the cath lab for creating such an enjoyable and professional atmosphere. Ladies, it has been a
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My friend, Docent Tapio Nousiainen from Kuopio, with whom I started my internship in Kuopio University Hospital in early 80’s has encouraged me through these years. Tapio, do you remember? Actually we promised to leave science to others! Professor Kalevi Pyörälä, my first professor, mentor and also a fatherly figure in Kuopio has had a great influence on my behaviour and performance in the demanding, sometimes difficult but always interesting field of Medicine and Cardiology. Kalevi, thank you for guiding me through my time in Kuopio.

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Above all, my warmest thoughts and thanks go to my wife Taina. After her own dissertation in the field of education she encouraged me to go for the research. Her patience and friendship has carried me through this project. My lovely children Minna, Anni and Eero has brought deeper happiness and meaning to my life. Therefore, this thesis is dedicated to you, children!
This work was supported by Finnish Cultural Foundation, Paavo Nurmi Foundation, Maud Kuistila Foundation and Päijät-Häme Central Hospital which I acknowledge with gratitude.

Lahti January 2009 Olli Anttonen
**Abbreviations**

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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
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<tr>
<td>ARVD/C</td>
<td>Arrhythmogenic right ventricular dysplasia cardiomyopathy</td>
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<tr>
<td>CPVT</td>
<td>Cathecolaminergic polymorphic ventricular tachycardia</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram, -phic, -phy</td>
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<tr>
<td>ERP</td>
<td>Effective refractory period</td>
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<td>EP study</td>
<td>Electrophysiological study</td>
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<tr>
<td>ICD</td>
<td>Implantable Cardioverter Defibrillator</td>
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<td>LQTS</td>
<td>Long QT Syndrome</td>
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<tr>
<td>PVC</td>
<td>Premature Ventricular Contraction</td>
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<tr>
<td>SIDS</td>
<td>Sudden Infant Death Syndrome</td>
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<tr>
<td>SCD</td>
<td>Sudden Cardiac Death</td>
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<tr>
<td>LQTS</td>
<td>Long QT Syndrome</td>
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<tr>
<td>SQTS</td>
<td>Short QT Syndrome</td>
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<tr>
<td>TDR</td>
<td>Transmural dispersion of repolarization</td>
</tr>
<tr>
<td>TPE</td>
<td>Tpeak-Tend interval</td>
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<tr>
<td>VF</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>VT</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>PMVT</td>
<td>Polymorphic ventricular tachycardia</td>
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List of original articles

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals


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1 Introduction

Sudden cardiac death (SCD) is usually defined as a natural and unexpected death due to cardiac causes that occur within 1 hour of onset of symptoms (Myerburg & Castellanos 2001). Coronary artery disease is by far the most common cause for SCD in an older adult population accounting more than 80% of all SCD. By contrast, in the younger population i.e. children and adolescents, SCD is rare and it has an clearly different aetiology (Myerburg 2001, Libethson 1996). Significant number of these deaths in a younger population is caused by inherited arrhythmia syndromes, the so-called channelopathies.

Since its invention more than a century ago by Einthoven, electrocardiogram (ECG) has remained the most valuable single method for detecting electrical abnormalities in primary malignant arrhythmias. These electrical changes are induced by subtle molecular genetic differences which reflect the altered electrical function of the heart leading to clinical syndrome.

Today when everything is computerized and information technology dominates daily practise in medicine, a simple 12-lead ECG which is readily available to all medical professionals is still able to produce new relevant information, particularly in the field of hereditary electrical disease. It still plays a fundamental role in the diagnosis and risk stratification of the arrhythmia syndromes.

The prototype of primary electrical disease, the long QT syndrome (LQTS) has been well known over half a century. Modern methods of cardiac molecular genetics have allowed researchers to characterize several mutations of genes encoding transmembrane cardiac ion channels leading to long QT syndrome. This opened a new era in the research of these arrhythmia syndromes (Wang et al. 1995). Other primary arrhythmia syndromes like the Brugada syndrome (Brugada & Brugada 1992), cathecolaminergic polymorphic ventricular tachycardia (CPVT) (Priori et al. 2002), arrhythmogenic right ventricle dysplasia (ARVD) (Corrado & Thiene 2006) and familial atrial fibrillation (Arnar et al. 2006) are also among genetically determined channelopathies. A common feature with these syndromes is, that still today, diagnosis, clinical judgement and prognosis is prominently determined by changes in a routine 12 – lead ECG or ambulatory long term monitoring of the heart rate.

Since the discovery of Long QT syndrome it has taken more than 30 years since the first gene linked to the syndrome was identified. However, the pace of research has increased and therefore for Brugada syndrome it has taken less than
ten years since the discovery of the syndrome to reveal its genetic background and even less time in the short QT syndrome (SQTS), an electrophysiological mirror image of the long QT syndrome.

The hallmark of the diagnosis of this latest “arrival” in the growing field of primary electrical diseases is a very short QT interval (usually < 320–340 ms), peaked, symmetrical T-wave and absent or nearly absent ST-segment in the ECG with propensity to atrial and ventricular tachyarrhythmias plus an increased risk for sudden cardiac death. This syndrome seems to be very rare and is believed to carry such a dire prognosis, that extreme actions regarding diagnosis and treatment are justified.

The focus of this thesis is to characterize clinical features of the short QT syndrome, to assess its prognosis and prevalence in the community and especially emphasize ECG changes which might determine the prognosis of the subjects with the syndrome.
2 Review of the literature

2.1 Action potential formation in the cardiac myocyte

Since the invention of the electrocardiogram by Willem Einthoven more than one hundred years ago, there still is a strong debate about the cellular basis of the various waves of the 12-lead ECG.

The cardiac action potential is generated by transient flow of Na, K, Ca and Chloride ions through sarcolemmal ion channels. Each of these ion channels is regulated by one or more genes. The action potential of the heart muscle consists of cardiac excitation (depolarization) and repolarization which are based on the consecutive activation of many membrane currents.

Fig. 1. The relative contribution in time of ionic currents, and the genes/or channels underlying these currents, to the cardiac action potential. Down deflection corresponds to inward current and upward deflection to outward current. Modified from Conrath & Opthof 2006 and Rosen 2002.
Each of these currents has their own role in the different phases of the action potential. The action potential configuration varies in different cardiac tissues according to local difference of the density of these currents.

The main depolarizing currents are the inward sodium current, giving rise to the upstroke of the action potential, and the inward L-type calcium current, underlying also the plateau phase of the action potential.

Two major repolarizing currents are the rapid (IKr) and the slow components (IKs) of the delayed rectifier potassium currents. In addition to these main currents there are also numerous other ionic currents that have a role in the electrical activation and repolarizing of the cardiac muscle.

Discrete balance between these depolarizing and repolarizing currents, and their voltage characteristics, determine the duration and shape of the action potential.

Action potential, depolarizing-repolarizing sequence, is different in various regions of the heart. In the ventricular muscle, the initial rapid depolarization (phase 0) is followed by fast repolarization; mainly in Purkinje fibre cells (phase 1). Phase 2 is composed of sequences of maintained depolarization and slow repolarization (plateau or dome). Phase 3 is due to more rapid phase of repolarization ending in the resting or diastolic potential (phase 4) (Figure 1).

### 2.2 Action potential in the electrocardiogram

The QT interval of the electrocardiogram represents the time required for completion of both ventricular depolarization and repolarization; i.e. the action potential of the cardiac myocyte. Although QRS complex duration (depolarization) is included in the measurement of the repolarization time, it is considered to have a minor role in the length of the QT interval and usually neglected in the analysis of the repolarization. Another reason for inclusion of the QRS complex into the measurement of the QT interval is that repolarization begins in some regions of the heart before depolarization has been completed in other areas (Abildskov 1979).

So, the only true repolarization waves of the ECG are the J-, T- and U-waves. The cellular basis for these repolarization waves has been debated for a long time and even today scientists have not reached a consensus on the complete origin of these waves.
2.3 Heterogeneous electrical activation of the myocardium

Previously it was believed that ventricular myocardium is electrically homogenous. However, recent studies have revealed that activation and repolarization of the myocardium is electrically and functionally inhomogeneous and is comprised of three electrically and functionally different cell types (Antzelevitch et al. 1999). There exists great regional variation of the electrical properties of the ventricular cells. These uncovered heterogeneities include electrophysiological characteristics of three different ventricular cell types located in the endocardium, epicardium and so called M cells which are found in the deep middle layers of the ventricles of the heart. Different electrophysiological behaviour of these cells during the activation and repolarization of the ventricles leads to arise of the J-, T- and U-waves (Hlaing et al. 2005).

2.4 Origin of the J-wave

A notch in action potential curve in the epicardium but not in the endocardium leads to transmural voltage gradient during late ventricular activation. This gives rise to a delta wave following the QRS complex, more commonly known as a J wave or earlier, the Osborn wave (Yan & Antzelevitch 1996). Transmural gradient in distribution of Ito, the transient outward current, is responsible for voltage gradient across ventricular myocardium and the presence of J point elevation or the J-wave. In humans this wave is usually considered pathognomonic of hypothermia (Clements & Hurst 1972) or hypercalcaemia (Sridharan & Horan 1984). It has also been described in sudden death syndromes including idiopathic ventricular fibrillation (Yan et al. 2003). The molecular basis of the distribution of Ito has long been debated and several genes are considered to be responsible. Clinically, the occurrence of the J-point elevation or J-wave can be important due to the increased possibility of marked dispersion of repolarization and hence developing life threatening arrhythmias (phase 2 reentry) such as in the Brugada syndrome (Bloch Thomsen et al. 2005, Yan & Antzelevitch 1999).

2.5 Origin of the T-wave

Earlier, there have been several different theories about the genesis of the T wave. It was thought to be generated by temporal and spatial sequence of rapid repolarization. More lately transmural gradients of repolarization, with earlier
repolarization occurring at the epicardium were considered to be responsible for the T-wave (Franz et al. 1987). Discovery of the M cells from canine wedge preparations, with longer action potentials than of the cells in subendocardium or subepicardium, have challenged the older concepts of the rise of the T-wave. Transmural and apico-basal heterogeneities of final repolarization of the action potential within the ventricular myocardium are thought to be responsible for the genesis of the T-wave.

