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Ventricular repolarization during cardiovascular autonomic function testing

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ACADEMIC DISSERTATION

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Abstract

The autonomic nervous system is an important modulator of ventricular repolarization and arrhythmia vulnerability. This series of investigations aimed to characterize the effects of standardized cardiovascular autonomic function tests on ventricular repolarization and repolarization heterogeneity, with a special reference to congenital arrhythmogenic disorders typically associated with stress-induced fatal ventricular arrhythmias.

Effects of autonomic adaptation on QT intervals in a 12-lead electrocardiogram and in multichannel magnetocardiography were studied in 10 healthy adults during mental stress, Valsalva manoeuvre, sustained handgrip, deep breathing, voluntary hyperventilation and cold pressor testing. Based on the experience gained from the studies on healthy subjects, a series of tests consisting of deep breathing, Valsalva manoeuvre, mental stress, sustained handgrip and mild supine exercise testing was subsequently performed in two patient groups, while a 25-lead body surface electrocardiogram was recorded. The first series comprised 9 asymptomatic patients with LQT1 subtype of the hereditary long QT syndrome and 8 healthy controls whereas the second series comprised 9 patients with arrhythmogenic right ventricular dysplasia (ARVD) and 9 healthy controls. Automated QT interval measurements with a validated computer-based method were used in all studies.

Even strong sympathetic activation had no effects on spatial QT interval dispersion in healthy subjects, but deep respiratory efforts and Valsalva manoeuvre influenced it in ways that were opposite in electrocardiographic and magnetocardiographic recordings. LQT1 patients showed blunted QT interval and sinus nodal responses to sympathetic challenge, as well as an exaggerated QT prolongation during the recovery phases. LQT1 patients showed a QT interval recovery overshoot in 2.4 ± 1.7 tests compared with 0.8 ± 0.7 in healthy controls ($P = 0.02$). Valsalva strain prolonged the T wave peak to T wave end interval only in the LQT1 patients, considered to reflect the arrhythmogenic substrate in this syndrome. ARVD patients showed signs of abnormal repolarization in the right ventricle, modulated by abrupt sympathetic activation. An electrocardiographic marker reflecting interventricular dispersion of repolarization was introduced. It showed that LQT1 patients exhibit a repolarization gradient from the left ventricle towards the right ventricle, which was significantly larger than in controls. In contrast, ARVD patients showed a repolarization gradient from the right ventricle towards the left. Valsalva strain amplified the repolarization gradient in LQT1 patients whereas it transiently reversed the gradient in patients with ARVD.

In conclusion, intrathoracic volume and pressure changes influence regional electrocardiographic and magnetocardiographic QT interval measurements differently. Especially recovery phases of standard cardiovascular autonomic functions tests and Valsalva manoeuvre reveal the abnormal repolarization in asymptomatic LQT1 patients. Both LQT1 and ARVD patients have abnormal interventricular repolarization gradients, which are modulated by abrupt sympathetic activation. Autonomic testing and in particular the Valsalva manoeuvre are potentially useful in unmasking abnormal repolarization in congenital arrhythmogenic syndromes.

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List of original publications

This thesis is based on the following original publications:

- I** Haapalahti P, Mäkijärvi M, Montonen J, Korhonen P, Salorinne Y, Oikarinen L, Viitasalo M, Toivonen L. Effects of cardiovascular autonomic function tests on QT dispersion in the 12-lead electrocardiogram of healthy patients. *J Electrocardiol* 2000; 33: 321-327
- II** Haapalahti P, Mäkijärvi M, Korhonen P, Takala P, Montonen J, Salorinne Y, Oikarinen L, Viitasalo M, Toivonen L. Magnetocardiographic QT dispersion during cardiovascular autonomic function tests. *Basic Res Cardiol* 2000; 95: 424-430
- III** Haapalahti P, Viitasalo M, Perhonen M, Mäkijärvi M, Väänänen H, Oikarinen L, Hekkala A, Salorinne Y, Swan H, Toivonen L. Ventricular repolarization and heart rate responses during cardiovascular autonomic function testing in LQT1 subtype of long QT syndrome. *Pacing Clin Electrophysiol* 2006; 29: 1122-1129
- IV** Haapalahti P, Viitasalo M, Perhonen M, Mäkijärvi M, Väänänen H, Oikarinen L, Salorinne Y, Swan H, Toivonen L. Interventricular dispersion of repolarization in LQT1 subtype of long QT syndrome. *Scand Cardiovasc J* 2008; 42: 130-136
- V** Haapalahti P, Viitasalo M, Kaartinen M, Mäkijärvi M, Väänänen H, Oikarinen L, Heliö T, Salorinne Y, Toivonen L. Electrocardiographic ventricular repolarization during cardiovascular autonomic function testing in patients with arrhythmogenic right ventricular dysplasia. Submitted.

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Abbreviations

AP(D)	action potential (duration)
ARVD	arrhythmogenic right ventricular dysplasia
bpm	beats per minute
BSPM	body surface potential mapping
ECG	electrocardiogram, electrocardiography, electrocardiographic
HR	heart rate
HRV	heart rate variability
$I_{Ca(L)}$	L-type calcium current
I_{K1}	inwardly rectifying potassium current
I_{Kr}	rapidly activating component of the delayed rectifier potassium current
I_{Ks}	slowly activating component of the delayed rectifier potassium current
I_{Na}	sodium current
I_{to1}, I_{to2}	transient outward potassium currents
LQT1(-8)	subtypes (1 to 8) of congenital long QT syndrome
LQTS	long QT syndrome
LV	left ventricle
MAP	monophasic action potential
M cell	midmyocardial cell
MCG	magnetocardiogram, magnetocardiography, magnetocardiographic
QTc	rate corrected QT interval (Bazett's formula)
QTend	the interval from the onset of the Q wave to the end of the T wave
QTpeak	the interval from the onset of the Q wave to the peak of the T wave
RV	right ventricle
TdP	torsade de pointes
TDR	transmural dispersion of repolarization
TPE	T wave peak to T wave end interval

1 Introduction

Evidence from population studies supports the general belief that strong psychological stress increases the incidence of sudden cardiac death (MEISEL ET AL. 1991, LEOR ET AL. 1996). Anger and physical exertion, both of which cause profound changes in the activity of the autonomic nervous system, are important triggers of symptoms in patients at known risk for serious ventricular arrhythmias (LAMPERT ET AL. 2002). Sympathetic activation brought on by mental stress causes temporal and spatial repolarization heterogeneity (i.e. dispersion) in the ventricles of these patients (KOP ET AL. 2004, LAMPERT ET AL. 2005). Increased dispersion of repolarization is a fundamental condition for ventricular arrhythmogenesis (HAN AND MOE 1964). Thus, direct influences of stress-induced sympathetic activation on ventricular repolarization and its heterogeneity appear to be pivotal mechanisms through which emotional or physical stress may trigger life-threatening ventricular arrhythmias.

Most sudden cardiac deaths in the general population are related to manifestations of coronary artery disease. However, a significant proportion of sudden cardiac deaths in younger populations occur in the absence of apparent heart disease, where congenital microscopic or micromolecular defects have brought about a permanent susceptibility to life-threatening arrhythmic events. So strong is the triggering role of sympathetic activation in many of these conditions that the most commonly known repolarization disorder, the congenital long QT syndrome (LQTS), was thought to arise from abnormalities of the autonomic nervous system (SCHWARTZ AND LOCATI 1985) before its recognition as primarily an ion channel disease.

In clinical settings, ventricular repolarization abnormalities are usually assessed by measuring the duration of the QT interval in the electrocardiogram (ECG) recorded on the body surface. Abnormal QT intervals have been linked to sudden death (ALGRA ET AL. 1991) and cardiac mortality (KARJALAINEN ET AL. 1997). Interlead variability of QT measured intervals (spatial QT dispersion) was earlier considered a general marker of repolarization heterogeneity (DAY ET AL. 1990). Recent experimental observations have underscored the importance of interventricular and especially transmural dispersion of repolarization as an arrhythmogenic substrate. Transmural dispersion of repolarization manifests on the ECG in the terminal portion of the T wave (YAN AND ANTZELEVITCH 1998), whereas there are as yet no established clinical markers for interventricular dispersion of repolarization.

Despite advances in gene technology, simple bedside testing is needed for diagnostic and counselling purposes in congenital arrhythmogenic syndromes. Standardized autonomic testing could provide an easily applicable tool in delineating arrhythmia provoking conditions. Abrupt changes in autonomic activity cause marked changes in QT interval adaptation even in healthy subjects (TOIVONEN ET AL. 1997), however, making the recognition of abnormal repolarization a difficult task.

The present series of investigations attempts to outline autonomic effects on traditional as well as proposed new ECG markers of repolarization and its heterogeneity. Sophisticated body surface recordings and automated QT interval measurements were used to follow repolarization changes induced by standardized cardiovascular autonomic

function tests, both in healthy subjects and in two patient groups with known hereditary propensity to stress-provoked arrhythmias.

2 Review of the literature

2.1 The cardiovascular autonomic nervous system

2.1.1 Anatomy and physiology

The cardiovascular autonomic nervous system maintains circulatory homeostasis of the organism, ensuring adequate tissue perfusion under varying environmental and internal demands. This rapid adaptation of the circulation is mainly accomplished through reflex arcs: Mechano- and chemosensory input from different systemic and central receptors are conveyed by afferent nerve fibres to medullary centres for integration, and efferent fibres in turn transmit impulses from the central nervous system to the heart and blood vessels, modulating their activity. The medullary centres also receive input from higher brain centres and the hypothalamus, important for instigating cardiovascular responses to emotion, stress and exercise.

Anatomically and functionally the autonomic nervous system is divided into the sympathetic and the parasympathetic divisions. The efferent limbs of both divisions consist of myelinated preganglionic nerve fibers connecting with unmyelinated postganglionic fibres in synaptic clusters called ganglia. Postganglionic fibres in turn innervate the effector organs.

Sympathetic nervous system. Preganglionic sympathetic fibres arise in the lateral horns of the spinal segments T1-L3 (WALLIN AND CHARKOUDIAN 2007). Most preganglionic fibres travel only a short distance in the spinal nerve, before branching off into the sympathetic ganglia which are arranged as two paravertebral chains (truncus sympathicus) extending from the cervical to the sacral region. Some fibres only traverse these sympathetic ganglionic chains, synapsing in separate cervical (the cervical or the stellate) or abdominal (the celiac or the mesenteric) ganglia (HARATI AND MACHKHAS 1997). The chemical neurotransmitter in sympathetic presynaptic nerve endings is acetylcholine. In most postsynaptic nerve endings, the transmitter is noradrenaline. Some preganglionic fibers traveling in the greater mesenteric nerve synapse with chromaffin cells in the adrenal medulla. Stimulation of these cholinergic preganglionic fibers results in the release of adrenaline and to a lesser extent noradrenaline into the bloodstream. The actions of adrenaline and noradrenaline are mediated by specific G-protein coupled adrenergic receptors on the surface of the cell. Pharmacologically, these adrenoceptors are divided into α and β receptors. Two main subtypes of α receptors (α_1 , α_2) and three main subtypes of β receptors (β_1 , β_2 , β_3) have been identified (Table 1) (BRISTOW ET AL. 1990, INSEL 1996, BOSCH ET AL. 2002).

Parasympathetic nervous system. Parasympathetic outflow arises in the motor nuclei of cranial nerves III, VII, IX and X in the brainstem and from the spinal segments S2-S4. Preganglionic fibres synapse with the postganglionic fibres within or close to the effector

organ (HARATI AND MACHKHAS 1997). The chemical neurotransmitter in both pre- and postsynaptic parasympathetic nerve endings is acetylcholine (cholinergic nerve fibres). The actions of acetylcholine are mediated by nicotinic and muscarinic acetylcholine receptors (Table 1). The nicotinic receptors are ligand-gated ion channels, mediating the effects of acetylcholine in the autonomic ganglia. The muscarinic receptors are G-protein coupled receptors, mediating the parasympathetic impulses to the effector organs.

Table 1. *Cholinergic and adrenergic receptors of the autonomic nervous system.*

<i>Receptor type</i>	<i>Agonists and order of potency</i>	<i>Antagonists</i>	<i>Main locations</i>
<i>Cholinergic</i>			
nicotinic	acetylcholine, nicotine >> muscarine	hexamethonium	postsynaptic neurons of autonomic ganglia (synaptic transmission), neuromuscular junctions, CNS
muscarinic (M ₁ -M ₅)	acetylcholine, muscarine >> nicotine	atropine, scopolamine	heart, vascular and nonvascular smooth muscle, glands, CNS
<i>Adrenergic</i>			
α ₁	phenylephrine, A = NA >> ISO	doxazosin	vascular and nonvascular smooth muscle, heart, CNS
α ₂	clonidine, A = NA >> ISO	yohimbine	presynaptic (inhibition of transmitter release), vascular smooth muscle, platelets, CNS
β ₁	dobutamine, ISO > A = NA	atenolol, metoprolol	heart
β ₂	salbutamol, ISO > A >> NA	butoxamine	vascular and nonvascular smooth muscle, skeletal muscle, heart
β ₃	BRL 37344, ISO = A > NA	SR59230A	adipose tissue, heart

A = adrenaline, NA = noradrenaline, ISO = isoprenaline, CNS = central nervous system

Innervation of the heart. Postganglionic sympathetic nerves travelling to the heart arise in the right and left stellate ganglia and the caudal halves of the cervical sympathetic trunks (JANES ET AL. 1986). Sympathetic nerves arising from the right stellate ganglia are more likely to supply the anterior regions whereas those from the left stellate ganglia are more likely to supply the inferoposterior regions of the heart (YANOWITZ ET AL. 1966, JANES ET AL. 1986). Parasympathetic fibres travel to the heart in the vagus nerves. Also the distribution of intrinsic cardiac autonomic nerve fibres exhibits local differences. The

atria are more densely innervated than the ventricles and the basal areas of the ventricles are more densely innervated than the apical areas (KAWANO ET AL. 2003). The right and left ventricles show similar nerve distributions, however. There are slightly more parasympathetic than sympathetic nerve fibres in the atria, whereas the ventricles have a sparse parasympathetic innervation (NAPOLITANO ET AL. 1965) but notably more sympathetic fibres (KAWANO ET AL. 2003). Sympathetic innervation is denser in the anterior as compared with the posterior parts of the ventricles (MOMOSE ET AL. 2001). There are more sympathetic nerves in the subepicardium than in the subendocardium, whereas there are more parasympathetic nerves in the subendocardium than in the subepicardium (KAWANO ET AL. 2003). Thus, autonomic innervation of the heart shows both transepical and transmural heterogeneities, which may carry functional significance in pathological circumstances.