According to this theory, under baseline conditions the T-wave begins when the plateau of the cardiac action potential separates from that of M cells. When the epicardium repolarizes, the voltage gradient between epicardium and the M cell region continues to grow formatting the ascending limb of the T-wave. The peak of the T-wave coincides with the full repolarization of the epicardium and when the voltage gradient between M cells and epicardium is highest. Repolarization of both endocardium and the M region contribute importantly to the descending limb of the T-wave which gets to the end when the M cell layer has been fully repolarized. Therefore, the Tpeak–Tend interval (TPE) is assigned a measure of transmural dispersion of repolarization (TDR). Recent studies have suggested that the TPE interval (especially TPE/QT ratio) may be useful as an index of transmural dispersion and thus a prognostic sign of arrhythmic risk under a variety of conditions (Gupta et al. 2008). However, to correlate the results of the studies on these dog heart muscle preparations with the conditions in living human heart has been strongly questioned (Opthof et al. 2007). These findings have not been clearly established in humans and this assumption that the TPE represents transmural dispersion of repolarization is not based on sufficient data and is, therefore, at least preliminary (Xia et al. 2005).

2.6 Origin of the U-wave

The origin of the U-wave in the ECG has been a matter of constant debate. After the original description of the U-wave in the electrocardiogram by Einthoven there have been many suggestions to explain its origin. It is believed to originate from several structures of the left ventricle including ventricular septum, papillary muscles and purkinje fibres (Antzelevitch 2006). Its origin has also been explained by negative afterpotentials, possibly caused by mechanoelectrical feedback in a filling ventricle (Lepechkin 1957). A very recent study provides further evidence supporting mechanoelectrical hypothesis for the origin of the U-wave (Schimpf et al. 2008). It seems likely, although there is no conclusive
evidence, that in normal condition the basis of the U-wave is different from the pathological state. As mentioned, normal U-wave is possibly generated by mechanoelectrical feedback and in a pathological state it could be caused by delayed repolarization of the M cell region leading to a U wave that is in fact part of the T wave, and therefore could also be called the T2 or second component of the interrupted T-wave. This could have clinical implications e.g. concerning QT interval measurements.

2.7 QT-interval

The QT-interval (time from the Q-wave to the end of the T-wave) of an ECG is considered to represent the time from the start of the myocardial depolarization to the final repolarization recorded in selected leads and thus comprises the sum of all transmembrane action potential durations; both short and long ones (Vaughan Williams 1982). In a healthy myocardium effective refractory period (ERP) is thought to represent the electrophysiological counterpart of the QT-interval, although in standard conditions the QT-interval is slightly longer than ERP. Since repolarization does not extend beyond the end of the QT-interval it is commonly accepted that the QT-interval is a valid reflector of the end of the myocardial repolarization (Surawicz & Knoebel 1984).

2.7.1 Measurement of QT-interval

The correct method for measuring the length of the QT interval has been under continuous debate since it became obvious that it is a major risk factor for serious cardiac arrhythmias and sudden cardiac death. It has been recognised for years that the QT interval measurements vary greatly depending on the leads that are used (Cowan et al. 1988). Usually this difference is thought to occur in the definition of the end of the T-wave but also onset of the Q-wave is sometimes questionable. However, this interlead variability of the QT-interval (QT dispersion) has been suggested as a cause for regional differences in repolarization (Day et al. 1990). This parameter is often defined as the difference between the longest and shortest QT-interval in the 12-lead ECG and earlier was widely accepted as a marker of arrhythmogeneicy. However, this technique is no longer used due to major problems in reproducibility (Kautzner & Malik 1997) and negative results of clinical studies on association between QT dispersion and
mortality (Zabel et al 1998). Recent observations have also revealed major technical problems in interpreting this phenomena (di Bernardo et al. 2000).

Not only is the definition of the duration of the QT-interval a problem. There are many different methods for making the measurement. QT-interval has been calculated from a variety of leads but there is no clear consensus upon the best method and best leads even among experts (Kautzner 2002). Technically QT-interval can be measured using a simple ruler, both using manual or electronic calipers connected to a digitizing pad. Whatever method is used the problem is great inter- and intraindividual variability with observers.

Usually the end of the T-wave is defined as a point where the descending limb of the T-wave intersects the baseline. The end of the T-wave may also be determined with a tangent fitted to the steepest slope of the descending T-wave. Occurrence of U-wave can also cause confusion; whether it should be taken as part of account or not.

Traditionally it is recommended that the measurements are made from leads II and V5 but also V2 or V3 are believed to provide close approximation to the maximum QT-interval.

2.7.2 Factors influencing QT-interval

Gender: It has been known for over a half of a century that QT-interval tends to be longer in females than in males (Bazett 1920, Lepechkin & Surawicz 1953). In general, the lengthening of the QT-interval in females compared to men is around 10%. During puberty, probably due to influence of sex hormones; the QT-interval shortens in males but remains almost constant in females, explaining at least partly the difference in measurements (Rautaharju et al. 1992). Also, studies on castrated men have shown that their repolarization configuration and length was different (slower and longer) compared to men with normal testosterone levels (Bidoggia et al. 2000). In later years this difference gets smaller.

Plasma electrolytes: Hypocalcaemia prolongs the QT-interval and hypercalcemia shortens it. Hyperkalemia tends to shorten the QT-interval but in hypokalemia measurement is more difficult due to commonly occurring T-U complex (Surawicz 1967).

Body temperature: Regardless of the heart rate, fever seems to shorten QT-interval (Karjalainen & Viitasalo 1986).

Drugs: A great number of both cardiac and noncardiac drugs affect QT-interval. Many antihistamines, antibiotics, antimalarials, antidepressants,
neuroleptics and antipsychotic drugs can cause QT-prolongation and hence increase risk for potentially fatal arrhythmias (Camm 2005).

**Autonomic nervous system:** Changes in autonomic nervous system tone can alter QT-interval both directly via heart rate modulation or more directly affecting depolarization and repolarization kinetics of a myocyte. QT-interval is significantly longer during sleep than during the waking state at the same heart rate (Viitasalo & Karjalainen 1992). It has been proposed that the increase of the QT-interval during sleep is a result of heightened vagal tone and/or decrease in levels of circulating catecholamines (Bexton et al. 1986).

**Heart rate:** Heart rate greatly influences the QT-interval. Under normal physiologic conditions normal heart has longer QT-interval at lower heart rate than at higher heart rate. Reproducibility and comparability of measurements of QT-interval in different studies or in clinical assessment of an individual subject requires compensation for this variation. Usually the QT-interval is corrected for heart rate by applying a mathematical correction formula. Many rate correction formulae have been developed in order to determine whether the QT-interval is prolonged in comparison to its predicted value at a reference heart rate of 60 beats/min (RR interval of 1.0 second).

Increase and decrease of the QT-interval due to heart rate change is a dynamic phenomenon and changes of QT-interval usually lag behind heart rate alteration. This hysteresis can take up to several minutes to stabilize and adaptation is highly individual (Pueyo et al. 2003). Therefore, it is obvious that QT/RR relationship is affected not only by the preceding interval between beats but also by prevailing heart rate in a longer period of time. Usually QT-correction formulae do not take this highly individual variation into account.

There are various different formulae, exponential, linear and logarithmic that has been proposed for adjusting the QT-interval for heart rate (Moss 1993). Major weakness in most of these formulae is that they are based on the predominant heart rate on a resting ECG in the studied population making conversion unreliable at slow and high heart rates. The most commonly used correction method for QT-interval is Bazett’s square root formula (QT measurement/√RR interval) which is rooted in medical practice so strongly that it is considered as a gold standard despite its well known deficiencies at low and high heart rates. Although it is widely used, it is also clearly understood that the QT interval corrected by Bazett is artificially prolonged at heart rates > 60/min and shortened at heart rates < 60/min making use of this formula unsatisfactory in many instances (Malik 2001). The cube root Fridericia formula (QT measurement / 3√RR interval)
R-R-interval) has the same limitations at high heart rates but is considered to perform better at low rates (Fridericia 1920). Also, the widely used Framingham linear correction formula (Sagie et al. 1992) tends to give too low values at slow heart rates compared to the probably most accurate formula at present time (Karjalainen et al. 1994). This corrects heart rate well over all sub ranges of heart rates using a nomogram method where a correcting number is added to a specific QT-interval.

There is no general consensus on the best formula to be used in clinical practise. All these formulae make assumptions about the linear nature of the QT/heart rate relationship, assumptions that may not apply to specific individuals with different physiological conditions or diseases or who are receiving drugs. Perhaps the best way to overcome this is to try to make measurement as close to heart rate of 60 to 70/min as possible.

2.7.3 Normal values of QT-interval

Despite it’s clear known weaknesses Bazett’s formula is by far the most popular method to perform rate correction for the QT-interval. Therefore, normal values for corrected QT-interval are most often derived from Bazett’s equation.

QT values seem to be quite stable for children under the age of 15 years, with no gender difference (Table 1) (Moss 1993). However, in an adult population QT-interval tends to be longer in females than in males (Bazett 1920, Rautaharju et al. 1992).

<table>
<thead>
<tr>
<th>Table 1. Suggested criteria for normal and prolonged QT values.</th>
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<tr>
<td>Suggested Bazett-corrected QTc values (ms)</td>
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<tr>
<td>1-15 yrs</td>
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It should be noted that recently almost all criteria have been developed to detect prolongation of the QT-interval, less focusing on the shorter end of the variation of QT-intervals.

Defining lower limits for QT-intervals in a normal population have been much more complicated than finding upper limits and data also sparse.
In Canada over 14,000 healthy individuals were studied to assess the deviation of QT-intervals in the general population (Rautaharju et al. 1992). They also set limits for the low and high boundaries of QT-intervals. In general, QT values below and beyond two standard deviations (SD) from the mean were considered as either short or long. In their study population of more than 14,000 individuals, 360 subjects (0.4%) had a QT-interval above or below two SD from the mean QT-interval.

They also proposed a formula: \( \text{QTpredicted (ms)} = \frac{656}{1 + \text{heart rate}/100} \) for calculation of predicted QT interval for a given subject with a given heart rate. Based on their study QT < 88% of QTpredicted has been proposed as the lower limit because it corresponds to the mean value – 2SD in the general population. This formula has been widely adopted among researchers focusing also on the lower end of QT-intervals.

2.7.4 Transmural Dispersion of Repolarization (TDR) as a marker for increased vulnerability for ventricular tachyarrhythmias

Originally QT dispersion was defined as the difference between the longest and shortest QT-interval measured from a 12-lead ECG. These differences between ECG leads were believed to reflect regional differences in repolarization (Day et al. 1990). Without clear clinical or experimental verification, this interlead variability was widely accepted as a marker of arrhythmogenicity. However, observed lack of reproducibility of measuring the QT dispersion (Kautzner & Malik 1997) and negative results of some major clinical studies on association between QT dispersion and mortality (Zabel et al. 1998, Brendorp et al. 2001) suggest that different QT-intervals in different 12-lead ECG leads do not reflect true dispersion of repolarization of the ventricular myocardium. Also, studies on technical aspects of QT-interval projection on the body surface have increased doubts regarding this method (Macfarlane et al. 1998) to the extent, that generally this method is no longer used.