Innervation of blood vessels and the arterial baroreflex. All blood vessels except the capillaries are innervated. The sympathetic nervous system controls the tone of vascular smooth muscle mainly through the vasoconstrictive effects of α_1 -adrenergic stimulation and the vasodilating effects of β_2 -adrenergic stimulation. Blood vessels of skeletal muscle contain also vasodilating cholinergic sympathetic fibres. Only visceral, cranial and genitourinary blood vessels exhibit direct parasympathetic innervation, but muscarinic receptors sensitive to vasodilatation through exogenous acetylcholine are found widely in vascular smooth muscle and endothelium. Thus, the autonomic nervous system directly controls peripheral resistance and the distribution of blood flow and perfusion of organs by modulating the tone of the smooth muscle in arteries and capacitance vessels.

Changes in transmural arterial pressure are sensed by numerous stretch-receptors called baroreceptors, located mainly in the aortic arch and the carotid sinus. Afferent impulses from the baroreceptors are conducted to cardioinhibitory and vasomotor centres in the medulla, resulting in inhibition of sympathetic and excitation of parasympathetic structures. Increased arterial pressure leads thus to decreased peripheral resistance and increased capacity of the capacitance vessels, as well as to decreased heart rate (HR) and myocardial contractility, resulting in decreased cardiac output and arterial blood pressure. Arterial pressure reduction, on the other hand, has opposite effects. This autoregulatory mechanism constitutes a control circuit where reflex changes in neuronal output triggered by the baroreceptors in response to sudden changes in blood pressure functions to rapidly restore initial conditions (LANFRANCHI AND SOMERS 2002). Local circulatory effects of autonomic adaptation are summarized in Table 2.

Table 2. *Circulatory effects of sympathetic and parasympathetic activation.*

	<i>Sympathetic</i>	<i>Parasympathetic</i>
<i>Sinoatrial node</i>	HR ↑ (β_1, β_2)	HR ↓ (M_2)
<i>Atrial muscle</i>	contractility ↑ (β_1, β_2)	contractility ↓ (M_2)
<i>Atrioventricular node</i>	conduction ↑ (β_1)	conduction ↓ (M_2)
<i>Ventricular muscle</i>	contractility ↑ (β_1, β_2)	-
<i>Vascular smooth muscle</i>	vasoconstriction (α_1) vasodilation (β_2, M_3)	-

See Table 1 for description of the receptors in parentheses.

2.1.2 Cardiovascular autonomic function testing

Heart rate variability and respiratory sinus arrhythmia. Beat-to-beat alterations in cardiac cycle length are referred to as HR variability (HRV). HRV is strongly coupled to respiration: HR increases during inspiration and decreases during expiration. The afferent limb of the reflex arc responsible for this respiratory sinus arrhythmia conveys input from arterial baroreceptors, low-pressure receptors in the heart and probably stretch receptors in the lungs (MELCHER 1976). The efferent limb of the reflex arc is vagal (WHEELER AND WATKINS 1973).

HRV may be assessed during either spontaneous breathing or during breathing cued at a specific frequency. It can be quantified with time-domain, frequency-domain and nonlinear indices, giving estimates of the relative contributions of parasympathetic and sympathetic control (TASK FORCE 1996). Parasympathetic activity is associated with decreased HR and increased HRV, whereas sympathetic activity conveys opposite effects.

Perhaps the most widely utilized test of parasympathetic function is the deep breathing test (WHEELER AND WATKINS 1973). The subject breathes deeply and slowly, usually at 6 breaths per minute using subjective maximal vital capacity, maximizing the magnitude of respiratory sinus arrhythmia. The difference between maximum and minimum HRs during a respiratory cycle (deep breathing difference) is calculated, and usually the mean of 4-6 successive differences is used as an index of HRV. Decreased HRV during controlled breathing is considered a sensitive marker of parasympathetic dysfunction. HRV decreases with age, but is not affected by gender or mean HR (SMITH AND SMITH 1981).

Valsalva manoeuvre. The Valsalva manoeuvre is usually performed by blowing against a pressure of 5.3 kPa (40 mmHg) for 15 seconds. This forced expiration against resistance elevates the intrathoracic pressure, causing a distinct series of reflex cardiovascular responses. In normal subjects, these can be divided into four phases. During the first 2-3 seconds of strain (phase 1), there is often a transient increase in blood

pressure, sometimes accompanied by a brief slowing of HR. As strain continues, the blood pressure falls progressively, due to impeded venous return (phase 2), causing reflex acceleration of HR. Ventricular dimensions reduce and the stroke volume falls by almost 30% during the strain (ROBERTSON ET AL. 1977, FELDMAN ET AL. 1985). Immediately after the cessation of strain, the blood pressure continues to fall due to the sudden decrease in intrathoracic pressure (phase 3). Improved venous return while the HR remains elevated then quickly raises the blood pressure, leading to marked reflex bradycardia (phase 4). The mechanisms of these circulatory responses are related to the baroreflex: Tachycardia during phases 2 and 3 are mainly due to combined parasympathetic withdrawal and sympathetic stimulation (LEON ET AL. 1970, BENNETT ET AL. 1976), while the bradycardia during phase 4 is a result of increased parasympathetic activity (BENNETT ET AL. 1976). The strain also induces direct sympathetic neural activation that is apparently independent of the baroreflex mechanisms (COOKE ET AL. 2003). Valsalva manoeuvre thus causes abrupt sympathetic activation, followed by reflex parasympathetic activation, occurring together with significant changes in cardiac filling.

HR responses during Valsalva are often described with indices of R-R interval changes. The Valsalva ratio (LEVIN 1966) is defined as the ratio of the longest R-R interval during phase 4 divided with the shortest interval during strain. The bradycardia ratio (BENNETT ET AL. 1978) is defined as the longest R-R interval after strain divided with the resting R-R interval. The tachycardia ratio (BALDWA AND EWING 1977) is calculated as the shortest R-R interval during strain divided by the longest R-R interval before strain. These ratios are considered to reflect parasympathetic control of HR.

Sustained handgrip. During isometric exercise, impulses from motor areas of the brain and muscle receptors cause a generalized increase in sympathetic outflow to blood vessels and the heart. These responses are usually studied during isometric handgrip, usually held at 30% of maximal voluntary contraction. During handgrip HR increases first as a result of vagal withdrawal and later due to both vagal withdrawal and sympathetic stimulation (MARTIN ET AL. 1974). The amplified sympathetic outflow to the heart enhances cardiac contractility (SHEPHERD ET AL. 1981). Vasoconstriction occurs in resistance and capacitance vessels, whereas vasodilatation occurs in cutaneous vessels (SHEPHERD ET AL. 1981). Cardiac output increases, elevating both systolic and diastolic blood pressure, while the total peripheral resistance remains relatively constant (LIND ET AL. 1964). Levels of plasma noradrenaline and adrenaline increase about twofold and fivefold, respectively (STRATTON ET AL. 1983). Clinically, the response to isometric exercise is used as a measure of sympathetic integrity: A diminished blood pressure elevation in response to handgrip is considered indicative of sympathetic neuropathy.

Cold pressor test. The cold pressor test, usually immersion of a limb in iced water, has been used in cardiovascular research to elicit a rapid blood pressure increase. Cold immersion elevates arterial blood pressure, HR and vascular resistance (GREENE ET AL. 1965). HR increase is usually limited to the early part of immersion; it appears to be related to pain and is mediated mainly by sympathetic activation (VICTOR ET AL. 1987). The increase in peripheral resistance is mediated by increased sympathetic neural outflow

to blood vessels (VICTOR ET AL. 1987). Plasma catecholamine levels usually increase only slightly (STRATTON ET AL. 1983).

Face immersion in cold water is considered to represent the dive reflex in humans. It is associated with increase in muscle sympathetic nerve activity and causes an initial increase and a subsequent decrease of HR; the latter due to both vagal activation and inhibition of sympathetic activity (FAGIUS AND SUNDLÖF 1986).

Mental stress. Cardiovascular responses to psychological stress are linked to the aetiology and prognosis of several cardiovascular disorders and a wide range of mental stress tests have therefore been used in cardiovascular research (STEPTOE AND VÖGELE 1991). The most commonly used methods consist of problem-solving or information-processing tasks, e.g. mental arithmetic or colour-word conflict testing. Mental stress elevates HR, blood pressure and stroke volume, but causes only a slight decrease or no change in vascular resistance (HJEMDAHL ET AL. 1984, GROSSMAN ET AL. 1989) and ejection fraction (BECKER ET AL. 1996). Hemodynamic responses are mainly thought to reflect increases in circulating adrenaline (adrenal response): Levels of plasma adrenaline but not of noradrenaline increase during mental stress testing (SAITOH ET AL. 1995, GROSSMAN ET AL. 1989, GOLDBERG ET AL. 1996).

Orthostatic and baroreflex testing. The change of posture from supine to upright leads to decreased venous return as a result of blood pooling to the blood vessels of the trunk and lower extremities. This leads to a transient fall in cardiac output and blood pressure, rapidly corrected by the baroreflex through peripheral vasoconstriction and accelerated HR. Normal subjects have a biphasic initial HR response: An immediate increase followed by a transient decrease. The initial tachycardia is mediated mainly by vagal withdrawal with concomitant slight sympathetic activation whereas the rebound bradycardia is of vagal origin (EWING ET AL. 1980). Continued upright posture is associated with persistent increase in efferent sympathetic activity. Orthostatic tests are performed either as active standing or with a tilt table, but the elicited responses are fundamentally different between these methods (WIELING ET AL. 1985). Orthostatic tests are useful in the assessment of orthostatic intolerance, vasovagal syncope and integrity of sympathetic function.

Baroreflex sensitivity can be assessed by measuring the instantaneous HR responses to sudden changes in blood pressure. The linear relationship of systolic blood pressure and R-R interval can be measured during reflex changes induced by phenylephrine infusion or Valsalva manoeuvre (AIRAKSINEN ET AL. 1993). Decreased baroreflex sensitivity is considered to reflect parasympathetic dysfunction.

Autonomic adaptation during physical exercise. Physical exercise is associated with an increase of sympathetic activity and a withdrawal of parasympathetic activity, resulting in increased blood pressure, HR and cardiac contractility. Physical exercise induces a mainly sympathetic nervous as opposed to an adrenal response, as suggested by the notably greater increases observed in plasma noradrenaline than in adrenaline (DIMSDALE AND MOSS 1980, SAITOH ET AL. 1995). Dynamic exercise induces more

profound hemodynamic changes and greater elevation of plasma catecholamines than mental stress, sustained handgrip or cold pressor testing (SAITOH ET AL. 1995, STRATTON ET AL. 1983).

2.2 Ventricular repolarization

2.2.1 Membrane currents and the cardiac action potential

Resting myocardial cells exhibit negative membrane potentials (-85 to -95 mV). Electrical stimulation of the cell induces opening of voltage-gated ion channels and influx of positive ions (cations) into the cell, thereby depolarizing it and initiating the cardiac action potential (AP). Depolarization propagates to adjacent cells through gap junctions, by this means conducting the activation to all cells of the heart, causing intracellular calcium ion release and ultimately myocardial contraction. Repolarization, on the other hand, is an intrinsic property of the cells that occurs regardless of the existence of conducting junctions.

Classically, the cardiac AP is divided into five phases numbered from 0 to 4 (Figure 1). *Phase 0* is the rapid upstroke of the AP, when fast sodium channels open causing an influx of Na^+ ions (the fast sodium current, I_{Na}) thus depolarizing the cell. Repolarization occurs in three phases: *Phase 1* represents the initial brief downward deflection of the AP, marking the inactivation of I_{Na} and activation of the transient outward potassium currents (I_{to1} and I_{to2}). Some myocytes exhibit a prominent AP notch during phase 1. *Phase 2* is the plateau of the AP, upheld mainly by a balance of inflow of calcium ions through L-type calcium channels ($I_{\text{Ca(L)}}$), inflow of sodium ions due to late I_{Na} , and outflow of potassium ions through channels responsible for the slowly (I_{Ks}) and rapidly (I_{Kr}) activating components of the delayed rectifier current. *Phase 3* represents the final rapid repolarization of the cell, when $I_{\text{Ca(L)}}$ channels close while I_{Ks} channels remain open. The ensuing negative change in membrane potential promotes further opening of potassium channels, augmenting I_{Kr} and the inwardly rectifying potassium current (I_{K1}), accelerating restoration of the resting potential. *Phase 4* is the interval between end of repolarization and the beginning of the next AP. The major currents of the cardiac action potential are summarized in Table 3 (ACKERMAN AND CLAPHAM 1997, CARMELIET 1999, SHAH ET AL. 2005).