Later, several investigators have proposed that TPE on the 12-lead ECG can be used clinically as a measure of transmural dispersion of repolarization (Tanabe et al. 2001, Lubinski et al. 2000). These suggestions are based on experimental studies in arterially perfused wedge preparations obtained from the canine left ventricle. Here the peak of the T-wave coincides with the end of epicardial repolarization and the end of the T-wave coincides with the end of repolarization of the midmural M cells (Antzelevitch 2001). These studies also support the
concept that an increased transmural dispersion of repolarization promote arrhythmogeneity (Akar et al. 2002). Recently, questions have been raised regarding the theory that the T-wave on the body surface ECG results from transmural differences in repolarization (Opthof et al. 2007, Coronel 2005). However, this concept is rooted strongly in electrophysiology and is promoted even in modern textbooks. Although the latter part of the repolarization has been of great interest for many years, information regarding the factors influencing the earlier phases of the T-wave is much more limited.

2.8 Inherited arrhythmia syndromes

2.8.1 Long QT syndrome

The long QT syndrome is characterized by increase of the QT-interval and propensity to ventricular tachyarrhythmias possibly leading to syncope, cardiac arrest and sudden cardiac death.

In 1957 Jervell and Lange-Nielsen described a family with congenital deafness, syncope and prolonged QT interval (Jervell & Lange-Nielsen 1957). A few years later Romano and Ward separately presented families with same kind of symptoms and ECG findings without deafness (Romano et al. 1963, Ward 1964). The latter syndrome was identified to have autosomal dominant inheritance whereas the former is inherited recessively. In the early reports, first estimations about the incidence of the LQT syndrome was 1 in 10000 but recently the incidence of mutations have been updated to 1 in 2000 (Roden 2008).

The typical electrocardiogram in the long QT syndrome comprises QTc (c corresponds to rate correction of QT-interval) prolongation, T-wave morphological abnormalities and polymorphic ventricular tachycardia, causing syncopal episodes or even sudden cardiac death.

Clinical presentation varies greatly from asymptomatic mutation carrier with normal QTc to infant sudden cardiac death. Clinical diagnostic criteria have been proposed by Schwartz less than two decades ago (Schwartz et al. 1993). These criteria include electrocardiogram findings, clinical history and specific features in the family history. Each of the criteria has weight points and total sum of the points in the point chart allows clinical classification for probability of having the syndrome. Several genes have been associated with the syndrome. In most of the syndromes, lengthening of QT-interval is due to loss-of-function mutation in
genes KCNQ1 (LQT1), HERG (LQT2), and gain-of-function mutation in SCN5A (LQT3). Although long QT syndrome is characterized by a significant genetic heterogeneity leading to as many as 8 different long QT syndrome, it should be noted that more than 90% of all genotype long QT syndrome patients have LQT1, LQT2 or LQT3 mutations (Splawski et al. 2000).

Genotype-phenotype correlation studies of patients with different LQT syndromes have revealed that different genetic subgroups tend to have different clinical presentations regarding T-wave morphology and arrhythmia triggers. Prognosis and response to therapy differs also between different genetic subgroups (Splawski et al. 2000, Moss et al. 1995, Zhang et al. 2000). Risk stratification schemes have also been developed according to QT interval lengthening, sex and the genotype (Priori et al. 2003).

The diagnosis of long QT syndrome based solely on length of QT-interval is sometimes difficult since there is a remarkable overlap with normal population QT-intervals and with long QT syndrome population QT-intervals (Vincent et al. 1992). Also, the QT-interval is inherently variable, changing in a given subject depending on heart rate, autonomic tone, age, use of different medication and presence of other medical conditions.

Already in 1970s autonomic nervous system bursts were described as a major factor in triggering syncope episodes in LQT subjects and beta-blockers were found to be very effective in inhibiting these symptoms (Schwartz et al. 1975). Many of the LQT syndrome patients experienced a syncope episode while exercising, swimming or with emotional arousal (Ackerman 1998). With beta-blockers, the 10-year mortality rate was reduced from 71% to 6% (Schwartz 1997, Eldar et al. 1992). Still, for the time being beta-blocker therapy seems to be the treatment of choice for all long QT patients whose condition warrant treatment i.e. their risk score is high enough to justify preventive treatment (Moss et al. 2000). The effect of the preventive function of beta blockers lowers in order LQT1-LQT2-LQT3 (Schwartz et al. 2001). Although policy with regard to treatment with beta-blockers is less clear cut for patients with LQT2 and LQT3 it is still considered correct to treat also these patients with this safe and reasonably effective medication.

If beta blocker treatment fails or the patient is considered to belong to a high risk group an ICD is indicated (Zareba et al. 2003).
2.8.2 Brugada syndrome

Brugada syndrome is characterized by typical coved ST-segment elevation in precordial chest leads of an 12-lead ECG (Brugada sign) and increased risk of potentially fatal ventricular arrhythmias, polymorphic ventricular tachycardia and/or ventricular fibrillation in patients with otherwise healthy hearts (Antzelevitch et al 2005). Typically, the syndrome manifests itself in adulthood, with a median age of sudden death of 41 ± 15 years. It is believed to be the one of the leading causes of death in men under age of 40 years, especially in south eastern Asia countries, where the syndrome is endemic (Nademanee 1997). In Europe the syndrome is much rarer and true incidence remains still unclear. In a hospital archive based ECG study in France the incidence of a definite Brugada 1 type ECG is 0.01% (Hermida et al. 2004). However, its true occurrence in the general population is likely to be less. There is also an association with atrial fibrillation and Brugada syndrome (Junttila et al. 2007).

The syndrome has a genetic background. Until now, only one gene (SCN5A) with several possible mutations has been associated with the syndrome (Chen et al. 1998). SCN5A mutations account for approximately 20% of Brugada syndrome cases. All mutations lead to loss-of-function in a sodium channel of cardiac muscle by affecting directly the protein or altering the trafficking of the protein to the cell membrane.

There are several modulating and precipitating factors that may elicit arrhythmias in Brugada syndrome or may unmask Brugada sign in otherwise normal 12-lead ECG. Pharmaceutical agents which have sodium channel blocking effects (class Ic), α-adrenergic agonists, β-adrenergic blockers, antidepressants, electrolyte disturbances, febrile state and cocaine abuse, among many other substances and states have been reported to be responsible for arrhythmias in otherwise silent form of the Brugada syndrome (Antzelevitch et al 2005).

Big issue since the discovery of the syndrome has been the risk stratification of individuals with this disease. Patients initially presenting with aborted sudden death are at high risk of SCD in the future (Brugada & Brugada 1992). Also, patients with Brugada sign in a native ECG are considered to carry a higher risk than patients who have Brugada sign only after drug challenge or when the sign is intermittent. A clear 8:1 male predominance in symptomatic individuals has been observed (Antzelevitch et al. 2002, Di Diego et al. 2002). Up until now there is no consensus even among experts about the role of electrophysiological testing in the risk stratifying of patients with the syndrome. The inducibility of sustained
ventricular tachyarrhythmias during EP testing has been used as a tool in risk stratification (Brugada et al. 2003). However, the value of the test is under scrutiny as some recent studies have reported also negative results (Eckardt et al. 2005). Currently an ICD is the only proven and effective treatment of the syndrome (Antzelevitch et al. 2005).

2.8.3 CPVT

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by physical or emotional stress induced polymorphic or bidirectional ventricular tachycardia carrying an increased risk of syncope or sudden cardiac death in patients with structurally normal hearts (Priori et al. 2002). Usually affected individuals have been young, from 2 to 36 years of age with a positive family history in approximately one third of cases. Pathognomonic feature with these patients is exercise dependent induction of ventricular arrhythmias beginning at a certain, individual heart rate. Until now, mutation in two genes, RyR2 and more rarely CASQ2, are responsible for this syndrome accounting for approximately 50% of the cases (Priori 2004). Beta blocking agents are usually effective and have been proposed the treatment. However, Priori showed that in spite of beta blockers these patients were at high risk of potentially fatal arrhythmias and strongly suggested ICD treatment, especially in RyR2 mutation positive males.

2.8.4 ARVC/D

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited heart muscle disease that occurs primarily in young and middle-aged individuals. It is characterized by ventricular arrhythmias, sudden death and heart failure occurring later in life (Corrado et al. 1997). Originally heart failure was believed to manifest only in the right ventricle but it has become evident that left ventricle can also be involved in the process. Although there exist standardized diagnostic criteria (McKenna et al. 1994), there is no diagnostic gold standard to verify the presence of the disease (Kies et al. 2006). There are proposed non-invasive and invasive tests including endomyocardial biopsy and magnetic resonance imaging to discover intramyocardial fat but it has become clear that one should not rely on any single criteria to arrive to diagnosis of ARVC/D. The prevalence of ARVC/D is approximately 1 in 5000 and it accounts for 5% of SCD of subjects less than 65 years old in the USA.
Risk stratification of individuals with the condition is problematic but several non-invasive, invasive and clinical features have been proposed. To date five genes have been linked to ARVC/D. There is no effective drug treatment for the syndrome but since exercise induced arrhythmias are common, beta blockers are usually indicated.

If the patient with ARVC/D is considered to belong to a high risk group, an ICD remains the only effective treatment (Priori et al. 2001).

### 2.8.5 Familial Atrial Fibrillation

AF is the most common sustained arrhythmia (Wolf et al. 1996). Usually it results from various pathological conditions including hypertension, chronic heart failure, valvular disorders, cardiomyopathies or endocrinological diseases such as hyperthyreosis. However, in 10-20% of AF patients, no underlying pathological mechanisms are found. These individuals are said to have “lone AF” or “idiopathic atrial fibrillation” (Patton et al. 2005). In this group of patients familial connection has been proposed. Several studies have delineated the prevalence of familial atrial fibrillation (Ellinor et al. 2005, Arnar et al. 2006). In the Framingham study the risk of having AF if both parents had AF at a young age was more than three fold (Fox et al. 2004). Until now, several mutations in many genes have been associated in familial AF. Mutations of these genes lead usually to early presentation of AF without underlying cause, usually before the age of 40.

### 2.9 Short QT syndrome

The first case of shorter than normal QT interval and sudden cardiac death was introduced in the literature less than a decade ago (Gussak et al. 2000). They also presented a connection of short QT interval and paroxysmal atrial fibrillation.

Before this an epidemiological relationship between short QT interval and increased risk of sudden death was presented (Algra et al. 1993). In a referral population with Holter recordings they observed that both prolonged and shortened mean QTc derived from 24 hour electrocardiography was related to a twofold risk of sudden death compared into intermediate QTc values (400-440 ms). Due to methodological problems in this study further conclusions about the correlation could not be drawn.
In 1997, Finnish investigators presented their data on QT-interval as a risk factor in a middle aged population (Karjalainen et al. 1997). They found an U-shaped risk profile among smokers with signs of cardiovascular disease; mortality was significantly higher in those subjects who had a shorter than normal QT-interval and who were smokers with cardiovascular disorder. This finding was unexpected and difficult to explain and was based on a small number of smoking subjects with heart disease. But it may explain partly why short QT-interval tended to increase risk in the Framingham study, as well (Goldberg et al. 1991).

These findings about epidemiological association of shorter than normal QT-interval and increased mortality remained unacknowledged until the early part of the 21st century when several families with short QT-interval and sudden cardiac death were described (Gaita et al. 2003).

2.9.1 Genetics of Short QT syndrome

Findings reported in 2004 suggested that short QT syndrome is a genetically determined heterogeneous disease similar to long QT syndrome. In two of the three families with short QT syndrome studied by Brugada, two different missense mutations were discovered, revealing the same amino acid change (Asn588→Lys) in the S5-P loop region of the cardiac IKr channel KCNH2 (HERG) (Brugada et al. 2004). As a result of this gain-of-function mutation there was a dramatic increase in IKr, leading to significant shortening of action potential duration and refractoriness (SQT-1). Interestingly, mutations of the same gene resulting in “loss of function” of the IKr channel cause long QT-2 syndrome (Curran et al. 1995).

Further, an elderly man was found with idiopathic ventricular fibrillation. His QT interval was 290 ms and he was identified to have a g919c substitution in the KCNQ1 gene encoding the K+ channel KvLQT1 (SQT-2) (Bellocq et al. 2004). Later another missense mutation leading to a gain of function of the same ion channel was found in a baby girl born prematurely with atrial fibrillation, bradycardia and short QT interval (Hong et al. 2005b). As a mirror image for SQT-2 it is known that loss of function of KCNQ1 gene cause LQT-1 syndrome.

In 2005, a third genetic mutation was found in an Italian family with SQTS (Priori et al. 2005). The defect was found in the gene encoding for the inwardly rectifying Kir2.1 channel. The affected members had a G514A substitution in Kir2.1 (KCNJ2) gene, resulting in a change from aspartic acid to asparagine at position 172 (SQT-3). The phenotype of this mutation is somewhat different from
SQT-1 and SQT-2 with peculiar asymmetrical T-waves. If the result of mutation of the this gene is loss-of-function it will cause so-called Andersen syndrome with skeletal abnormalities, developmental dysmorphology and increased risk for ventricular tachycardia by prolonging the QT interval (Andersen et al. 1971, Plaster et al. 2001).

The first observation that loss-of-function in a calcium channel might be responsible for a familial sudden cardiac death syndrome came from Antzelevitch who reported that of loss-of-function mutations in genes encoding the $\alpha_1$ (SQT-4) and $\beta_{2b}$-subunits (SQT-5) of the L-type calcium channel are to be associated with a familial sudden death syndrome in which a Brugada syndrome phenotype is combined with shorter-than-normal QT intervals (Antzelevitch et al. 2007).

All different mutations in patients with SQTS identified to date have also been investigated in vitro. Gain of function of potassium channels is mainly due to a large increase in potassium current with failure to rectify at physiological membrane potentials, or change in action towards an earlier phase of action potential. This leads to abbreviation of action potential and refractoriness; lead elements in re-entry mechanism behind many tachyarrhythmias, being also the main reason for increased risk to atrial and ventricular fibrillation seen in SQTS (Priori et al. 2005, Wolpert et al. 2005b).

To conclude molecular genetics of SQTS, it is interesting that four of those genes are the same as those involved in LQTS; however mutations leading to SQTS have the net effect of increasing rather than decreasing repolarization forces. Currently SQT-1, SQT-3, SQT-4 and SQT-5 have been reported to occur in familial cases and SQT-2 is reported only in a sporadic setting. In familial cases an autosomal dominant mode of inheritance is suggested since the disease is usually seen in each generation of the family and in both sexes. Obviously, genetic heterogeneity prevails since as in LQTS, no genetic mutation can be found in many patients with SQTS.

2.9.2 ECG in SQTS

Apart from constantly short QT interval (< 340 ms) most patients with short QT syndrome present with tall, symmetrical and peaked precordial T-waves taking off immediately from the S-deflection of the QRS complex, and absent or nearly absent ST segment (Gaita et al 2003)(see also Figure 2 in page 41). However, this is not observed in all patients. An Italian group described a novel variant of short QT syndrome (SQT3). These patients present with tall and clearly asymmetrical
T-waves and the QT interval is shorter than normal but not as short as in patients with mutation in SQT-1 (KCNH2, HERG) (Priori et al. 2005).

Although in the majority of cases QT interval has been extremely short it has also been proposed that the definition of short QT syndrome should be less restrictive in terms of defining short QT interval to prevent under diagnosis of some cases of short QT syndrome (Maury et al. 2005).

A common feature in patients with short QT syndrome is the lack of adaptation of the QT interval to heart rate (Wolpert et al. 2005a). Compared to normal subjects they demonstrated that there was only a shallow slope of the linear decrease of QT interval with increasing heart rate making this unique feature an additional diagnostic prospect in the diagnosis of the short QT syndrome. Results of a very recent Holter study indicate that SQTS patients have higher diurnal heart rates compared to healthy controls and their T waves were also higher and more symmetrical than in control subjects (Extramiana et al. 2008).

2.9.3 Clinical Electrophysiology of short QT syndrome patients

Given the malignant nature of the disease most of the symptomatic patients have undergone electrophysiological testing. During programmed atrial and ventricular stimulation extremely short atrial (AERP 120–180 ms, mean 143 ± 14 ms) and ventricular effective refractory periods (VERP 120–180 ms, mean 148 ± 11 ms) were discovered and ventricular fibrillation was inducible in most of the patients (8 out of 9) by programmed ventricular stimulation (Borggrefe et al. 2005). In many cases VF was induced by mechanical instrumentation of the heart which is in general a very uncommon event. This points to increased excitability or vulnerability of the myocardium of the patients with short QT syndrome. Interestingly, same finding has been reported in other species having short QT intervals. Many marsupials have short effective refractory periods and in an electrophysiological study, inducibility of ventricular fibrillation was observed in most of the kangaroos during the manipulation of the left ventricle (QTc intervals 262 ± 50 ms) (O’Rourke et al. 1986). Of note, in one family with short QT syndrome, atrial fibrillation was readily inducible in most of the members, also stressing increased atrial vulnerability (Hong et al. 2005a).
2.9.4 Clinical presentation

As is the case with a long QT syndrome, clinical presentation of SQTS patients is highly heterogeneous, with a remarkable variation of the symptoms, clinical course and outcome between different families and even among members of the same family (Gaita et al. 2003). In most patients with a short QT syndrome, the risk of syncope or sudden cardiac death is considered to be high. Furthermore, atrial fibrillation at different ages seems to be surprisingly common in these individuals. The age distribution in patients with syncope, aborted sudden death or SCD wide, from infancy to old ages; a median being 39 years (Borggrefe et al. 2005).

Sudden infant death syndrome (SIDS) is also considered to be one of the possible manifestations of the short QT syndrome.

The reported number of patients with short QT syndrome is still very small and data comes mainly from a couple of European families. Published data about the incidence and significance of short QT syndrome is also limited but recent reports have indicated that a short QT interval is still a rare finding and may not always indicate an increased risk for cardiac mortality (Gallagher et al. 2006, Reinig & Engel 2007, Moriya et al. 2007). However, in a recent study of 28 patients with idiopathic ventricular fibrillation it was found that shorter-than-usual QTc values are commonly seen in male patients with idiopathic VF. Still, major overlap occurred with those patients who had short QTc values and with healthy controls. In this study, short QTc values were not that rare among healthy, young adults, especially at slow heart rates (Viskin et al. 2004).

2.10 Therapy of short QT syndrome

Since the risk of dying suddenly is considered to be high in patients with short QT syndrome and risk stratification is not fully established, an ICD has been proposed as the therapy of choice for majority of the patients (Schimpf et al. 2005). However, ICD treatment sometimes carries significant problems. Since implantation of an ICD in young children is problematic, a pharmacologic solution would also be needed. Until now, most of the patients published in the literature have received an ICD but there are also reports of beneficial drug effects in the treatment of short QT syndrome (Gaita et al. 2004).
2.10.1 Drug treatment of patients with short QT syndrome

Although an ICD is the first choice in the treatment of most SQT patients, antiarrhythmic drug therapy may offer a potential alternative or at least adjunct therapy, especially in children or in people who have declined the offered device. Several anti-arrhythmic agents have been tested in patients with KCNH2 (HERG) mutations (SQT-1), both in vivo and in vitro (Borggrefe et al. 2005).

Since SQTS is caused by gain of function mutation of IKr, sotalol as an IKr blocker was initially studied along with ibutilide which has the same kind of properties in IKr channel. Both drugs failed to prolong QT interval (Gaita et al. 2004). Only quinidine, and also in lesser extent, disopyramide have been demonstrated to be effective in restoring QT interval, prolonging the ventricular effective refractory period and normalizing the heart rate/QT interval relationship in exercise (Gaita et al. 2004, McPate et al. 2006). Furthermore, quinidine rendered ventricular tachyarrhythmias noninducible during an electrophysiological study in patients with HERG mutation (Wolpert et al. 2005a). There are two potential reasons why both quinidine and disopyramide are beneficial in IKr mutations but more specific blockers such as sotalol and ibutilide are not. First, quinidine and disopyramide have a higher affinity for the open state of the IKr channel than specific IKr blockers and secondly, both quinidine and disopyramide also potentially block IKs and If which both have a role in the genesis of repolarization currents (Schimpf et al. 2007).