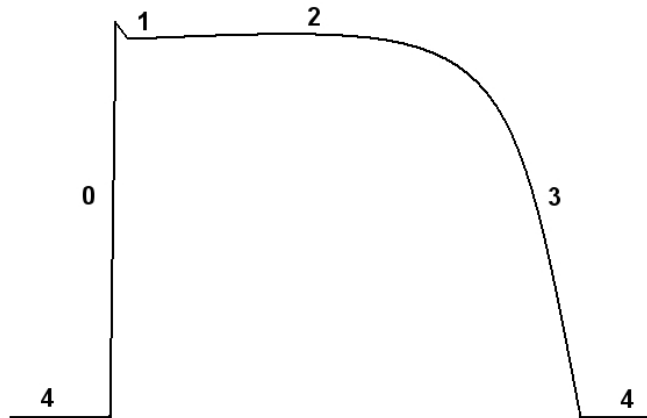


Figure 1. *Phases of the ventricular action potential (see text for details).*

Table 3. *Major ionic currents responsible for the ventricular action potential.*

<i>Current</i>	<i>Ion</i>	<i>Genes</i>	<i>AP phase</i>
I_{Na}	Na^+	SCN5A	0, 1, 2
$I_{Ca(L)}$	Ca^{2+}	CACNA1C	0, 1, 2
I_{to}	K^+	KCND2/KCND3	1 (notch)
I_{Ks}	K^+	KCNQ1 + KCNE1	2, 3
I_{Kr}	K^+	KCNH2 (hERG) + KCNE2	2, 3
I_{K1}	K^+	KCNJ2/KCNJ12/KCNJ4	3

Bold indicates the action potential phase during which the majority of the current occurs. AP = action potential.

2.2.2 Measurement

Repolarization time. AP duration (APD) represents the time interval between the onset of phase 0 to the onset of phase 4. It is common to measure APD to the point of 90% repolarization, because the exact point of complete repolarization is difficult to identify. Repolarization time is the sum of the activation time and the local APD. APD measurements are usually performed either with intracellular microelectrodes on single

cells or with floating microelectrodes on tissue wedges. Multiple simultaneous recordings over a greater area can be performed by optical mapping with voltage-sensitive dyes and photodiode arrays or CCD-cameras (EFIMOV ET AL. 1994). These methods are constrained to in vitro settings.

Monophasic action potential (MAP) recordings are usually obtained with contact electrode catheters and they measure the potential difference between the electrode and adjacent myocardial cells (an injury current). MAP recordings give reliable estimates of the time-course of local transmembrane APs (FRANZ ET AL. 1986). Local repolarization can also be measured from local unipolar electrograms. While the MAP waveforms resemble transmembrane APs, unipolar electrograms exhibit distinct QRS and T waves like surface ECGs. Estimation of repolarization from unipolar electrograms is usually done by measuring the activation-recovery interval, commonly defined as the time between the minimum first derivative of the QRS complex and the maximum derivative of the T wave. In the absence of ischemia, activation-recovery intervals reflect transmembrane APDs under various physiological conditions (HAWS AND LUX 1990). Unipolar electrograms can be obtained with needle electrodes (MILLAR ET AL. 1985), conventional electrode catheters (XIA ET AL. 2005a) or with noncontact multielectrode arrays (YUE ET AL. 2005).

Refractory period. During phase 2 and the beginning of phase 3, an additional electrical stimulus is not able to instigate another AP. This is referred to as the effective refractory period. APD and the recovery of excitability show a close temporal correlation under non-ischemic conditions (LEE ET AL. 1992), therefore the effective refractory period is often used as a measure of repolarization duration. Classically, the effective refractory period is measured with the extrastimulus technique, where regular basic pacing trains (S1) are followed by premature stimuli (S2) at progressively shorter coupling intervals, and defined as the shortest extrastimulus interval that captures (HAN AND MOE 1964). Normally this occurs at approximately 70% repolarization of the preceding steady state AP. Activation intervals during ventricular fibrillation have also been used as a measure of refractoriness in experimental settings (OPTHOF ET AL. 1991).

2.2.3 Modulating factors

Cycle length and diastolic interval (AP restitution). The most important physiological determinant of APD is the cardiac cycle length. Generally, a reduction in cycle length shortens the APD. In humans, steady-state APD shows a linear correlation with cycle length, except at very long cycle lengths (FRANZ ET AL. 1988). After a sudden change in basic cycle length APD first shortens or lengthens abruptly, followed by a more gradual change that reaches a new steady state after a few minutes (FRANZ ET AL. 1988).

APD is dependent not only on the preceding cycle length, but also on the duration of the preceding diastolic interval (BASS 1975, FRANZ ET AL. 1983). The adaptation of APD to (abrupt) changes in the diastolic interval is referred to as APD restitution. Usually the restitution properties of APD are described with electrical restitution curves obtained with

the extrastimulus technique, where the APD is plotted against the diastolic interval at different S1-S2 coupling intervals at a given stable S1 rate. Electrical restitution curves in humans show a characteristic triphasic shape (FRANZ ET AL. 1988): The duration of the most premature AP is markedly reduced, increasing steeply at progressively longer S1-S2 intervals to an initial maximum occurring at 50-150 ms after the effective refractory period. Thereafter it shortens again at growing S1-S2 intervals (completing a “hump”), before gradually prolonging again to a maximum occurring at around 1000 ms (FRANZ ET AL. 1988). Thus, the relationship between APD and cycle length is different whether assessed at a steady HR, after a sudden but sustained change in HR or after a premature stimulus.

Incomplete recovery of membrane currents and ion accumulation are probable mechanisms responsible for rate dependent APD shortening (BOYETT AND JEWELL 1978). The immediate AP adaptation is thought to be a result of increased I_{Ks} , because it accumulates during rapid pacing, thus changing from a transient to a more constant current (LU ET AL. 2001). Simulation studies suggest that the relative densities of I_{Ks} and I_{Kr} importantly affect the rate adaptation of APD (ZENG ET AL. 1995, VISWANATHAN ET AL. 1999). However, the role of I_{Ks} at physiological HRs in humans has been debated: It has been observed not to contribute significantly to APD in the absence of sympathetic stimulation or compromised repolarization (diminished repolarization reserve) (VOLDERS ET AL. 2003, JOST ET AL. 2005). Other simulation studies have suggested that I_{to1} and $I_{Ca(L)}$ are important for APD rate adaptation (HUND AND RUDY 2004).

Autonomic effects. Catecholamines modulate repolarization mainly by augmenting $I_{Ca(L)}$ (VELDKAMP ET AL. 2001) and I_{Ks} (SANGUINETTI ET AL. 1991). In isolated cells, activation of β -receptors abbreviates whereas activation of α -receptors prolongs APD (GIOTTI ET AL. 1973). Priori and Corr reported that small concentrations of isoprenaline prolonged whereas larger concentrations markedly abbreviated APD (PRIORI AND CORR 1990). In accordance with these experimental observations, β -adrenergic stimulation shortens and α -adrenergic stimulation prolongs the ventricular effective refractory period in humans (MORADY ET AL. 1988, WEISS ET AL. 1998). Adrenaline infusion steepens the APD restitution curves both in experimental models (TAGGART ET AL. 1990) and in humans (TAGGART ET AL. 2003), meaning that adrenergic stimulation alters the relationship between HR and timing of repolarization.

Due to marked discrepancy between in vivo and in vitro findings, it was long debated whether acetylcholine had any direct effects on APD in ventricular myocytes. Litovsky and Antzelevitch then discovered that although acetylcholine had little if any effect on APD in isolated endocardial cells, small concentrations of acetylcholine prolonged and large concentrations markedly abbreviated APD in isolated epicardial cells (LITOVSKY AND ANTZELEVITCH 1990).

Direct stimulation of the right or left stellate sympathetic ganglion abbreviates left ventricular refractory periods, whereas stellate ganglionectomy prolongs them (YANOWITZ ET AL. 1966, MARTINS AND ZIPES 1980). These effects are not necessarily universal, because ganglion stimulation can also induce a prolongation of refractoriness in some regions of the heart, with marked variability between individual hearts (OPTHOF ET

AL. 1991). In isolated rabbit hearts with intact dual autonomic innervation, direct stimulation of sympathetic nerves steepened the APD restitution slope and increased the susceptibility of the preparation to ventricular fibrillation (NG ET AL. 2007). In the same preparations, direct stimulation of vagal nerves flattened the APD restitution slope and raised the ventricular fibrillation threshold. During simultaneous stimulation of sympathetic and parasympathetic nerves, the shortening effect of the former has been observed to dominate (INOUE AND ZIPES 1987).

Combined, these previous findings demonstrate that the effects of autonomic adaptation on ventricular repolarization can be difficult to predict. In the intact organism, autonomic reflexes involve complex and combined neural and humoral changes. In addition, the autonomic nervous system modulates APD indirectly through simultaneous changes in HR.

Activation-recovery coupling and cardiac memory. Activation time and APD show a close negative correlation, with shorter APDs occurring at sites activated later (FRANZ ET AL. 1987). This inverse coupling of activation and repolarization, observed both at steady state and after premature stimulation, may act to preserve electric stability in the normal ventricle (YUE ET AL. 2005). The dependence of repolarization on preceding activation patterns is referred to as cardiac memory (COSTARD-JÄCKLE ET AL. 1989). Several molecular mechanisms are probably involved, among others changes in I_{to} , $I_{Ca(L)}$ and I_{Kr} (ROSEN AND COHEN 2006). While memory effects are considered reversible, permanent functional changes to sustained abnormal activation patterns has been referred to as electrical remodelling (VOS ET AL. 1998).

Other factors. Any factor modulating the transmembrane ionic currents active during the cardiac AP has the potential to affect repolarization. These include among others ischemia (DOWNAR ET AL. 1977, TAGGART ET AL. 1988a, LUKAS AND ANTZELEVITCH 1993), cardiac and noncardiac drugs (TAMARGO ET AL. 2004), changes in ion homeostasis (especially hypokalemia) (ANTZELEVITCH ET AL. 1991), gender and sex hormones (HARA ET AL. 1998, JAMES ET AL. 2007), and mutations or polymorphisms of genes encoding ion channel proteins (SPLAWSKI ET AL. 2000, SANGUINETTI AND TRISTANI-FIROUZI 2006). In addition, mechanical stretch of myocardial fibres directly modulates APD, a phenomenon referred to as mechanoelectric feedback (LAB 1982, FRANZ ET AL. 1992).

2.2.4 Dispersion

Dispersion of ventricular repolarization denotes the degree of spatial or temporal inhomogeneity in repolarization times or refractoriness and is classically defined as the difference between the longest and shortest measured time interval. Although increased dispersion of repolarization is usually associated with pathological states, some degree of physiological dispersion of repolarization is apparent under normal conditions as a result of structural and cellular heterogeneities.

Transmural dispersion of repolarization. Ventricular muscle contains three main types of excitable cells, namely endocardial, midmyocardial (M) and epicardial cells (SICOURI AND ANTZELEVITCH 1991, ANTZELEVITCH ET AL. 1991) Owing to differences in ion channel densities their electrophysiological properties differ, causing heterogeneity in the shape and behaviour of APs within the ventricular wall. APs of epicardial cells show a more prominent phase 1 notch than endocardial cells, due to a more prominent I_{to} in the former, giving epicardial APs a spike-and-dome appearance (ANTZELEVITCH ET AL. 1991). APDs are also shorter in epicardial than in endocardial cells at fast to moderate stimulation rates. M cells exhibit longer APDs and a steeper AP rate dependence (manifesting as greater prolongation with slowing of rate) than epicardial or endocardial cells (SICOURI AND ANTZELEVITCH 1991, YAN ET AL. 1998). These differences are ascribed to weaker I_{Ks} and larger late I_{Na} in M cells than in endocardial or epicardial cells (LIU AND ANTZELEVITCH 1995, VISWANATHAN ET AL. 1999, ZYGMUNT ET AL. 2001, SZABO ET AL. 2005), resulting in decreased repolarization current during phases 2 and 3 of the AP. Therefore agents or conditions that reduce I_{Kr} or augment late I_{Na} produce a much greater prolongation of M cell APD (weak I_{Ks} and strong late I_{Na} → less total repolarizing current) than of epicardial or endocardial APD (strong I_{Ks} and weak late I_{Na} → more total repolarizing current). This amplifies transmural dispersion of repolarization (TDR) (SHIMIZU AND ANTZELEVITCH 1997, EMORI AND ANTZELEVITCH 2001). Reduced I_{Ks} , however, amplifies TDR only in the presence of β -adrenergic influence, due to a larger augmentation of residual I_{Ks} in epicardial and endocardial cells than in M cells (SHIMIZU AND ANTZELEVITCH 1998).