2.10.2 ICD therapy

Episodes of ventricular fibrillation in patients with short QT syndrome can be effectively treated with implantable cardioverter defibrillators (Schimpf et al. 2003, Schimpf et al. 2005). However, inappropriate therapies delivered by the ICD seem to be very common in patients with SQT syndrome. With standard programming of the devices, patients are at risk of inappropriate shocks for several reasons. Oversensing of short coupled and tall, peaked T waves may cause inappropriate shocks due to double counting and meticulous programming of the ICD device is needed (Schimpf et al. 2003). Modern device algorithms that permit reduced sensitivity and programmable decay after the R-wave may reduce the possibility of inappropriate therapy. As a majority of the patients are young and active and otherwise in good health, sinus tachycardia may cause problems in
these patients as well as atrial fibrillation, which seems to be quite common in SQT syndrome.
3 Purpose of the present study

After finding the first subject in Finland with SQTS we designed a complete study protocol to evaluate clinical findings, epidemiology and prevalence of individuals with short QT interval in an ECG. We were also interested to identify ECG and ambulatory ECG markers that could define the prognosis of the patients with the syndrome.

The specific aims of the study were:

1. To evaluate ECG morphology, clinical presentation and the occurrence of sudden death in a relatively large group of patients with short QT syndrome collected from different European centres. We also studied the prevalence of genetic mutations and available therapies for the syndrome.
2. To assess prevalence and prognostic importance of shorter-than-normal QT intervals in a large Finnish general population with a very long follow up.
3. To compare diurnal QT dynamics of patients with short QT syndrome with their age and sex matched controls.
4. To assess prognostic determinants of 12-lead ECG taken from symptomatic and asymptomatic individuals with short QT intervals.
4 Study populations

4.1 Finnish family with a short QT syndrome

The idea for this study came after encountering a young man who experienced aborted sudden cardiac death whilst playing a computer game. His 12-lead ECG was otherwise normal but had an unusually short QT interval (QT < 300 ms) and very tall, peaked T waves (Fig. 2). The father (53 years) of this 18 years old man complained of palpitations during exercise and presented runs of polymorphic ventricular tachycardia on a bicycle exercise test. The grandfather of the proband (80 years) had complained of disturbing palpitations when young causing him early retirement from his profession as a farmer (family D in figure 3). Thorough clinical cardiac examinations including echocardiography and coronary angiogram were normal in each case. Genetic screening did not reveal any known mutations causing SQTS. An electrophysiological study was negative for induction atrial fibrillation, ventricular tachycardia or ventricular fibrillation. Also, both atrial and ventricular refractory periods of the proband and his father were not as short as reported in other cases. The proband was implanted with an ICD but his father refused recommended therapy. Grandfather also declined offered EP study.

Fig. 2. ECG of the proband. Note tall, peaked T waves and virtually absent ST segment. QT < 300 ms. Paper speed 25mm/s.

After almost four years of follow up all three family members with short QT syndrome are well, without any occurrence of significant tachyarrhythmias.
4.2 Study population I

The patients of the first study comprised 29 individuals belonging to 8 different families from several European countries. 4 of the patients were labelled as sporadic cases since there was no evidence of short QT intervals in the immediate family of the victims although in one family there was a suspected sudden death at the age of 60. In total, in the studied families there were 12 sudden deaths without ECG documentation. Although their association with SQT could be hypothesized, they were not included in the study.

Fig. 3. Family trees of eight affected families and of the four sporadic patients are shown. Family D corresponds to the Finnish family.

4.3 Study population II

The study population in the second study composed of a cohort of 10 957 men and women aged 30 to 59 years (mean age 44 ± 8.4 years) drawn from 12 different geographic areas of Finland participating in the Social Insurance Institution’s Coronary heart Disease Study (Reunanen et al. 1983). QT interval could be measured reliably in 10 822 subjects who comprised the present study group. The participation rate was very high (> 90%) and all invited individuals
were considered to be a good geographic representation of the people of that age in Finland. Also the range of occupations of the study participants was similar to that of the Finnish population at that time.

All the initial examinations were performed between 1966 to 1972 and the follow up was completed by 2005 when mortality and other parameters of prognosis were assessed.

4.4 Study population III

In the third study the study population comprised three male individuals from a single family with short QT syndrome (Finnish family, see above). All three subjects had abnormally short QTc intervals < 320 ms at baseline. The proband subject was an 18 year old male who had experienced aborted sudden death. His father (53 years) complained of palpitations during exercise and was found to have runs of polymorphic ventricular tachycardia during exercise testing. Grandfather of the proband (80 years) had complained of disturbing palpitations when young but was now asymptomatic apart from paroxysmal atrial fibrillation. The control population comprised genotyped unaffected family members of a long QT patient database. For each study patient we took three age matched males as the control subjects. These 9 family members with the mean age of 41 ± 15 years and with normal baseline QTc intervals were tested and found not to have the currently known long QT syndrome causing mutations of the family.

4.5 Study population IV

In the fourth study we collected ECG’s of short QT syndrome patients from different countries obtained from physicians known to have such patients. A strict criterion for entry to the study was aborted sudden cardiac death or documented sustained VT and/or VF. In this study we did not include individuals with short QT syndrome and unwitnessed syncope or other episodes that were not considered to be life threatening since the aim of the study was to compare ECG’s from patients with serious events to those who have survived for decades (short QT population from study II) without any episodes of ventricular arrhythmias or signs of excessive mortality.

We performed a Europe wide survey of SQTS subjects with severe symptoms and were able to collect 10 probands (39 ± 19 years) with documented VT or aborted SCD. From the general population we found 12 subjects with SQT
interval (QTc ≤ 320 ms) and without any serious events, even after a very long follow up of 29 ± 10 years. The control population for SQTS subjects was age and gender matched individuals from a healthy cohort of medical students and volunteer middle-aged subjects without overt cardiovascular diseases (Pietilä et al. 2002). The control subject number for each SQTS subject was doubled (n = 20).
5 Study protocols and methods

5.1 Study I. Clinical findings and diagnostic-therapeutic implications in SQTS

In the first study the aim was to report as extensively as possible clinical presentation, occurrence of sudden infant death, diagnostic criteria, and results of available therapies in the largest group of patients with short QT syndrome studied so far. A detailed clinical work up was performed including careful history, physical examination, 12-lead ECG, exercise stress testing, echocardiogram and cardiac magnetic resonance imaging (MRI) to rule out structural abnormalities of the heart. Blood samples were taken to exclude electrolyte abnormalities and to carry out genetic testing. The median follow-up of surviving patients was 23 month, range 9–49months.

QT interval was measured at a speed of 25 or 50mm/sec and calculated with a magnification of 200% in V2 lead using routine tangential method. QT, QTc and QTp (QTpredicted) values were calculated from 12-lead ECG but QT calculations during the stress test were analyzed using Framingham linear regression formula for better performance in higher heart rates. A QT/QTpredicted value of < 80% based on Rautaharju formula was considered abnormally short value. Eighteen patients underwent a detailed electrophysiological study where both atrial and ventricular refractoriness were studied and inducibility assessed. An ICD therapy was proposed all patients except young children. Those children and adults who were not offered or who declined ICD therapy were recommended to begin quinidine which has already been proved to prolong QT interval in a previous study, especially in patients with a HERG mutation (Gaita et al 2004).

5.2 Study II. Prevalence and prognosis of short QT intervals in Finland

In the second study the participants completed a detailed questionnaire that included questions on health habits, known diseases and any current medication before the examination by study doctor and nurses. Detailed reports about drug usage were obtained and particular attention was paid to the use of cardiac medication. ECG recordings with a QT interval of less than 360 ms were reanalysed after a computer search and the rate corrected QT interval was
analyzed using three different correction methods. The standard Bazett’s equation (QTc) was used but also the Fridericia (QTfc) method and the nomogram formula (QTnc) were also used because they are known to perform better at low and high heart rates.

QT intervals were measured from the original paper recordings using the average value of two consecutive cycles in leads II or V2. A standard tangential method was used to delineate the end of the T-wave.

In this study, individuals with QTc, QTnc and QTfc of less than 320 ms were considered to have very short QT interval and those with QT interval less than 340 ms were classified as to short QT interval group.

All ECG analysis were performed blind to the follow-up data. The mean follow up was 29 ± 10 years and end points were total mortality, cardiovascular mortality and coronary mortality until the end of 2005. Death certificates and cause-of-death registers were used to assess mortality statistics and specific causes of death during the follow-up period. Detailed follow-up data was available for more than 98% of the study subjects. Mode of death was classified for each deceased individual. Usage of cardiovascular medication was also monitored during the observation period.

5.3 Study III. Transmural dispersion of repolarization in patients with SQTS

In the third study all patients and control subjects underwent one 24 hour ECG recording. The tapes were initially analyzed with a Marquette 8000 Holter analysis system and subsequently ECG data was transferred to a personal computer for further analysis and for the measurement of the QT and TPE (Tpeak–Tend) intervals. The measured QT and TPE intervals as well as computed TPE/QT index were analyzed by plotting all measured values against preceding RR intervals. Maximal diurnal QT, TPE and TPE/QT intervals were measured and QT intervals were also analyzed at stable heart rates. In this study maximal QT peak, QT and TPE are recorded at different RR intervals with steps of 100 ms (from 500 ms to 1100 ms). To analyze patients and control subjects capacity to change their QT end and TPE length at different RR intervals, the difference between maximal QT interval and rate-adapted QT interval as well as the difference between maximal TPE and median TPE is presented. Individual QT/RR slopes for maximal and median values were also studied. Baseline ECG
characteristics were analyzed in lead II from 12 lead ECG and adjusted for heart rate using the Bazett’s formula.

5.4 Study IV. Differences in repolarization between symptomatic SQTS patients and asymptomatic individuals with short QT interval

In the fourth study we measured from a standard 12-lead ECG (paper speed 25mm/s or 50mm/s, gain 10mm/mV) PR-, QRS-, QTc-, QTf-, Jpoint–Tpeak-, Tpeak–Tend- and R–R intervals. T-, R- and S-wave amplitudes were also calculated from the lead with the highest T-wave amplitude. Additionally, TPE/QT ratio was measured for the determination of transmural dispersion of repolarization. All interval measurements were also corrected using Bazett’s and Fridericia’s equations to eliminate possible influence of the heart rate.

5.5 Statistical analysis

Continuous values in all studies are presented as mean (SD or as mean ± SD) and when presented, categorical variables as prevalences. In studies I and II Kaplan-Meier estimates were used for either cumulative freedom from cardiac arrest (study I) or for overall mortality (study II). Also, in these two studies hazard ratios and 95% CIs of mortality were computed with Cox proportional hazard models. In study II models were first adjusted for age and sex and thereafter for other known covariates that were selected on the prior knowledge of association with cardiovascular and overall mortality, such as age, cholesterol, heart rate and blood pressure which were added as continuous variables and sex, smoking and cardiovascular health at baseline as categorical variables.