Most current knowledge of TDR stems from studies on cells isolated from the different myocardial layers or from experiments on canine perfused ventricular wedge preparations. Although transmural repolarization gradients have been observed in vivo (EL-SHERIF ET AL. 1996, MEROT ET AL. 1999), several studies have failed to detect such gradients at physiological HRs (BAUER ET AL. 1999, JANSE ET AL. 2005, TAGGART ET AL. 2001). It has been suggested that strong electrotonic coupling by gap junctions hides the electrophysiological manifestations of M cells under normal conditions (CONRATH ET AL. 2004). Others have suggested that the M cells may be a transient functional state rather than a distinct anatomical subset of cells (UEDA ET AL. 2004). Marked AP prolongation in M cells causing augmented TDR nevertheless becomes evident in abnormal conditions associated with increased arrhythmia susceptibility, such as LQTS and heart failure (AKAR ET AL. 2002, AKAR AND ROSENBAUM 2003).

Apicobasal dispersion of repolarization. The direction and magnitude of apicobasal repolarization gradients have varied in different experimental settings (isolated cells vs. intact hearts) and in different species. In isolated canine and human hearts apical APDs are shorter than basal APDs, presumably due to twice larger densities of I_{to} and I_{Ks} in apical than in basal myocytes (SZENTADRASSY ET AL. 2005). In the rabbit heart, isolated cells from the apex show longer APDs than in isolated cells from the base (CHENG ET AL. 1999). In intact hearts, an APD gradient from base to apex has been observed in the pig (DEAN AND LAB 1990), whereas the opposite has been observed in the dog (BAUER ET AL. 2002). Janse et al. reported shortest repolarization times in anterobasal areas and longest

repolarization times in posteroapical areas of the intact canine left ventricle (JANSE ET AL. 2005).

Interventricular dispersion of repolarization. In experimental studies, APs of the left ventricle (LV) are longer than those of the right ventricle (RV) (DI DIEGO ET AL. 1996, VERDUYN ET AL. 1997a, VOS ET AL. 1998). Epicardial (DI DIEGO ET AL. 1996) and M cells (VOLDERS ET AL. 1999) from LV exhibit smaller I_{to} and I_{Ks} densities than those from RV, contributing to the repolarization gradient from LV to RV.

Alternans. A change in an amplitude or time interval of the electrogram that repeats every other beat is referred to as electrical alternans. Beat-to-beat alternation of APD is a rate dependent intrinsic property of myocardial cells that occurs above a critical threshold HR (PASTORE ET AL. 1999), probably reflecting time dependent recovery kinetics of transmembrane ionic currents. Abnormalities in e.g. $I_{Ca(L)}$ and I_{to} have been implicated (LUKAS AND ANTZELEVITCH 1993). Alternation with opposite phase between neighbouring cells (discordant alternans) produces spatial repolarization gradients (PASTORE ET AL. 1999).

Rate dependence. Global dispersion of repolarization does not show HR dependence at steady state (LAURITA ET AL. 1996, ZABEL ET AL. 1997). Premature stimulation significantly augments dispersion, however (MEXX ET AL. 1977, KUO ET AL. 1983, LAURITA ET AL. 1998). Considerable heterogeneity of AP restitution kinetics has been observed both across the epicardium (LAURITA ET AL. 1996) and transmurally (ANTZELEVITCH ET AL. 1991). APD in epicardium is shorter than in endocardium at rapid stimulation rates but longer at slower rates (LITOVSKY AND ANTZELEVITCH 1989), whereas M cells show considerably steeper rate dependence than either epicardial or endocardial cells (SICOURI AND ANTZELEVITCH 1991) potentially affecting TDR.

Autonomic effects. Han with co-workers observed that stimulation of cardiac sympathetic nerves increased whereas infusion of catecholamines decreased the dispersion of the recovery of excitability (HAN AND MOE 1964, HAN ET AL. 1964). Opthof et al. observed similarly that left, right or combined stellate stimulation could increase the dispersion of refractoriness, but not necessarily in every heart (OPTHOF ET AL. 1991). Regional differences have also been observed in response to right or left vagus nerve stimulation, most notably a failure of the anterior RV to respond to vagal stimulation despite significant prolongation of repolarization elsewhere (MARTINS ET AL. 1983). In the rabbit heart, however, bilateral autonomic nerve stimulation (both sympathetic and vagal) caused a reversal of the repolarization sequence between apex and base, a phenomenon not observed during pharmacological autonomic stimulation (MANTRAVADI ET AL. 2007). Yoshioka et al. studied the effects of noradrenaline infusion and direct stellate stimulation on activation recovery intervals in the in situ rabbit heart after regional denervation with topical phenol (YOSHIOKA ET AL. 2000). They observed consistent shortening of activation recovery intervals in denervated regions in response to

noradrenaline. However, during stellate stimulation a shortening was observed in only 30% and a prolongation in 70% of the regions.

Also transmural differences in responses to autonomic challenge exist, as suggested by the observation that epicardium is more sensitive than endocardium to the APD-modulating effects of acetylcholine and isoproterenol (LITOVSKY AND ANTZELEVITCH 1990). However, in an in vivo canine experiment, sympathetic stimulation reduced TDR by causing a greater abbreviation of MAPs in the M region than in epicardium or endocardium (TAKEI ET AL. 1999).

Dispersion of repolarization is thus significantly influenced by regional changes in sympathetic innervation and by dynamic changes in autonomic activity. Furthermore, different types of autonomic stimulation (neural or humoral) may cause dissimilar responses.

Other modulating factors. Hypothermia and regional warm blood perfusion increases dispersion of ventricular repolarization (KUO ET AL. 1983). Ischemia increases both spatial and transmural dispersion of APDs (KIMURA ET AL. 1988, LUKAS AND ANTZELEVITCH 1993), an effect further augmented by adrenergic stimulation (TAGGART ET AL. 1988b). In ischemic conditions, repolarization alternans has been observed to be related to cyclic changes in TDR occurring as a result of an alternating loss of the AP dome in epicardium but not in endocardium (LUKAS AND ANTZELEVITCH 1993). Pharmacologic blockade of transmembrane currents modulates transmural (SHIMIZU AND ANTZELEVITCH 1998, WU ET AL. 2005), apicobasal (BAUER ET AL. 2002) and interventricular (VAN OPSTAL ET AL. 2001, VERDUYN ET AL. 1997b) dispersion of repolarization. Changes in ion homeostasis may amplify transmural (WOLK ET AL. 1998) and apicobasal (WOLK ET AL. 2002) dispersion of repolarization. Mechanical factors such as acute left ventricular dilatation (REITER ET AL. 1988) and sustained left ventricular load (ZABEL ET AL. 1996) can increase dispersion of repolarization, possibly due to augmentation of apicobasal gradients (DEAN AND LAB 1990). Ventricular hypertrophy is associated with increased spatial (KOWEY ET AL. 1991), interventricular (VOS ET AL. 1998) and transmural (YAN ET AL. 2001a) dispersion of repolarization. Also gender-related transmural differences in ionic currents may exist (XIAO ET AL. 2006) contributing to TDR. Reversing the activation sequence to occur from the epicardium towards the endocardium (e.g. epicardial pacing) augments TDR (FISH ET AL. 2004).

2.2.5 Pathophysiological significance of repolarization

The refractory period and its adaptation to cycle length serve two important physiological functions. First, it prevents compounded APs such as occurs in skeletal muscle (tetanus). Second, the refractoriness of recently activated myocardial cells prevents circular reactivation, known as re-entry.

The development of re-entry requires the presence of unidirectional block within a conducting pathway and sufficiently slow conduction to enable recovery of excitability to allow for circular re-excitation by the next depolarizing wavefront. Classically, the

presence of an anatomical obstacle has been considered a prerequisite for re-entry. However, re-entry may occur even in the absence of anatomical obstacles if temporal differences in recovery of excitability are large enough (ALLESSIE ET AL. 1976). Functional unidirectional block then develops transiently during the absolute refractory period, whereas the necessary slowing of conduction occurs due to encroachment into the relative refractory period. In this way, steep repolarization gradients may create conditions facilitating re-entry (KUO ET AL. 1983, KUO ET AL. 1985, LAURITA AND ROSENBAUM 2000).

In keeping with these inferences, increased spatial dispersion of ventricular repolarization is associated with a susceptibility to ventricular arrhythmias (VASSALLO ET AL. 1988, MISIER ET AL. 1995, YUAN ET AL. 1995, CHAUHAN ET AL. 2006). Increased TDR is associated with re-entrant ventricular arrhythmias in a variety of congenital and acquired conditions (SHIMIZU AND ANTZELEVITCH 1998, AKAR AND ROSENBAUM 2003, FENICHEL ET AL. 2004, EXTRAMIANA AND ANTZELEVITCH 2004), underlining that potentially arrhythmogenic local re-entrant circuits may arise transmurally. Increased interventricular dispersion of repolarization has been associated with the occurrence of ventricular arrhythmia (VERDUYN ET AL. 1997b, VERDUYN ET AL. 1997a, VOS ET AL. 2000) and arrhythmic sudden death (VAN OPSTAL ET AL. 2001) in animal models. Electrical alternans is common in patients at increased risk for ventricular arrhythmias (ROSENBAUM ET AL. 1994, GOLD ET AL. 2000).

Exaggerated prolongation of APs favours the development of early afterdepolarizations. These can also be induced by β -adrenergic stimulation (PRIORI AND CORR 1990). The polymorphic ventricular tachyarrhythmia usually associated with AP prolongation, torsade de pointes (TdP), is considered to be triggered by premature ventricular beats arising from early afterdepolarizations (EL-SHERIF ET AL. 1988, YAN ET AL. 2001b), with increased TDR serving as a substrate for re-entry (EL-SHERIF ET AL. 1996, EL-SHERIF ET AL. 1997, YAN ET AL. 2001b).

The autonomic nervous system affects conduction velocity and APD – crucial determinants for re-entry – as well as the occurrence of early afterdepolarizations. Thus, alterations in autonomic activity can modulate both the substrate and the trigger for arrhythmia, through effects on ventricular repolarization.

2.3 Projections of repolarization on the body surface

2.3.1 ECG and MCG

At any given instant during cardiac excitation there are potential differences between excited and unexcited regions, therefore the electrical behaviour of the heart has often been described as a dipole. The orientation of such a dipole changes during the spread of excitation, and the ensuing potential changes can be detected with appropriately placed electrodes on the body surface. Recorded as a function of time, these potential changes are referred to as ECGs. An electrical vector moving towards the exploring (positive)

electrode causes a positive deflection on the ECG whereas a vector moving away from the exploring electrode causes a negative deflection. Activation wavefronts perpendicular to the exploring electrode are seen as isoelectric. ECG leads in contact with the heart are called direct, leads close to the heart (less than two cardiac diameters) are called semidirect and leads further away are called indirect. In bipolar leads, both the positive and negative electrodes face similar potential variations. In unipolar leads, the negative (by definition) electrode faces negligible potential variations compared with the positive electrode; the direction of the exploring positive electrode is thus radially outward from the centre of the heart.

The standard 12-lead ECG has three limb leads (I, II and III), three augmented limb leads (aVR, aVL and aVF) and six precordial leads (V1-V6). All of these leads are effectively bipolar (KLIGFIELD ET AL. 2007), although especially the precordial leads are commonly described as being unipolar. Being relatively distant, all limb leads are indirect. In the standard limb leads, one limb electrode is connected to the negative and the other to the positive terminal of the recorder. In the augmented limb leads, all three limb electrodes are connected to the negative terminal; a combination of two of these leads then serves as the negative electrode (“Goldberger central terminal”) whereas the remaining one connected to the positive terminal serves as the exploring electrode. Exclusion of the potential of the exploring lead from the central terminal “augments” the signal. Precordial leads (V1-V6) are semidirect, because the exploring electrodes are placed on the chest wall. They are connected to the positive terminal, whereas electrodes from right arm, left arm and left leg are all connected to the negative terminal (“Wilson central terminal”). An electrode placed on the right leg is earthed to minimize interference.

A low frequency filter (high-pass filter) is commonly applied to the signal to reduce wandering of the baseline, such as that caused by breathing movements. A high frequency filter (low-pass filter) can be used to minimize higher frequency noise. If the low frequency cut-off is set too high, it may distort the signal in areas with abrupt change of frequency content and wave amplitude. If the high frequency cut-off is set too low, it may cause inaccuracy in the assessment of QRS amplitudes and detection of small waveforms. A low frequency cut-off at 0.05 Hz and a high frequency cut-off at 150 Hz has been recommended for use in routine settings (KLIGFIELD ET AL. 2007).

The spatial sampling of surface ECG may be extended from the standard 12-lead positions to body surface potential mapping (BSPM) systems consisting of up to over a hundred chest leads. This widespread torso sampling facilitates better detection of local cardiac events (MIRVIS 1987) and has revealed that the electrical behaviour of the heart is more complex than a simple dipole. BSPM recordings are often presented as isopotential maps instead of traditional scalar waveforms, further emphasizing the localizing power of increased spatial sampling.

Magnetocardiography (MCG) measures the weak magnetic fields generated by the same potential changes, and consequently the MCG exhibits similar morphological and temporal features as the ECG (SAARINEN ET AL. 1978). Theoretically, ECG is more sensitive to radial currents, whereas MCG is more sensitive to tangential currents. In heart diseases, the proportion of tangential currents may increase, and MCG may in these

circumstances contain information of complementary nature to that of ECG (SILTANEN 1989, LANT ET AL. 1990).

2.3.2 Cellular basis of the T and U waves

It is generally accepted that the T wave in ECG represents repolarization gradients within the ventricles. The shape and duration of the T wave is affected both by the sequence of recovery across the ventricular and by differences in AP duration between different areas of the ventricles (VAN DAM AND DURRER 1964). In normal conditions, the QRS and T wave polarities are concordant, suggesting that normal ventricular electrical recovery occurs from the epicardium towards the endocardium (BURGESS ET AL. 1972, BURGESS 1979, FRANZ ET AL. 1987). Studies have shown also apico-basal (NOBLE AND COHEN 1978) and epicardial (COWAN ET AL. 1988a) repolarization gradients to be related to the T wave configuration.