In the epidemiological study (study II) we also used κ-coefficient factor for assessing agreement between different rate-correction formulae. Pearson correlation coefficient was used to assess the concordance of initial measurements in 1966 to 1972 with recent measurements by an experienced cardiologist (study II). In study III, the comparisons between 2 study groups were performed using Mann-Whitney U test. Two tailed p < 0.05 was considered significant in all studies where this analysis was performed. In study IV the comparison between groups was performed by one way ANOVA Bonferroni Post Hoc analysis.
6 Results of the studies

6.1 Clinical findings and diagnostic-therapeutic implications in SQTS (study I)

Of the 29 patients included in study I, 21 were males and eight females. The median age at diagnosis was 30 years. 62% of the patients were symptomatic when entering the study. 31% (nine patients) had a history of cardiac arrest, six of whom were resuscitated. In eight of these nine patients cardiac arrest was the first clinical presentation and it occurred from 4 months to 62 years of age. Less commonly (seven patients) the first presentation was syncope. Nine patients had atrial fibrillation or flutter. Frequent ventricular premature beats were documented in five patients.

In all ECG recordings QT interval was clearly abnormally short. Absolute QT interval was less or equal to 320 ms in all cases and when corrected according to Bazett’s formula it was still less than 340 ms in every patient. QT/QTpredicted was always shorter than 80% indicating remarkably short QT interval. Most of the ECGs showed typical findings in patients with short QT syndrome, narrow, tall and peaked T-waves and virtually absent ST segment. T-wave characteristics, sex or length of the QT interval did not have any relationship regarding the prognosis of the patients. Thirteen patients had an exercise test. Typical finding in all patients was lack of shortening of the QT interval with increasing heart rates. Electrophysiological testing using standard protocol revealed uniformly short refractory period both in the atrial and ventricular level between 120–180 ms and 140–180 ms, respectively. Unusually, in 11 out of eighteen patients ventricular fibrillation was induced. Inducibility did not have prognostic significance for serious cardiac events since sensitivity of an electrophysiological study was only 50%. Genetic analysis was performed in eight affected families and in two of the four sporadic patients. HERG mutation (encoding for IKr) was found in two families. However, most of the families and half of the sporadic patients tested negative for known mutations.

The therapeutic approach to the patients included ICD in 14 of them. 12 refused the implant and 2 were considered to be too young for the treatment. Three patients died before therapeutic considerations were possible. 10 patients were placed on hydroquinidine. In particular those patients with the HERG mutation seemed to have a beneficial response to the drug treatment. In patients
with HERG mutation, an electrophysiological study performed during therapy showed a mean ERP increase from $150 \pm 2$ ms to a mean of $200 \pm 21$ ms and rendered the patients also noninducible. In those patients without HERG mutation, the QTc increment was much more modest, from $307 \pm 22$ to $352 \pm 41$ ms.

There were five aborted sudden deaths of young children in studied families. However, two babies died without ECG documentation and were not included in to the study. Two of the three remaining children were HERG positive; one baby was not tested. One child received an ICD.

### 6.2 Prevalence and prognosis of short QT intervals in Finland (II)

In the epidemiological study (II) we found 11 subjects from the population of 10 822 individuals who had QTc < 320 ms (0.10%). 9 (0.08%) and 7 (0.06%) of the individuals had QTfc (heart rate correction according to Fridericia equation) and QTnc (heart rate correction according to nomogram method) < 320 ms, respectively. If we used a less stringent cut off value for short QT interval (< 340 ms) we were able to identify 43 subjects (0.4%) when analyzed according to Bazett’s equation and 33 of 10 822 (0.3%) had QTfc less than 340 ms. Use of the nomogram method revealed 34 (0.3%) of the subjects with QTnc < 340 ms.

The overall $\kappa$-score for defining the short QT interval with three different equation formulas was 0.85 for short QT interval (< 340 ms) and 0.56 for very short QT interval (< 320 ms) (Table 2).

<table>
<thead>
<tr>
<th>Rate-corrected QT interval</th>
<th>QTc, n</th>
<th>QTnc, n</th>
<th>QTfc,n</th>
<th>$\kappa$-score</th>
<th>QTc</th>
<th>QTnc</th>
<th>QTfc</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 320 ms</td>
<td>§§</td>
<td>5</td>
<td>5</td>
<td>0.50 (0.23–0.77)</td>
<td>0.56 (0.28–0.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc</td>
<td>5</td>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTnc</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>0.62 (0.35–0.90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTfc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 340 ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc</td>
<td>43</td>
<td>32</td>
<td>30</td>
<td>0.83 (0.74–0.92)</td>
<td>0.79 (0.69–0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTnc</td>
<td>32</td>
<td>34</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTfc</td>
<td>30</td>
<td>30</td>
<td>33</td>
<td>0.90 (0.82–0.97)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The 95% CIs of the $\kappa$-score are given in parenthesis.
As expected, women seemed to have significantly higher cut off values for short QT interval when 2 and 3 SD of means of the corrected QT intervals were used (Table 3). Accordingly, the proportion of women who had short QT interval (QTc < 360 ms) was clearly less than that of the men, 1.3% and 4.4%, respectively.

Table 3. Mean values and 2 and 3 SD: s of QT intervals for men and women separately.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>2 SD</th>
<th>3 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTfc</td>
<td>391</td>
<td>347–435</td>
<td>324–457</td>
</tr>
<tr>
<td>QTc</td>
<td>402</td>
<td>348–456</td>
<td>322–482</td>
</tr>
<tr>
<td>QTnc</td>
<td>394</td>
<td>351–436</td>
<td>330–457</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTfc</td>
<td>398</td>
<td>353–442</td>
<td>331–464</td>
</tr>
<tr>
<td>QTc</td>
<td>415</td>
<td>364–467</td>
<td>338–493</td>
</tr>
<tr>
<td>QTnc</td>
<td>401</td>
<td>360–442</td>
<td>340–462</td>
</tr>
</tbody>
</table>

Values are milliseconds.

In addition to gender difference, subjects with short QT intervals were younger and their heart rate and blood pressure were lower than in those with normal QT intervals.

The prognosis of the subjects with a short QT interval was not worse than that of subjects with a normal QT interval (Figures 4 and 5). There were no differences in all cause mortality between the 2 groups, even after adjustments to all possible confounding factors. In fact cardiovascular mortality seemed to be lower in individuals with shorter QT intervals and analysis of specific causes of deaths during a very long follow up did not reveal any sudden deaths.

We also reviewed the medical records of those subjects whose QTfc was < 340 ms and we were not able to find any hospital visits due to syncope, serious ventricular tachyarrhythmias, or even atrial fibrillation. Interestingly, none of the already dead individuals or those still living with short QT interval had received reimbursement for antiarrhythmic medication.
Fig. 4. Kaplan-Meier curves for mortality in subjects with different QTc intervals. Dotted line represents individuals with a short QTc interval; solid line individuals with a normal QTc. Pts indicate number of subjects.

Fig. 5. Kaplan-Meier curves for mortality in subjects with different QTfc intervals. Dotted line represents individuals with a short QTfc interval; solid lines, individuals with a normal QTfc. Pts indicate number of subjects.
6.3 Transmural dispersion of repolarization in patients with SQTS (III)

In the study III we compared the behaviour of electrocardiographic analogue of TDR in three symptomatic SQTS patients and in their nine healthy controls. Figure 6 illustrates that there was a great difference in study groups’ capacity to change the TPE intervals from median to abrupt maximal values. Another interesting finding was that diurnal average of TPE/QT ratio (0.28 ± 0.03) was significantly and constantly increased in SQT patients compared to control subjects (0.21 ± 0.02) (Figure 7). We also noticed that during night, average QT intervals prolonged only modestly in SQTS patients compared to control subjects (data not shown).
Fig. 6. Maximal T-wave peak to T-wave end (TPE) intervals (triangles, mean ± SEM) and median TPE intervals (squares) at specified heart rates in control subjects (broken lines) and in short QT syndrome patients (solid lines) during 24-h daily activities.

Fig. 7. Median T-wave peak to T-wave end (TPE) interval divided by the corresponding QT end interval (mean ± SEM) at specified heart rates in short QT syndrome patients (closed symbols) and in control subjects (open symbols).
6.4 Differences in repolarization between symptomatic SQTS patients and asymptomatic individuals with short QT interval (IV)

In the fourth study (IV) we compared the electrocardiograms between the symptomatic SQTS patients and subjects with a short QT interval but without documented arrhythmias or sudden cardiac death. Major ECG abnormality in patients with short QT syndrome was the Jpoint–Tpeak interval, which was significantly shorter ($p < 0.001$) in SQTS ($101 \pm 18$ ms, range from 80 to 120 ms) compared to subjects with asymptomatic short QT interval ($184 \pm 27$ ms, range from 150 to 240 ms) or matched controls ($p < 0.001$) with normal ECG ($203 \pm 33$ ms, range from 160 to 280 ms). This difference in Jpoint–Tpeak interval between SQTS patients and both control groups was highly significant ($p < 0.001$), resulting in 100% accuracy in differentiating the SQTS patients from the others (Figure 8). Also, the heart rate was significantly higher among SQTS patients than both of the control groups ($p < 0.001$).

Fig. 8. Distribution of uncorrected Jpoint–Tpeak-intervals between study groups. Bars represent mean and corresponding 95% confidence intervals.
Tpeak–Tendc/QTc ratio was also significantly higher in SQTS patients compared to short QT subjects (p = 0.004) and controls with normal QT interval (p = 0.001) but did not differ between two control groups. The corrected and uncorrected Jpoint–Tend interval differed also significantly between SQTS patients and controls (p < 0.001 for both).
7 Discussion

7.1 Clinical, electrophysiological and molecular genetic features of a group of patients with SQTS collected from Europe

As with many other novel inherited arrhythmogenic syndromes, the first observational study (1) presents obviously the most seriously symptomatic subjects and dramatic cases with the syndrome (Giustetto et al. 2006). Because up to present time most of the identified cases have been spread around Europe and rest of the world, it would have been very difficult to plan a systematic prospective study. Therefore we set out to study clinical characteristics, electrocardiology, invasive electrophysiology and genetics of already known 29 patients, 25 of them belonging to eight families and four sporadic cases.