The experimental studies of Yan and Antzelevitch (YAN AND ANTZELEVITCH 1998) on canine left ventricular wedge preparations brought new insight on the genesis of the T wave. They described that voltage gradients between M cells and epi/endocardial cells contribute prominently to the shape of the T wave on a pseudo-ECG measured across the ventricular wall. T wave onset occurred when phase 2 of the epicardial AP separated from that of the M region, and T wave peak occurred when the repolarization of the epicardium was complete. Voltage gradients between M cells and endocardial cells (opposite to those between M cells and epicardial cells) limited the amplitude of the T wave, and outlined the initial part of the descending limb of the T wave. The end of the T wave coincided with full repolarization of the M region. These findings indicate that local T wave morphology is influenced more by transmural than transventricular repolarization gradients. Direct in vivo validation of this theory is lacking, however (XIA ET AL. 2005b).

The origin and physiological significance of the U wave remains unresolved. It has been suggested to arise from afterdepolarizations (LEPESCHKIN 1957), the Purkinje network (WATANABE 1975), M cells (DROUIN ET AL. 1995) and from mechanoelectric events (SURAWICZ 1998). Recently, it was shown that catecholamine infusion causes distinct alterations in the duration and amplitude of the U wave, differing from the effects on the T wave, underlining that the U wave represents a component of cardiac repolarization that is electrocardiographically and physiologically distinct from the T wave (MAGNANO ET AL. 2004). Small U waves and large U waves may have a different origin, however. In a number of pathological conditions a low amplitude T wave is followed by prominent U wave. Experimental studies suggest that the forces responsible for such pathologic U waves are similar to those responsible for the T wave, indicating that the latter is likely a second component of a bifid T wave. Also clinical observations support this view (VIITASALO ET AL. 2006), suggesting that it would be more appropriate to use the terms “T2 waves” or “notched T waves” for these repolarization patterns.

2.3.3 QT interval measurement

The QT interval is considered to reflect the time from earliest activation to latest repolarization of ventricular myocardium and to represent the sum of all transmembrane APs in a given axis (VAUGHAN WILLIAMS 1982). In most clinical settings, measurement of the QT interval from the ECG remains the method of choice to assess perturbations of ventricular repolarization. However, no consensus exists as to the precise methodology and lead selection in QT interval measurements. Moreover, manual QT measurements show considerable intraobserver variation (AHNVE 1985), making comparisons between different studies even more difficult. The term QT interval generally refers to the time interval from the beginning of the Q wave to the end of the T wave (QTend). It is methodologically easier to measure the interval to the peak of the T wave (QTpeak), but its information content is different (YAN AND ANTZELEVITCH 1998, DAVEY 1999a).

Lead selection. In clinical studies, the QT interval has been measured from the lead in which the QT interval is longest, from the lead where the T wave is most prominent or its descending limb steepest, from lead aVL or II where the U wave is usually flat, or from a lead with a distinct initial Q wave (CAMPBELL ET AL. 1985). Various lead selections may give different results (SADANAGA ET AL. 2006). Based on their risk stratification study in families with congenital LQTS, Mönnig et al. suggested using lead II if measurable, and V5 as a second choice (MÖNNIG ET AL. 2006). Others have suggested using one of the leads V3-V4 (SADANAGA ET AL. 2006) or V2-V3 (KAUTZNER 2002). Using the average of all measured leads or a superimposition of simultaneously recorded leads may overcome problems of lead selection.

QRS onset. Timing of QRS onset varies slightly between different ECG leads (COWAN ET AL. 1988b). Resulting interlead variability of QT duration, whether real or artefact, may be eliminated by selecting the earliest QRS onset in any lead when assessing several synchronously recorded leads.

QTpeak. Identification of the peak of the T wave is usually straightforward, but difficulties may arise if the T wave is flat. Biphasic T waves are often excluded from measurements altogether, but this may seriously compromise the recognition of repolarization abnormalities. In such cases various strategies have been used, with T wave peak defined as the first peak, the second peak, or the highest of the peaks.

QTend. The end of the T wave is usually defined as the point where its descending limb meets the baseline, or alternatively, the point where a tangent fitted on the steepest downward slope of the T wave crosses the baseline. The latter method may somewhat underestimate the duration of the QT interval, but it is usable at higher HRs when the end of the T wave may be interrupted by the P wave. Both methods are, however, sensitive to drift of the isoelectric baseline. U waves should be excluded, but sometimes a notched or biphasic T wave may be mistakenly defined as a U wave. If the second apex occurs ≤ 150 ms after the first, it should be considered a biphasic T wave (LEPESCHKIN AND SURAWICZ

1952, LEHMANN ET AL. 1994). Partial fusion of the U wave with the terminal portion of the T wave is problematic. Lepeschkin and Surawicz, in the perhaps the most frequently cited study on the methodology of QT measurement (LEPESCHKIN AND SURAWICZ 1952), suggested using the tangent method on the descending limb of the T wave in the case of partial T-U fusion. Many investigators, however, define the nadir between the curves as the end of the T wave.

To overcome intra- and interobserver variation of QT measurements, several computer-based automatic methods have been introduced. Many of these have proven reproducible, practical and user-independent (SAVELIEVA ET AL. 1998a, OIKARINEN ET AL. 1998). However, some algorithms may have technical sources of error (MCLAUGHLIN ET AL. 1995, SMITH ET AL. 2003) and automated methods may be less reliable in cardiac patients than in healthy controls (MCLAUGHLIN ET AL. 1996), particularly in the case of difficult T wave morphologies (GLANCY ET AL. 1996a). It has been suggested that automated measurements may not significantly improve the accuracy of QT measurements, due to the inherent difficulties in identifying the end of the T wave precisely (KAUTZNER 2002).

2.3.4 Modulation of the QT interval

2.3.4.1 Rate dependence

HR is the most important determinant of QT interval duration. Normally, an increase in HR abbreviates the QT interval, whereas a decrease in HR prolongs it. Changes in QT duration in response to HR change are dependent on both instantaneous cycle length and on the duration of the prevailing HR (SEED ET AL. 1987). After a change in HR it can take up to two minutes for the QT interval to reach a new steady state (LAU ET AL. 1988). The QT interval and HR relation exhibits hysteresis phenomenon, probably related to concomitant changes in autonomic activity as well as to a time-dependency of QT interval adaptation to rapid change in cycle length (ARNOLD ET AL. 1982, SARMA ET AL. 1987).

A QT interval that is normal at a given HR may thus be abnormal at another. Therefore a number of normalization formulas have been utilized. Most of them are expressed in the form $QT_c = QT/RR^\alpha$, where QT is the measured QT interval and RR is the measured cycle length in seconds. Such formulas normalize the QT interval to the cycle length of 1 second, attempting to describe what the QT interval would have been, had it been measured at a HR of 60 beats per minute (bpm). The calculated QT_c interval may then be compared to a defined normal range without further attention to the measured QT interval or the prevailing HR. The most widely used formulas are the ones introduced by Bazett ($\alpha = 0.5$) (BAZETT 1920) and Fridericia ($\alpha = 0.333$) (FRIDERICIA 1920). Other approaches involve e.g. a linear regression equation ($QT_c = QT + 0.154[1 - RR]$) (SAGIE ET AL. 1992) or a nomogram method ($QT_c = QT + \text{correcting number}$)

(KARJALAINEN ET AL. 1994). A major limitation of any general formula attempting to normalize for HR is that the QT/RR dependence shows substantial interindividual variability (MALIK ET AL. 2002). However, as QT/RR dependence at the same time exhibits a high intraindividual stability, some authors have suggested that subject-specific rate correcting formulas should be used (BATCHVAROV ET AL. 2002).

During physical exercise the QT-HR relationship may be characterized by a linear regression equation (VIITASALO ET AL. 1996, KLIGFIELD ET AL. 1996). The slope of this equation (ranging from around -1.3 to -1.7 ms/beats/min in normal subjects) can be used as a measure of HR dependency of the QT interval.

2.3.4.2 Autonomic nervous system

The autonomic nervous system influences QT interval duration both directly and indirectly through changes in HR. The role of changes in autonomic activity in the modulation of QT duration has been studied by observing effects of 1) direct stimulation or interruption of cardiac nerves in animal experiments 2) drugs that stimulate or block cholinergic or adrenergic receptors 3) physiological manoeuvres that invoke reflex changes in autonomic activity (e.g., cardiovascular autonomic function tests) and 4) observing the relationship between QT changes and other markers of autonomic activity, e.g. from ambulatory ECG recordings.

Direct neural effects. Brief electrical stimulation of cardiac sympathetic nerves prolongs the QT interval, but prolonged stimulation abbreviates it (ABILDSKOV 1976). Interruption of sympathetic innervation by stellate ganglionectomy prolongs the QT interval, but effects of right or left stellate innervation show functional and regional differences (YANOWITZ ET AL. 1966). Stimulation of sympathetic nerves modulates the QT/RR relationship both at steady-state and during rapid rate adaptation (ZAZA ET AL. 1991) whereas no direct parasympathetic effects have been observed (MALFATTO ET AL. 1993).

Pharmacological autonomic effects. Rapid infusion of adrenaline ($\alpha/\beta_1/\beta_2$ agonist) transiently prolongs the QT interval, whereas slow infusion shortens it (ABILDSKOV 1976). Slow intravenous infusions of isoprenaline (β_1/β_2 agonist) (CUOMO ET AL. 1997, BALAJI ET AL. 1997, LOWE ET AL. 2001) and salbutamol (β_2 agonist) (LOWE ET AL. 2001) abbreviate QT duration. Magnano et al. observed that the QT interval shortened less during isoprenaline infusion than during exercise or atropine, after a similar increase in HR (MAGNANO ET AL. 2002). They also observed that QT-HR slopes were similar during exercise and atropine infusion, but were significantly less steep during isoprenaline infusion. Infusion of catecholamines may cause marked changes in T and U wave morphologies even in healthy subjects, complicating the interpretation of QT responses (MAGNANO ET AL. 2006). During atrial pacing, atropine and atropine plus propranolol shorten the QT interval independently of HR (AHNVE AND VALLIN 1982, BROWNE ET AL. 1982) showing a direct influence of vagal activity on the QT interval. Propranolol alone,

on the other hand, has no effect on QT duration at steady HR (BROWNE ET AL. 1982). Pharmacologic blockade at the level of sympathetic and parasympathetic ganglia has also been shown to prolong the QT interval (DIEDRICH ET AL. 2002).

Autonomic reflexes and exercise. QT duration varies with breathing phase, but it has been suggested that this is secondary to the cyclic changes in R-R intervals rather than a result of direct vagal modulation of repolarization (EMORI AND OHE 1999). Kautzner et al. reported that reflex parasympathetic activation induced by a phenylephrine bolus did not modulate the QTend or QTpeak interval, when HR was kept constant by atrial pacing (KAUTZNER ET AL. 1997).

During dynamic exercise, QT duration shortens linearly with increasing HR but shows considerable hysteresis during recovery, possibly related to autonomic effects (SARMA ET AL. 1987, SUNDQVIST AND SYLVÉN 1989). In addition, a paradoxical early prolongation of QT duration in response to exercise has been described in patients with permanent pacemakers (COGLAN ET AL. 1992), possibly related to the mechanism of transient prolongation seen during rapid adrenaline infusion (ABILDSKOV 1976). Mental stress testing abbreviates the QT interval even when HR remains constant, as shown in patients with high-degree atrioventricular block (HEDMAN AND NORDLANDER 1988). Paavonen et al. observed that the measured QT intervals shorten during mental stress testing, but to a lesser degree than during physical exercise at comparable HR (PAAVONEN ET AL. 2001).

In a study by Davidowski and Wolf (DAVIDOWSKI AND WOLF 1984), dynamic exercise was associated with considerable changes in both HR and QT interval, whereas Valsalva manoeuvre, dive reflex, hyperventilation, breath-holding and cold pressor testing showed only minimal or no change in QT duration, despite significant changes in HR. As a result, the use of QTc intervals was concluded to yield paradoxical results during reflex manoeuvres. Similarly, sustained handgrip has been reported to shorten the QT interval in healthy patients (DE CAPRIO ET AL. 1986), whereas others have reported QTc prolongation (DAVEY 1999b, FREDERIKS ET AL. 2001). It follows that the use of HR correction formulas is inappropriate when studying the effects of autonomic manoeuvres or stimulation on QT duration. This makes the interpretation and comparison of most previous studies difficult, as studies reporting in detail the behaviour of uncorrected QT intervals during autonomic testing are scarce.

Davidowski and Wolf further suggested that HR and QT interval may be governed by different sympathetic fibres. Similar conclusions were drawn in the study of Arrowood et al., examining normal subjects and cardiac transplant patients during exercise, Valsalva and the cold pressor test (ARROWOOD ET AL. 1993). Furthermore, their results suggested that during exercise, the QT interval was regulated primarily by increases in circulating catecholamines rather than neurally mediated reflex autonomic changes.

Ambulatory recordings. QT intervals in hearts with an intact autonomic innervation show a diurnal variation, whereas such variation is blunted in transplanted hearts and absent in diabetic autonomic neuropathy (BEXTON ET AL. 1986). It has been observed that QT intervals are longer during sleep than during comparable HRs in the waking state, indicating effects of increased vagal activity or decreased sympathetic activity

(VIITASALO AND KARJALAINEN 1992, MURAKAWA ET AL. 1992). Maximum QTc duration and QTc variability generally occur shortly after awakening, possibly due to autonomic instability at this time (MOLNAR ET AL. 1996). Arousal reactions during ambulatory recordings are associated with marked inertia of QT interval adaptation to HR (TOIVONEN ET AL. 1997). These observations underline the difficulties in interpreting QT intervals measured in uncontrolled settings. It has been suggested that changes in autonomic activity may be taken into account by plotting QT intervals against R-R intervals measured at similar basic HRs during different physiological conditions (VIITASALO AND KARJALAINEN 1992).

2.3.4.3 Other factors

Women generally exhibit longer QT intervals than men (BAZETT 1920, RAUTAHARJU ET AL. 1992). It has been shown that women exhibit steeper QT/HR slopes than men during isoprenaline and atropine infusions (MAGNANO ET AL. 2002) as well as during exercise (KLIGFIELD ET AL. 1996, MAGNANO ET AL. 2002, CHAUHAN ET AL. 2002). Women also exhibit steeper QTpeak/RR and QTend/RR slopes than men in ambulatory ECG recordings (OIKARINEN ET AL. 1998). Recent findings have indicated that there are gender differences in the QT responses to sympathetic stimulation, as observed during mental stress (INSULANDER AND VALLIN 2005) and in response to isoprenaline infusion (NAKAGAWA ET AL. 2005).

Plasma electrolyte disturbances are known to influence the QT interval; hypocalcaemia and hypokalemia prolong whereas hypercalcaemia and hyperkalemia generally shorten it. Fever abbreviates the QT interval independently of HR (KARJALAINEN AND VIITASALO 1986). Changes in ventricular loading may alter the QT interval (TAGGART ET AL. 1992) possibly related to mechanoelectric feedback (LAB 1982). A vast number of both cardiac (e.g., sotalol, quinidine, ibutilide, disopyramide, amiodarone) and noncardiac (e.g., macrolide antibiotics, several antipsychotics and antidepressants) drugs are known to prolong the QT interval (see www.torsades.org).

2.3.5 Spatial QT dispersion

2.3.5.1 Background and definition

The observation that interlead QT interval variation is greater in patients with heart disease than in controls (SYLVEN ET AL. 1984, MIRVIS 1985) and its association with arrhythmia risk (DAY ET AL. 1990) led to the hypothesis that QT dispersion reflects dispersion of ventricular refractoriness. The association between QT dispersion and dispersion of ventricular repolarization was validated in an experimental study, comparing multiple simultaneous MAP recordings with simulated 12-lead ECG in Langendorff-perfused rabbit hearts (ZABEL ET AL. 1995). QT dispersion was subsequently

adopted as a non-invasive method of measuring spatial dispersion of repolarization from body surface recordings, giving rise to a large number of studies on the diagnostic, prognostic and therapeutic value of this measure in both cardiac and non-cardiac conditions.

QT dispersion is classically quantified as the difference between the maximum and the minimum QT interval in any lead (DAY ET AL. 1990). To diminish the influence of single outliers and measurement error, the standard deviation (DAVEY ET AL. 1994) and the coefficient of variability (relative QT dispersion) (PRIORI ET AL. 1994) of QT intervals in all leads have also been used.

2.3.5.2 Measurement

There is no universally accepted standard method for QT dispersion measurement, but the principles of QT interval measurement generally apply to dispersion measurements as well. Simultaneous measurement of all leads is preferred, but probably not mandatory in resting measurements due to the lag in QT adaptation to HR change. Rate correction should not be used, because neither the dispersion of APs (ZABEL ET AL. 1997) nor QT dispersion (ZAREBA AND MOSS 1995) is HR dependent. Generally, QT intervals should be assessed from all available leads, but it is common practice to exclude leads in which the T wave is not well defined. The minimum number of accepted leads has varied among studies, but the numerical values of QT dispersion generally become smaller when the number of included leads is reduced. Significant differences between study groups have been detected using only the six precordial leads (HII ET AL. 1992) or even as few as three leads (GLANCY ET AL. 1995a). It has been proposed that QT dispersion should be adjusted to compensate for missing leads, by dividing with the square root of the number of measurable leads (DAY ET AL. 1991). However, this may distort the results; instead it has been suggested that unadjusted QT dispersion should be reported together with the number of accepted leads (GLANCY ET AL. 1995b).

Reproducibility of QT dispersion measurements has been a matter of concern, having low short-term reproducibility as well as significant interobserver errors in manual measurements (KAUTZNER ET AL. 1994). Automatic assessment of QT intervals eliminates observer bias, but has not solved the reproducibility problems of QT dispersion measurements (GLANCY ET AL. 1996a, SAVELIEVA ET AL. 1998a). However, in serial measurements on the same subject, the automatic method appears more reproducible than manual assessment (SAVELIEVA ET AL. 1998b).

2.3.5.3 Modulating factors

Physiological and chemical factors. QT dispersion was found not to be influenced by age or gender in a large sample of healthy subjects (MACFARLANE ET AL. 1998), although others have reported that males exhibit slightly more QT dispersion than females in certain age groups (TRAN ET AL. 2001, TANEJA ET AL. 2001). Krupienicz et al. reported

that both maximum expiration and maximum inspiration reduced QT dispersion by about 20% compared with normal breathing (KRUPIENICZ ET AL. 1997). In contrast, Gang and coworkers observed that QT dispersion was unaffected by respiration phase and posture (GANG ET AL. 1998). Sinus arrhythmia was observed not to influence QT dispersion in healthy children (TUTAR ET AL. 1998). A sudden decrease in ventricular filling brought about by altering the atrioventricular pacing mode increased QT dispersion in subjects with abnormal ventricular function but not in subjects with normal ventricles (JAMES ET AL. 2002). An increase in afterload during phenylephrine infusion increased QT dispersion independently of changes in HR or vagal activity (YEE ET AL. 2000). Hypoglycaemia increased QT dispersion in patients with type 2 diabetes (LANDSTEDT-HALLIN ET AL. 1999). One study reported that hypokalemia increased QT dispersion, whereas hyperkalemia, hypocalcaemia or hypercalcaemia had no significant effects (YELAMANCHI ET AL. 2001).

Influences of the autonomic nervous system. Two studies have reported increased QT dispersion in diabetics with autonomic dysfunction and abnormal scintigraphic patterns of cardiac sympathetic innervation (WEI ET AL. 1995, SHIMABUKURO ET AL. 1996). One of these studies (SHIMABUKURO ET AL. 1996) found a correlation between QT dispersion and cardiac adrenergic denervation whereas the other did not (WEI ET AL. 1995). Patients with primary autonomic failure, however, have no greater QT dispersion than controls despite prolonged QT intervals (LO ET AL. 1996). In healthy subjects, diurnal changes in QT dispersion have been observed to correlate with HRV indices reflecting increased sympathetic or decreased vagal activity (ISHIDA ET AL. 1997).

Neither reflex parasympathetic activation to a bolus of intravenous phenylephrine (KAUTZNER ET AL. 1997) nor parasympathetic blockade with atropine changed QT dispersion (YEE ET AL. 2000) in healthy subjects. Intravenous adrenaline, however, increased QT dispersion in healthy male subjects (LEE ET AL. 2003), and salbutamol and isoprenaline infusions increased QT dispersion both in patients with coronary artery disease and in healthy controls (LOWE ET AL. 2001).

Sympathetic activation elicited by sustained handgrip augmented a number of other ECG parameters describing dispersion of repolarization, but QT interval dispersion did not change significantly (VAN HUYSDUYNEN ET AL. 2004). The Valsalva manoeuvre was observed not to modify QT dispersion in healthy subjects (GHURAN ET AL. 2000). Reports on effects of sympathetic activation elicited by orthostatic stress are conflicting: Some investigators have observed increased QT dispersion during tilt testing (NAKAGAWA ET AL. 1999) whereas others have observed reduced QT dispersion in the standing compared with the supine posture (GHURAN ET AL. 2000). Orthostatic stress brought about by leg lowering, on the other hand, has been observed not to modify QT dispersion (VAN HUYSDUYNEN ET AL. 2004). Physical exercise has been reported to reduce QTpeak dispersion (CHAUHAN ET AL. 2002) whereas QTend dispersion has been reported not to change (ZABEL ET AL. 2000). In patients with coronary artery disease, QT dispersion has been shown to increase during mental stress testing (JAMES ET AL. 2000) and the strain phase of the Valsalva manoeuvre (BALBAY ET AL. 2001).

Cardiac diseases. Increased QT dispersion has been observed in a great number of pathological circumstances, e.g. acute myocardial infarction (GLANCY ET AL. 1996b), left ventricular dysfunction (ZAIDI ET AL. 1997, BONNAR ET AL. 1999), left ventricular hypertrophy (DAVEY ET AL. 1994, PERKIÖMÄKI ET AL. 1996), hypertrophic cardiomyopathy (ZAIDI ET AL. 1996), arrhythmogenic right ventricular dysplasia (BENN ET AL. 1999) and LQTS (PRIORI ET AL. 1994). Moreover, changes in QT dispersion have been reported to follow the dynamics of the underlying pathological processes. QT dispersion shows dynamic changes during acute myocardial infarction (GLANCY ET AL. 1996b) as well as induced ischemia in chronic coronary artery disease (SPORTON ET AL. 1997, MICHELUCCI ET AL. 1996, KOIDE ET AL. 2000, CARLUCCIO ET AL. 2003). Treatment has been shown to reduce QT dispersion in some disease states, e.g. in response to reperfusion after thrombolysis (MORENO ET AL. 1994) or revascularization (KELLY ET AL. 1997) in myocardial infarction, drug treatment of heart failure (BROOKSBY ET AL. 1999, BONNAR ET AL. 1999), regression of left ventricular hypertrophy after antihypertensive therapy (KARPANOU ET AL. 1998) and β -blockade in patients with LQTS (PRIORI ET AL. 1994).

2.3.5.4 Clinical significance

The prognostic value of QT dispersion with respect to mortality and adverse events has been studied extensively. Pooling a large number of studies on patients with or without ventricular arrhythmias in various cardiac diseases revealed a significantly greater QT dispersion in patients with arrhythmia, but the values of dispersion largely overlapped (MALIK AND BATCHVAROV 2000). Some large epidemiological studies have found increased QT dispersion a predictor of mortality (OKIN ET AL. 2000, PADMANABHAN ET AL. 2003) whereas others have not (BRENDORP ET AL. 2001, SHAH ET AL. 2004). Increased QTpeak dispersion was observed to be an independent risk factor for sudden cardiac death in middle aged men with otherwise normal ECG (MÄNTTÄRI ET AL. 1997). The large variation and overlap of the results in the studies have precluded the establishment of any meaningful reference values for QT dispersion (MALIK AND BATCHVAROV 2000).

Lately, the pathophysiological basis of QT dispersion has been questioned (MALIK AND BATCHVAROV 2000). A growing body of evidence suggests that QT dispersion is not only dependent on intrinsic spatial properties of the repolarization process, but also on the projection of the repolarization vector in different ECG leads. It has been suggested that QT dispersion mainly arises from variations in the T loop morphology and its variable projections into individual ECG leads (KORS ET AL. 1999). Recent investigations have shown a poor correlation between surface QT measurements and local ventricular refractoriness (VOSS ET AL. 2005) as well as between dispersion of repolarization and dispersion of QT intervals (FULLER ET AL. 2000, LIANG ET AL. 2005). Consequently, QT dispersion has been proposed to be an indirect measure of general repolarization abnormalities, rather than a marker of spatial repolarization inhomogeneity (MALIK AND BATCHVAROV 2000).

2.3.6 ECG manifestations of transmural dispersion

Experimental studies have indicated that the T wave peak to T wave end interval (TPE) represents the difference between the longest (M cells) and shortest (epicardial cells) AP durations across the ventricular wall (YAN AND ANTZELEVITCH 1998) and can thus be considered as the ECG counterpart of TDR (SHIMIZU AND ANTZELEVITCH 1997, SHIMIZU AND ANTZELEVITCH 1998, SHIMIZU AND ANTZELEVITCH 2000). This concept (presented schematically in Figure 2) is supported by evidence from clinical studies in patients with congenital LQTS (LUBINSKI ET AL. 1998, TANABE ET AL. 2001, VIITASALO ET AL. 2002a, TAKENAKA ET AL. 2003), in post myocardial infarction patients susceptible to ventricular tachycardia (OIKARINEN ET AL. 2001) and in high risk patients with organic heart disease (WATANABE ET AL. 2004). TPE was recently observed to correlate with the risk of TdP during acquired bradyarrhythmias (TOPILSKI ET AL. 2007). It is also prolonged in patients with left ventricular hypertrophy (SABA ET AL. 2005). However, some recent studies have reported findings suggesting that TPE is a more general measure of repolarization dispersion rather than a specific marker of TDR (XIA ET AL. 2005c, OPTHOF ET AL. 2007).