Regarding symptoms, cardiac arrest was surprisingly common. Nine patients (31%) had a history of cardiac arrest whereas for example in patients with long QT syndrome the mortality seems to be less (13% in 28 years) but appears to depend greatly on the mutation in question (Priori et al. 2003). Although age distribution of cardiac arrest was wide, ranging from 4 months to 62 years, the syndrome seems to manifest itself most commonly during early adulthood. The same finding has been observed with Brugada syndrome (Nademenee et al. 1997) and long QT syndrome (Locati et al. 1998). Due to the manifestation of the syndrome in infancy it is believed that short QT syndrome may also be linked to sudden infant death syndrome (SIDS) together with other channelopathies (Perez Riera et al. 2005). Less serious symptoms than cardiac arrest were palpitations, atrial or ventricular extrasystoles and atrial fibrillation/flutter which were seen frequently in seven (24%) patients. Atrial fibrillation was also observed in young patients and should presumably be related to the presence of short ERPs in the atria.

In this study we were not able to find any correlation between the T-wave amplitude and the prognosis of the patient, as cardiac arrest was observed both in subjects with typical high and peaked T-waves and in the subjects without high, peaked T-waves. This finding contradicts the results of study IV where we focused more on specific characteristics of 12-lead ECG. Nor did the length of the QT interval influence the occurrence of cardiac arrest although it would be reasonable to suppose that shorter QTc would predispose one to a greater risk for serious ventricular arrhythmias (Algra et al 1993, Priori et al 2005).
Less than half of the patients had an exercise test. Physiological response of the heart rate with increasing work load was observed but a uniform finding was also the lack of adaptation of QT interval with increasing heart rates. This lack of QT shortening with increasing heart rates seems to be so clear that it could even be used as a diagnostic tool for assessing patients with shorter than normal QT intervals. However, we did not test the possible favourable effect of drugs that are known to lengthen the repolarization but in an earlier study it was shown that quinidine rendered HR/QT relationship closer to the normal during an exercise test (Wolpert et al. 2005).

Out of eighteen patients who had an electrophysiological study, ventricular fibrillation was induced in eleven of them (61%). However, as only three patients out of six with documented ventricular fibrillation were induced it does not allow us to use an EP study for risk stratification of these patients with SQTS (sensitivity 50%).

There exist two possible explanations for the easy inducibility of these patients. First, an EP study revealed extremely short refractory periods at both atrial and ventricular level. Since it is well known that short refractory periods cause a reduction in the wavelength (the product of refractory period and conduction velocity), this might explain atrial and ventricular vulnerability to arrhythmias. Secondly, experimental data supports the theory that heterogeneous shortening of action potentials in different areas of ventricular wall and in different cell types creates an increase in ventricular dispersion of repolarization and promotes VF in short QT conditions (Extramiana & Antzelevitch 2004).

Until now, mutations in four different genes have been linked to the short QT syndrome. Two separate missense mutations in KCNH2 (HERG), the gene encoding for IKr, the rapidly activating delayed rectifier potassium channel, causing gain of function in the channel (Brugada et al. 2004), two mutations in KCNQ1 (KvLQT1), causing gain of function in IKs, the slowly activating delayed rectifier potassium channel (Bellocq et al. 2004, Hong et al. 2005b) and a mutation in KCNJ (Kir2.1) causing a mutation in Ik1 (Priori et al. 2005). Later a mutation in calcium signalling genes was discovered. However, it seems that the prevalence of these mutations is not high since HERG mutation was found only in two families described in this study and neither of the two remaining mutations were present in the studied families or in sporadic cases.

Since genotyping was possible only in two families and the incidence of sudden death was high in all families it is reasonable to assume, that at least today genetic screening does not help in identifying high-risk patients.
At the time of the study, all patients having short QT syndrome were considered to be at high risk of sudden death. Therefore an ICD was offered to all patients apart from 2 very young children. 10 patients refused offered therapy.

Most of the patients who refused an ICD were placed on hydroquinidine which had already been proved to prolong the QT interval in previous studies (Gaita et al. 2004, Wolpert et al. 2005). Although theoretically oral disopyramide may be a suitable alternative to quinidine for prolonging the QT interval and ventricular effective refractory period in patients with short QT syndrome (especially SQT1 = HERG) it was not used in this study. Of the 10 patients who received hydroquinidine 5 had HERG mutation. These patients had clearly a higher increase in QT interval and effective refractory period than those without HERG mutation and these patients also rendered noninducible for ventricular tachyarrhythmias. These beneficial effects were less prominent in HERG negative patients. On the basis of these results it could be speculated that quinidine testing might prove useful in assessing potential responders to quinidine therapy and a clear prolongation of the QT interval might suggest a HERG mutation.

According to the results of the study I one can easily come to a conclusion that short QT syndrome or even the presence of short QT interval in a 12 –lead ECG is a life threatening condition. However, at that time there was no information on the prevalence of short QT in the general population and it was possible that known cases presented only the tip of an iceberg of the individuals with shorter than normal QT intervals. This was the reason why we set out to solve the problem and study the prevalence and prognostic significance of short QT intervals in a general population (study II).

### 7.2 Prevalence and prognostic significance of a short QT interval in a middle-aged Finnish population

The main finding of study II was that a short QT interval does not mean an increased risk of cardiovascular mortality or sudden death even during a very long follow-up in a middle-aged, general population. We could not even record excess hospitalisations or usage of antiarrhythmic medication in this population. Contrary to recent belief that short QT interval as a sole determinant of abnormal ventricular repolarization is a life threatening condition we were able to show that middle-aged individuals with short QT interval seem to live a normal life span. Furthermore, we emphasize that not all subjects with short QT interval belong to short QT syndrome. This finding concurs with other recent observations.
(Gallagher et al. 2006, Viskin et al. 2004). Another important finding from our study is that the prevalence of QT < 320 ms based on corrected QT interval is low (11 of 10822 subjects or 0.10% when corrected according to Bazett’s formula).

In his study of over 12,000 subjects, Gallagher found only 4 subjects with QTc ≤ than 340 ms and the shortest QTc they encountered was 335 ms. Study population comprised young, healthy employees of Italian Armed Forces and therefore could not be considered as a general population. However, their prognosis was excellent since there was not a single case of sudden death that occurred among these subjects at 7.9 ± 4.5 years after the registration of the qualifying ECG.

Viskin studied 28 patients with idiopathic VF. Control group comprised of 270 healthy controls. He was able to show that shorter than normal QT values are commonly seen in male patients with idiopathic VF but they also showed that short QT values are not rare among healthy adults, especially at slow heart rates.

Reinig and Engel studied a large computerized ECG database in a referral hospital. They were unable to find one patient among a population > 100,000 patients with true QTc of < 300 ms and only one patient with QTc < 350 ms (Reinig & Engel 2007). Again, this population is highly selected including only hospital based subjects which might carry several diseases or medications affecting the repolarization of the myocardium and hence prolonging the QT interval. Furthermore, they did not present any data on the prognosis of the cases with different QT intervals.

### 7.2.1 Measurement and definition of short QT interval

The relationship between duration of cellular action potentials and the QT interval recorded at the body surface is very complex and as a result, the QT interval is difficult to measure with precision; even for cardiologists or arrhythmia specialists (Viskin et al. 2005). One could speculate about the validity and concordance of the initial measurements made by technicians in late 60’s and those made by an experienced cardiologist during this study. To overcome this, we took for a measurement a sample of 366 random ECG’s including 54 with normal QTc in the original measurements. A relatively good correlation was observed between these measurements (Pearson correlation coefficient 0.78, p < 0.0001). Importantly to the credibility of the measurements none of the 54 subjects with a QTc interval > 360 ms in the initial measurement by fairly non experienced person was reclassified as having a short QTc (< 340 ms).
In this study we used QT intervals < 320 ms for very short and < 340 ms for short QT representing clearly abnormally short QT intervals in the present population (3.3 SD and 2.4 SD of the mean respectively). Furthermore, we wanted to analyze also subjects with QT interval > 340 ms but < 360 ms to include more women in the analysis. Based on different analysis, these subjects could also be considered to have shorter than normal QT interval (Maury et al. 2005). However, even with the inclusion of these subjects in the analysis, the results with respect to mortality did not change.

7.2.2 Determinants of a short QT interval

As discussed earlier there are many physiological and pharmacological factors that affect the length of myocardial repolarization i.e. QT interval. After correcting QT interval for the heart rate, perhaps the most important factor is gender. Experimental studies on canine muscle preparations have shown that testosterone markedly accelerates ventricular repolarization (Fulop et al. 2006). Human ECG studies accord well with the experimental data (Rautaharju et al. 1992, Bidoggia et al. 2000). During puberty, the QT interval tends to shorten in males but remains almost constant in females. In the present study almost all individuals with short QT interval were young males. It is possible that a short QT interval just reflects higher testosterone level in these individuals and hence short QT interval individuals represent only the tail of the normal Gaussian distribution of QT interval in a general population. On the other hand it is possible that these young males really have short QT syndrome caused by inherited or sporadic mutation in the gene(s) regulating the ion channels, but the outcome of the syndrome in this middle-aged Finnish population is good.

Heart rate was lower among individuals with a short QT interval. This could be at least partly due to the poor performance of all correction formulae in low heart rates. Therefore we used three different formulae to overcome this. As expected, all individuals with discordance of QTc with QTnc of QTf values had lower heart rates making their QT interval shorter corrected by Bazett’s method than that measured with other 2 methods. Overall, concordance of measurement with different correction methods was fairly good. Because the cubic root correction of Fridericia is more familiar to the medical community than the nomogram method it was also used in determining the prognosis during a long follow-up. Another explanation for the low heart rate is that there may be
common ion channel alterations in sinus node and in ventricular myocardium making repolarization short and sinus node activity low in these subjects.

The autonomic nervous system plays also an important role in the repolarization of the myocardium (Bexton et al. 1986). Hormonal effects and effects of the autonomic nervous system can also affect repolarization of the heart and sinus node activity. Lower systolic blood pressure in subjects with short QT interval might point to a role of the autonomic nervous system. Although difference between smokers and non-smokers was not significant there tended to be fewer smokers in short QT group. We could not confirm earlier results that smoking and short QT interval in 12-lead ECG is associated with worse prognosis (Karjalainen et al. 1997).

### 7.2.3 Pathophysiology and QT interval dynamics in patients with short QT syndrome

After assessing clinical and epidemiological features of subjects with short QT syndrome we wanted to go deeper into the pathophysiology and repolarization dynamics of the patients with short QT intervals. Furthermore, we wanted to study 12-lead ECG of patients with short QT syndrome in order to identify parameters which would allow us to discover any risk of life threatening arrhythmic events among subjects with SQT interval (studies III and IV).