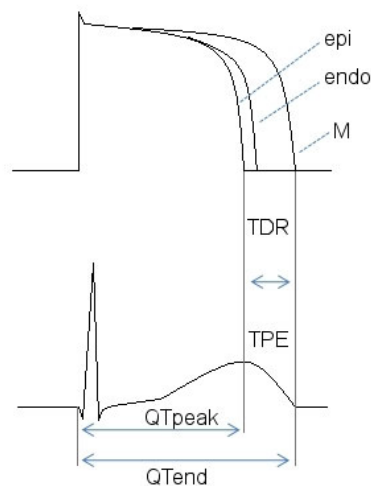


Figure 2. Schematic presentation of action potentials from epicardium (*epi*), endocardium (*endo*) and midmyocardium (*M*) together with a simultaneous ECG tracing, demonstrating that the T wave peak to T wave end interval (TPE) is the ECG counterpart of transmural dispersion of repolarization (TDR). QT_{peak} = Q wave to T wave peak interval, QT_{end} = Q wave to T wave end interval.

2.3.7 ECG manifestations of interventricular dispersion

In BSPM recordings QT intervals have distinctive spatial distributions consistent with regional myocardial electrophysiological properties, with longer QT intervals recorded over the left lateral thorax and shorter intervals over the right inferior thorax (MIRVIS 1985). Hlaing et al. reported that in healthy subjects QT intervals were longer in left

precordial ECG leads than in right precordial leads (HLAING ET AL. 2005). In the same study it was observed that systemic hypertension with left ventricular hypertrophy increased the QT difference between right and left precordial leads whereas pulmonary hypertension decreased the difference. These observations suggest that it may be possible to obtain an ECG index describing interventricular dispersion of repolarization.

2.3.8 Other ECG markers of repolarization heterogeneity

QT variability. QT duration exhibits beat-to-beat variability. Berger et al. introduced a means to quantify QT variability normalized to HRV (i.e., QT fluctuation not attributed to change in HR) by using a QT variability index (BERGER ET AL. 1997). This index has been shown to be increased in heart diseases associated with increased risk of arrhythmia and sudden cardiac death (BERGER ET AL. 1997, GALEANO ET AL. 2003, BILCHICK ET AL. 2004). Temporal variability of QT duration has also been quantified using the standard deviation of QT intervals, showing a distinct diurnal pattern with increased variability in the morning hours (BONNEMEIER ET AL. 2003), similar to those of sympathetic activity and the incidence of ventricular arrhythmias.

T wave alternans. Cyclic beat-to-beat variation of T wave amplitude, morphology or polarity is referred to as T wave alternans and is considered the ECG manifestation of AP alternans (PASTORE ET AL. 1999). T wave alternans associates with increased repolarization heterogeneity and susceptibility to ventricular arrhythmias (ROSENBAUM ET AL. 1994, CHAUHAN ET AL. 2006). Rashba et al. reported the magnitude of T wave alternans to be influenced by sympathetic but not parasympathetic activity (RASHBA ET AL. 2002). Exercise and mental stress testing induces T wave alternans in patients at high risk for malignant arrhythmias (KOP ET AL. 2004).

T wave complexity. Other approaches in the assessment of regional repolarization inhomogeneity include principal component analysis of T wave morphology (PRIORI ET AL. 1997), descriptors of the 3-dimensional T loop (BATCHVAROV ET AL. 2000), singular value decomposition of the T wave (VAN HUYSDUYNEN ET AL. 2004) and parameters describing T wave area, amplitude and symmetry (VAN HUYSDUYNEN ET AL. 2005).

2.4 Congenital arrhythmogenic disorders

2.4.1 Congenital long QT syndromes

2.4.1.1 Pathophysiology and clinical characteristics

The spectrum of congenital LQTS (formerly referred to as Romano-Ward syndrome, or when associated with congenital deafness, Jervell and Lange-Nielsen syndrome) encompasses a number of ion channel defects that produce alterations in cardiac ionic currents resulting in prolonged ventricular repolarization times. LQTS is characterized clinically by prolonged QT intervals and susceptibility to ventricular arrhythmias associated with syncopal spells, and potentially, sudden cardiac death.

At least eight subtypes of LQTS have been described (LQT1-LQT8). Loss-of-function mutations in *KCNQ1* and *KCNE1* reduce I_{Ks} , forming the LQT1 (WANG ET AL. 1996a) and LQT5 (SPLAWSKI ET AL. 1997) subtypes of LQTS, respectively. Analogously, loss-of-function mutations in *KCNH2* (*hERG*) and *KCNE2* reduce I_{Kr} , forming the LQT2 (CURRAN ET AL. 1995) and LQT6 (ABBOTT ET AL. 1999) subtypes. Gain-of-function mutations in *SCN5A* cause defective inactivation of I_{Na} , forming the LQT3 subtype (WANG ET AL. 1996b). LQT4, arising from Ankyrin-B mutation, is the only subtype of LQTS recognized so far not caused by an ion channel defect (MOHLER ET AL. 2003). LQT7 (Andersen syndrome) and LQT8 (Timothy syndrome) are very rare multisystem disorders caused by defective inward rectifier potassium channel Kir2.1 (TRISTANI-FIROUZI ET AL. 2002) and mutations causing amplified $I_{Ca(L)}$ (SPLAWSKI ET AL. 2005, SICOURI ET AL. 2007), respectively.

Arrhythmias tend to occur in different circumstances in the subtypes of LQTS (SCHWARTZ ET AL. 2001). In LQT1, symptoms are commonly associated with sympathetic activation at elevated HRs, such as during exercise and strong emotions. In LQT2 symptoms occur during arousal, startle or sudden exercise, whereas in LQT3 symptoms typically occur during sleep. Swimming appears to be a genotype-specific trigger in LQT1 (MOSS ET AL. 1999), whereas auditory stimuli are specific triggers in LQT2 (WILDE ET AL. 1999).

2.4.1.2 Electrophysiological characteristics

APs and cellular basis of abnormal T waves. In experimental studies the most common LQTS subtypes have been modelled with selective pharmacologic blockade of ionic currents. The effects of such blockade on epicardial, endocardial and M cell APs and a transmural ECG have been extensively studied in arterially perfused canine left ventricular wedge preparations (YAN AND ANTZELEVITCH 1998, SHIMIZU AND ANTZELEVITCH 1998, SHIMIZU AND ANTZELEVITCH 2000). The LQT1 model prolonged APs of all cell types homogeneously, resulting in QT prolongation but little or no change

in T wave morphology. In the LQT2 model, APs of M cells prolonged more than those of endo- or epicardial cells, increasing TDR and causing bifid T waves with prolonged TPE intervals. The LQT3 model prolonged phase 2 of the AP in all cell types, resulting in a markedly prolonged QT interval with a late onset T wave.

QT intervals and morphology of the T wave. Prolonged QTc is by definition considered as one of the major diagnostic criteria of LQTS (SCHWARTZ ET AL. 1993). Nevertheless, a substantial overlap in QT duration has been reported between affected and unaffected relatives and many gene carriers have QTc intervals in the normal range (VINCENT ET AL. 1992, PIIPPO ET AL. 2001). Even carriers with normal QTc appear to be at risk for cardiac events, however (PIIPPO ET AL. 2001). Biphasic, notched or double-peaked T waves are more frequently encountered in LQTS than in healthy controls (LEHMANN ET AL. 1994, MALFATTO ET AL. 1994), especially in the LQT2 genotype (LUPOGLAZOFF ET AL. 2001). Genotype-specific differences in T wave morphologies have been described (MOSS ET AL. 1995, ZHANG ET AL. 2000, STRUIJK ET AL. 2006), corresponding to the features observed in experimental LQTS models. It has been suggested that abnormal T wave morphology is a phenotypic expression of LQT2 and that its quantification could be useful in borderline diagnostic cases (COUDERC ET AL. 2006). Moreover, Viitasalo et al. observed that the maximal amplitude ratio between late and early T wave peaks was independently associated with the occurrence of symptoms in both LQT1 and LQT2 patients (VIITASALO ET AL. 2006).

TPE interval. The association between TdP and TDR observed experimentally suggests that a prolonged TPE interval in ECG may indicate arrhythmia risk in LQTS (SHIMIZU AND ANTZELEVITCH 1998, SHIMIZU AND ANTZELEVITCH 2000). Prolonged TPE has been reported in patients with both congenital (LUBINSKI ET AL. 1998, KHOSITSETH ET AL. 2003) and acquired LQTS (YAMAGUCHI ET AL. 2003). Furthermore, assessment of TPE from ambulatory ECG was shown to be useful in differentiating LQT1, LQT2 and unaffected subjects (VIITASALO ET AL. 2002b). TDR was shown to be greater in LQT2 compared with LQT1, but LQT1 patients showed abrupt increases in TDR at elevated HRs (VIITASALO ET AL. 2002a).

QT dispersion. Spatial dispersion of refractoriness (VASSALLO ET AL. 1988) and dispersion of MAP duration were shown to be increased in LQTS patients (BONATTI ET AL. 1983); therefore QT dispersion has been studied extensively in LQTS populations. A number of studies have reported more QT dispersion in LQTS patients than in healthy controls, both in non-genotyped (LINKER ET AL. 1992, PRIORI ET AL. 1994, LUBINSKI ET AL. 1998) and genotyped populations (SWAN ET AL. 1998a, MÖNNIG ET AL. 2001, INOUE ET AL. 2003). Inoue et al. reported that although dispersion of QTend intervals was similarly increased in LQT1 and LQT2 patients compared with controls, dispersion of QTpeak was increased only in LQT2 patients (INOUE ET AL. 2003). Some investigators have found a greater QT dispersion in symptomatic than in asymptomatic patients (MÖNNIG ET AL. 2001) whereas others have not (SWAN ET AL. 1998a, LINKER ET AL. 1992). Priori et al. observed a reduction in QT dispersion after β -blockade and left stellate

ganglionectomy, and suggested that QT dispersion could predict the efficacy of antiadrenergic treatment (PRIORI ET AL. 1994). Increased QT dispersion has been reported to be associated with local wall motion abnormalities (mechanical dispersion) (NAKAYAMA ET AL. 1998) and the same group reported later that these abnormalities were related to inhomogeneities in myocardial sympathetic innervation (YAMANARI ET AL. 2000). Increased spatial inhomogeneity of ventricular repolarization has been observed in LQTS also with BSPM (SHIMIZU ET AL. 1994) and MCG mapping (KANDORI ET AL. 2002). Both of these studies reported observations suggesting that repolarization times were longest over the LV. The concept of interventricular QT dispersion has not been assessed clinically, however.

Rate adaptation of APD and QT intervals. In experimental LQTS models, rate adaptation of APD is steeper in LQT1, LQT2 and LQT3 than in normal preparations (PRIORI ET AL. 1996, SHIMIZU AND ANTZELEVITCH 1997, SHIMIZU AND ANTZELEVITCH 1998) and steeper in LQT3 than in the other models. Transmural differences in rate-dependency of APD (LITOVSKY AND ANTZELEVITCH 1989, ANTZELEVITCH ET AL. 1991) due to non-uniform expression of defective ion channels in epicardial, endocardial and M cells (SHIMIZU AND ANTZELEVITCH 2000) are likely to explain these differences. With one exception (LINKER ET AL. 1991), similar observations have been made in clinical studies: In ambulatory ECG recordings, LQTS patients had steeper QT_{peak}/RR slopes than controls (MERRI ET AL. 1992, EMORI ET AL. 1995). QT_{end}/HR slopes during recovery after exercise were steeper in children with LQTS than in their healthy relatives (SWAN ET AL. 1998b). During face immersion testing QT/HR slopes were significantly steeper in children with LQTS than in controls (HIRAO ET AL. 1996). However, these studies comprised non-genotyped populations, and thus probably a mixture of the LQTS subtypes.

More recent clinical studies on genotyped populations have also supported the previous experimental observations. In ambulatory ECG recordings LQT1 patients had steeper QT_{peak}/RR and QT_{end}/RR slopes than controls at night, but not during the day (NEYROUD ET AL. 1998). In exercise testing, QT/HR slopes during exercise were steeper in LQT2 patients than both in LQT1 patients and controls, whereas during the recovery phase QT/HR slopes were steeper both in LQT1 and LQT2 than in controls (SWAN ET AL. 1999a). Viitasalo et al. described genotype-specific patterns in the rate adaptation of QT intervals after cycle length grouping, allowing differentiation between LQT1 and LQT2 patients with ambulatory ECG recordings (VIITASALO ET AL. 2002b). Observations from ambulatory recordings indicate that LQT2 and LQT3 patients exhibit steeper HR dependency of QT duration than LQT1 patients, with the former having longer QT intervals at slower but not at faster HRs (NĚMEC ET AL. 2004). Extramiana et al. reported that both QT_{peak} and QT_{end} intervals were longer in LQT1 patients than controls at all measured HRs in ambulatory ECG (EXTRAMIANA ET AL. 2005). They demonstrated further that symptomatic LQT1 patients exhibited a lack of shortening of the late phase of the T wave in response to increasing HR, in contrast to asymptomatic patients and controls. One study noted no significant differences in the QT/HR slopes assessed during

mental and physical stress testing between LQT1, LQT2 and controls (PAAVONEN ET AL. 2001).

QT interval variability. Temporal variability in the form of T wave alternans has been associated with LQTS (ZAREBA ET AL. 1994, KAUFMAN ET AL. 2001). Time-domain measures of QT interval variability calculated from ambulatory recordings were shown to be greater in LQTS patients than controls, despite similar HRV in both groups (PERKIÖMÄKI ET AL. 2002). LQT1 (except those with G589D mutation) and LQT2 patients have shown an increased QT variability index compared with controls (BILCHICK ET AL. 2004). Furthermore, the spread of QT interval durations at a given HR has been shown to be larger in LQT2 and LQT3 than in LQT1 patients (NĚMEC ET AL. 2004). Thus, the QT interval exhibits temporal as well as spatial dispersion in LQTS physiology.