The main findings in study III were that in symptomatic SQTS patients TDR, measured as TPE/QT was abnormally high and SQTS patients had in addition lesser capacity to change QT and TPE intervals than control subjects.

In an experimental SQTS model, shortening of ventricular action potential duration by a potassium current activator amplified TDR and was followed by easier induction of PMVT. They also report that under conditions associated with short QT intervals the threshold at which TDR can induce PMVT is less than the corresponding threshold under long-QT conditions. The value of the electrocardiographic index for TPE/QT was 0.13 under baseline conditions and 0.21 under short QT conditions when PMVT was inducible in this SQTS models. Previously it has been reported that the same threshold for developing of PMVT in patients with acquired long QT syndrome was 0.28(Yamaguchi et al. 2003).

Constantly high level of TDR may increase SQTS patients susceptibility to polymorphic ventricular tachycardia. The normal response of the index, which was observed in our control population and also in healthy children, is a decrease below the level of 0.20 with decreasing heart rates (Viitasalo et al. 1996). Because
SQTS subjects have short QT intervals, unrelated to heart rate, it follows that SQTS patients showed abnormally high values of TPE/QT index compared with control subjects. Continuous high level of TDR in SQTS patients differs from the behaviour of TDR in patients with the congenital long QT syndrome since in a previous study among patients with LQTS the minimal value of the TPE/QT index was 0.19 in LQT1 and 0.23 in LQT2 patients (Viitasalo et al. 2002). Taking all this data together it seems that under normal condition, in an asymptomatic acquired long QT condition and as well as in familial long QT condition TPE/QT index is clearly lower than in symptomatic short QT syndrome patients and symptomatic acquired long QT condition where the index approaches value of 0.28.

We noticed that SQTS patients had diminished capacity to change both QT and TPE interval from basic conditions to abrupt maximal values compared to control subjects. We also observed that compared to the behaviour of a healthy population (Molnar et al. 1996), SQTS patients failed to prolong QT intervals during sleep (data not shown). Our results indicate that ventricular repolarization responses, heart rate changes and alterations in the autonomic tone are impaired in SQTS patients. However, although earlier studies indicate that both blunted autonomic control and impaired rate adaptation of electrocardiographic ventricular repolarization have been connected to increased probability of sudden cardiac death after myocardial infarction (Yi et al. 1998, Järvenpää et al. 2007), the clear arrhythmogenetic significance of these parameters in short QT syndrome remains obscure.

7.2.4 Determinants of abnormal repolarization in Short QT syndrome

In the fourth study we presented ECG characteristics which are specific to patients with SQTS who have experienced life-threatening ventricular tachyarrhythmias and/or aborted SCD. All patients with symptomatic SQTS had shorter Jpoint–Tpeak-interval than the event free subjects with a short QT interval or healthy individuals with completely normal QT interval. Also, rate corrected Tpeak–Tend /QTc-ratio was significantly higher among SQTS patients compared to other two groups.

From the large random cohort of more than 10 000 individuals we were able to find 12 subjects in whom the duration of QTc interval was ≤ 320 ms, similar to patients with SQTS. However, the prognosis for these subjects was remarkably good, even after an extended follow up for almost 30 years (Anttonen et al.
In this respect, the phenotype characteristics of these subjects clearly differed from the SQTS patients. Almost all individuals with a “benign” form of short QT interval were males and were relatively bradycardic at the time of ECG recording. This observation might be due to a bias caused by Bazett’s formula which is known to over shorten measured QTc interval at low heart rates (Puddu et al. 1988). However, the uncorrected QT interval and that corrected by the Fridericia method also showed shorter repolarization time. Repolarization pattern was clearly different among these subjects compared to SQTS patients. In the benign form of short QT, the early phase of repolarization was normal, whereas this interval, from J point to the peak of T-wave, was clearly shortened among the SQTS patients.

As a consequence of shortened early phase repolarization without abnormal late repolarization, the patients with SQTS also had prolonged Tpeak–Tend /QTc –ratio measured from 12-lead ECG. From an electrophysiological point of view, this ratio has been suggested as reflecting the increased transmural dispersion of repolarization which might lead to the occurrence of ventricular tachyarrhythmias. In an experimental model of SQTS, an increase in transmural dispersion of repolarization was observed, which resulted in an increased likelihood of polymorphic VT (Extramiana & Antzelevitch 2004). They also calculated the Tpeak–Tend/QT -ratio and came to the conclusion that the increase from baseline ratio of 0.13 to 0.21 under SQT-interval conditions was associated with vulnerability to ventricular tachyarrhythmias. The same relationship has been observed also in long QT syndrome, where the threshold value of Tpeak–Tend/QT -ratio 0.28 appeared to differentiate between symptomatic and asymptomatic patients (Yamaguchi et al. 2003). Also an earlier study from our group has shown that SQTS patients have higher values and lesser changing capacity of Tpeak–Tend/QT -ratio at various heart rates (Anttonen et al. 2008). All these observations support the hypothesis that increased transmural dispersion of repolarization, reflected as a high Tpeak–Tend/QT -ratio on standard 12-lead ECG, is one of the main factors increasing the vulnerability to ventricular tachyarrhythmias in different clinical settings. Notably, subjects with short QT interval without shortened early repolarization and with normal Tpeak–Tend/QT -ratio do not seem to be at risk for serious arrhythmias.

Regarding the methodology that we used it should be noted that when repolarization patterns are measured from 12-lead ECG, the definition of the end of the T-wave is sometimes problematic. In this respect, the measurement of Jpoint–Tpeak may be more reliable because of easier detection of the sharp turn
of the inclination of T-wave (Tpeak) than a gently sloping end of the wave (Tend). The interobserver variability of the Jpoint–Tpeak measurement was relatively small, i.e. the 95% confidence interval of the difference was < 15 ms, which is much smaller than the smallest difference between the longest Jpoint–Tpeak in SQTS patients and smallest value among subjects with benign form of short QT interval (30 ms). One important feature in QT interval measurement is the R–R interval and rate corrections. It must be emphasized here that uncorrected Jpoint–Tpeak interval was the best index differentiating the subjects with malignant and benign forms of short QTc. Although the rate corrected Jpoint–Tpeak also differed between the groups, there was some overlapping in individual values between the groups in rate-corrected values. In the Tpeak–Tend c/QTc ratio measurement we used heart rate corrected intervals, since in all studies where this equation was used the measurements were selected from the optimal rate e.g. near 60bpm. The results in this study in respect of Tpeak–Tend c/QTc are similar to that of long QT syndrome studies and experimental SQTS studies.
8 Limitations of the studies

Of course, a major limitation in the conclusions of the first study is that the study is observational. It is partly prospective, partly retrospective and the small number of affected individuals makes generalization of the results inappropriate to larger populations. Also, these individuals are highly symptomatic representing most likely the “tip of an iceberg” of subjects with short QT interval and even the asymptomatic individuals came from families with strong penetrance of symptomatic SQTS. Median follow-up for the surviving patients (23 months, range 9–49 months) was also too short to draw any definite conclusions about the long term prognosis of these subjects.

A noteworthy limitation in the second study was that only middle-aged subjects were included. Therefore, it is not appropriate to generalize the results to younger subjects. In addition the number of subjects with short QT interval was perhaps too small and study underpowered to give a definite answer regarding the prognostic significance of a short QT interval. When 2 or 3 SDs were used in defining the cut off values for short QT interval it became evident that for women values were constantly longer. Therefore, different cut off values should perhaps be used for both sexes.

An important limitation of the third study was that we were able to investigate only three symptomatic SQTS patients with unknown genotype. Therefore, one cannot generalize these findings to all subjects presenting with short QT interval. Although control subjects were genotype negative, one could question the use of these controls from families with long QT syndrome. Also, the TPE/QT ratio as a index for altered transmural dispersion of repolarization needs to be confirmed in a larger series of patients.

Again, the small sample size is a potential limitation of the fourth study. The syndrome is rare and we were not able to collect more ECGs from symptomatic cases.
9 Conclusions and clinical implications

This thesis adds new information to the existing data on this novel and potentially life threatening arrhythmogenic syndrome. Until now it has been a generally accepted that a shorter than normal QT interval in an ECG is a serious condition carrying a major risk for sudden cardiac death and hence, aggressive preventive therapy is justified.

The results of the first study (I) show that in some individuals with a short QT interval the syndrome can be extremely malignant and sudden death may occur anytime at any stage of life. The prevalence of known mutations causing SQTS seems to be low and in this study we could genotype only two families for mutation in HERG. Since the risk of sudden death was high in studied families it seems relevant to conclude that for the time being genetic screening is not helpful in risk stratifying these subjects. However, a rare finding of a short QT interval should initiate exclusion of a familial occurrence of syncope or sudden death. Those patients with gain-of-function mutation in KCNH2 (HERG) might benefit from quinidine therapy but if an individual is considered to have high risk features, an ICD is the only effective preventive treatment.

The main finding of study II was that an abnormally short QT interval in a general middle-aged population may not be a life threatening condition that requires extensive risk stratification or antiarrhythmic treatment at least in a nonreferral, community based group of subjects. However, as with many other hereditary arrhythmia syndromes the results might be different in a highly selected referral sample of subjects. It is also important to note that our findings might not apply to familial cases and younger individuals.

The main finding of the third study (III) was presence of abnormally high transmural dispersion of repolarization (TDR), measured as TPE/QT, in symptomatic SQTS patients. SQTS patients also had a lesser capacity to change QT and TPE intervals than control subjects. Both these repolarization abnormalities might explain partly increased vulnerability to ventricular arrhythmias and risk of sudden cardiac death.

In the last study (IV) we found that increased transmural dispersion is characteristic of SQTS patients with vulnerability to life-threatening ventricular arrhythmias. Furthermore, the uncorrected Jpoint–Tpeak interval measured from 12-lead ECG was highly specific in diagnosing the SQTS, and this index should probably be included as one of the diagnostic criteria of SQTS. As observed here, few asymptomatic subjects, especially males with low heart rate, can have short
QTc (< 320 ms) suggesting to a SQTS. The present observations strongly support the notion that the diagnosis of SQTS should not be made in these subjects, if they are asymptomatic without a family history of SCD or serious arrhythmias, and if their Jpoint–Tpeak interval is not shortened (e.g. JTp over 150 ms).
References


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PREVALENCE, PROGNOSIS AND CHARACTERISTICS OF SUBJECTS WITH SHORT QT INTERVAL IN AN ELECTROCARDIOGRAM