2.4.1.3 Autonomic nervous system

Autonomic innervation and activity. Scintigraphic studies have described local sympathetic dysinnervation in LQTS patients (GOHL ET AL. 1991, YAMANARI ET AL. 2000). Moreover, Shamsuzzaman et al. reported a selective reduction of sympathetic nerve traffic to muscle blood vessels in LQTS patients, and they speculated that this may also be the case in the heart (SHAMSUZZAMAN ET AL. 2003). However, others have found quite normal scintigraphic patterns of cardiac sympathetic innervation in LQTS patients (CALKINS ET AL. 1993). Earlier studies have reported both higher (KATO AND YANAGAWA 1994) and lower (MORITA ET AL. 1996) sympathetic activity in LQTS patients than in controls, when assessed by HRV indices. In a more recent study, however, no differences were found between LQT1, LQT2, LQT3 and controls in any of the parameters describing 24-hour HRV (PERKIÖMÄKI ET AL. 2002).

Pharmacological autonomic interventions in experimental models. Shimizu and Antzelevitch described the role of β -adrenergic agonists and antagonists under LQTS conditions in canine LV wedge preparations (SHIMIZU AND ANTZELEVITCH 2000). In the LQT1 model, isoprenaline prolonged APD of M cells, but abbreviated APD in epi- and endocardial cells, thereby increasing TDR markedly. Spontaneous or induced TdP occurred only in the presence of isoprenaline. This dramatic increase in TDR in response to β -adrenergic stimulation and its association with arrhythmia explains the arrhythmia propensity during increased sympathetic activity in LQT1 patients. In the LQT2 model, isoprenaline increased TDR only transiently, due to an initial prolongation and subsequent abbreviation of M cell APD, but a persistent abbreviation of epicardial APD. In the LQT3 model, isoprenaline abbreviated APD in all myocardial layers, thereby causing a decrease in TDR. Isoprenaline transiently increased the incidence of TdP in LQT2 while it suppressed TdP in LQT3. All actions of isoprenaline were abolished in the presence of propranolol.

Pharmacological autonomic interventions in patients. Studies conducted before the recognition of the genetic background of LQTS probably contained a mixture of different genotypes, making the results of many older studies difficult to interpret. The importance of sympathetic stimulation was noted in many of these early studies, however. Shimizu et al. reported that isoprenaline infusion and exercise prolonged the QTc interval in LQTS patients, but atrial pacing did not, indicating that sympathetic stimulation played an important role in generating the repolarization abnormalities in LQTS (SHIMIZU ET AL. 1991a). Another study described QTc prolongation during isoprenaline, but not during exercise (KATAGIRI-KAWADE ET AL. 1995). It was further reported that isoprenaline increased both the duration and spatial dispersion of MAPs in LQTS patients, and induced early afterdepolarizations in some of them (SHIMIZU ET AL. 1991b). Similar effects on MAP duration and dispersion were described in response to adrenaline (HIRAO ET AL. 1996). Sun et al. studied symptomatic LQTS patients during steady-state adrenaline and phenylephrine infusions, both during sinus rhythm and atrial pacing (SUN ET AL. 1998). At constant paced HR, adrenaline prolonged the QTend interval and markedly increased QTend dispersion and QTpeak dispersion in LQTS patients but not in controls. Phenylephrine did not modulate QT duration or dispersion. Aizawa et al. described, in a study of only five LQTS patients, prolongation of QTc during intracoronary administration of acetylcholine; inducing TdP in two of the patients (AIZAWA ET AL. 1996).

Genotype-specific responses to adrenergic agonists have subsequently been described, proving similar to those expected from the experimental models. In a landmark clinical study, Tanabe et al. recorded BSPM in LQT1, LQT2 and controls before and after a continuous adrenaline infusion (TANABE ET AL. 2001). Adrenaline significantly prolonged the rate-corrected QTend and TPE intervals but not the QTpeak interval in both LQT1 and LQT2 patients. In addition, rate-corrected QTend dispersion but not QTpeak dispersion increased in both patient groups. All adrenaline-induced changes were of greater magnitude in LQT1 than LQT2, suggesting that LQT1 patients are more sensitive to sympathetic stimulation. Noda et al. studied the effects of a bolus injection of adrenaline, followed by a continuous steady-state infusion (“Shimizu protocol”) in LQT1, LQT2 and LQT3 patients (NODA ET AL. 2002). In LQT1 patients, the QTc interval prolonged markedly in response to the bolus and remained prolonged during continuous infusion. LQT2 patients showed dramatic prolongation of QTc after the bolus, but QTc shortened to baseline level during steady-state infusion. The responses of LQT3 patients did not differ significantly from controls, showing only small increases in QTc during the bolus. Ackerman et al., on the other hand, reported that adrenaline infusion in gradually increasing doses (“Mayo protocol”) prolonged the uncorrected QT interval only in LQT1 patients, but not in LQT2, LQT3 or controls (ACKERMAN ET AL. 2002), referring to it as a paradoxical QT response. They reported in a subsequent larger study that a paradoxical QT response, when defined as a QT prolongation of ≥ 30 ms during low-dose adrenaline infusion, had 93% sensitivity and 86% specificity for LQT1 status (VYAS ET AL. 2006). The paradoxical QT response identified even concealed LQT1 (genotype-positive patients with unequivocal QTc) with high accuracy. Similar observations were made in a study by Shimizu et al. (SHIMIZU ET AL. 2003), where adrenaline administered by the “Shimizu

protocol” prolonged rate-corrected QTpeak, QTend and TPE duration and increased QTpeak dispersion also in asymptomatic LQT1 mutation carriers with only borderline resting QTc. In an invasive study, adrenaline infusion was shown to prolong phase 3 of RV MAPs and to increase the rate dependence of MAP durations in symptomatic LQT1 patients, but not in LQT2 patients or controls (VIITASALO ET AL. 2005). Adrenaline infusion has also been observed to precipitate genotype-specific T wave abnormalities (KHOSITSETH ET AL. 2005) and to accentuate the beat-to-beat variability of QT intervals in LQT1 patients (SATOMI ET AL. 2005).

Phenylephrine-induced bradycardia has been reported to shorten the TPE interval in symptomatic LQT1 patients but to prolong it in symptomatic LQT2 patients (KHOSITSETH ET AL. 2003). Kaufman et al. found no difference in the QT responses to an intravenous phenylephrine bolus between LQT1, LQT2 and control subjects, whereas during adrenaline infusion a cut-off QTc-value of 600 ms distinguished LQT1 patients from controls with 80% sensitivity and 80% specificity (KAUFMAN ET AL. 2005). Nĕmec et al. observed that phenylephrine and dobutamine infusion caused nonalternating beat-to-beat T wave lability in LQT1, LQT2 and LQT3 patients (NĕMEC ET AL. 2003).

Combined, these previous reports underscore the importance of sympathetic stimulation particularly in LQT1 subtype of LQTS, providing clinical evidence in support of the previous experimental findings. They also suggest that sympathetic challenge may be used as a diagnostic test especially among suspected LQT1 carriers exhibiting normal QT intervals.

Physical exercise. Exercise was observed to induce QTc-prolongation in LQTS patients but not in controls (SHIMIZU ET AL. 1991a, VINCENT ET AL. 1991). In contrast, Krahn with colleagues reported that the rate corrected R wave peak to T wave peak interval shortened to a greater extent in LQTS patients than in controls during exercise (KRAHN ET AL. 1997). They also described a persistent shortening of this interval during recovery in LQTS, which caused a hysteresis loop of the RT/RR relationship in almost all LQTS patients but only in a few of the controls. Treatment with β -blockers reduced this hysteresis (KRAHN ET AL. 2002). Swan et al. measured QTpeak and QTend intervals at similar HRs during and after exercise in children with LQTS and their healthy relatives (SWAN ET AL. 1998b). In control subjects, both QTpeak and QTend intervals were significantly shorter during recovery than it was during exercise at the same HR. In contrast, LQTS patients exhibited abnormal lengthening of QTend during recovery. The varying results of these previous studies may perhaps be explained by the confounding effects of mixed LQTS populations, the inappropriate rate correction of QT intervals and differing exercise protocols. It has been shown that in LQTS patients, sudden intense exercise induces more pronounced repolarization abnormalities and steeper QT-HR relations than observed during graded exercise (CHAUHAN ET AL. 2004, WALKER ET AL. 2005).

Swan et al. compared the QT and HR responses to exercise in the two most common genotypes of LQTS (LQT1 and LQT2) (SWAN ET AL. 1999a). LQT1 was associated with a diminished chronotropic response to exercise and exaggerated prolongation of QT interval during recovery. LQT2 patients showed more pronounced abbreviation of QT

interval during exercise than LQT1 patients. In a similar study, significant prolongation of QTc and rate-corrected TPE at peak exercise was observed in LQT1 but not in LQT2 patients (TAKENAKA ET AL. 2003).

Cardiovascular autonomic function tests. A case report first described that adrenergic stimulation by Valsalva manoeuvre and cold pressor testing precipitated ventricular bigeminy in a patient with LQTS (RUBIN ET AL. 1979). A later clinical study reported QTc interval prolongation in response to the Valsalva manoeuvre in LQTS patients (MITSUTAKE ET AL. 1981). This prolongation was particularly pronounced in patients with frequent symptoms and was associated with T wave alternans and short runs of ventricular tachycardia in one of them. These repolarization abnormalities were suppressed by propranolol, and the authors suggested that the Valsalva manoeuvre might be useful in evaluating both arrhythmia risk and efficacy of treatment in LQTS. Another study described longer QTc in LQTS compared with controls during cold pressor testing and Valsalva manoeuvre, but the QTc values during the tests were not significantly different compared with baseline values in either group, however (EGGELING ET AL. 1992). Effects of the Valsalva manoeuvre have not been studied in genotyped populations.

In LQTS patients, QTc prolongation has been described both during the HR acceleration (KATAGIRI-KAWADE ET AL. 1995) and HR deceleration phases (YOSHINAGA ET AL. 1999) of face immersion in cold water. It was observed in a small study that treatment with propranolol or mexiletine attenuated the prolongations of QTc and TPE induced by face immersion (HARAGUCHI ET AL. 2005).

Paavonen et al. compared the QT interval adaptation to mental and physical stress at similar HRs in asymptomatic LQT1 patients, LQT2 patients and controls (PAAVONEN ET AL. 2001). In controls, QT interval shortening was more pronounced during exercise than during mental stress at comparable HR, whereas no such difference was seen in either LQT1 or LQT2 patients. QT interval responses to the interventions did not differ between LQT1 and LQT2 patients.

2.4.2 Arrhythmogenic right ventricular dysplasia

Arrhythmogenic right ventricular dysplasia (ARVD) is a familial cardiomyopathy associated with potentially life-threatening arrhythmia of RV origin, involving diffuse or segmental loss of RV myocardium and replacement with fibrofatty tissue (MARCUS ET AL. 1982, THIENE ET AL. 1988). Many of the thus far identified causative mutations reside in genes encoding for key components of desmosomes (SEN-CHOWDHRY ET AL. 2005), which are scaffolding proteins involved in cell-to-cell adhesion. Consequent defective mechanical coupling between cells may result in gap junction remodelling, accounting for the increased arrhythmia propensity. After an initial “concealed” phase, ARVD has been thought to progress from localized to a more global RV dysfunction, ultimately followed by LV involvement and biventricular failure (SEN-CHOWDHRY ET AL. 2005). More recently, disease variants with early LV involvement have been identified, suggesting the

use of the broader term “arrhythmogenic cardiomyopathy” (SEN-CHOWDHRY ET AL. 2007).

Diagnosis of ARVD relies on a set of major and minor criteria encompassing structural, histological, ECG, arrhythmic and genetic features, as proposed by an international working group (MCKENNA ET AL. 1994). Major criteria include severe RV dysfunction or dilatation, fibrofatty replacement of RV myocardium, local conduction abnormalities and family history confirmed by autopsy or surgery. Minor criteria include mild RV dysfunction or dilatation, inverted T waves in leads V2-V3, late potentials on signal-averaged ECG, ventricular tachycardia or frequent premature beats (>1000/24 hours) of RV origin, and family history of ARVD. The presence of 2 major criteria, or 1 major + 2 minor criteria, or 4 minor criteria are required for diagnosis of ARVD.

ECG abnormalities. Among the international diagnostic criteria, epsilon waves and QRS duration >110 ms in leads V1-V3 (in the absence of right bundle branch block) are considered major criteria whereas the occurrence of inverted T waves in leads V2-V3 is considered a minor criterion (MCKENNA ET AL. 1994). ECG manifestations of ARVD mostly involve abnormalities of the QRS complex (METZGER ET AL. 1993, KINOSHITA ET AL. 1995, KAZMIERCZAK ET AL. 1998, PETERS ET AL. 2007), and a prolonged S wave upstroke has been reported to be the most frequent ECG abnormality (NASIR ET AL. 2004). Endocardial electroanatomic mapping has shown that the dysplastic regions of the RV exhibit discrete areas of low amplitude electrograms (BOULOS ET AL. 2001). ARVD patients exhibit abnormal QRST integral maps indicative of delayed RV repolarization in BSPM (PEETERS ET AL. 1997, DE AMBROGGI ET AL. 1997). In addition, principal component analysis of the T wave was reported to detect repolarization abnormalities not apparent in QRST integrals or 12-lead ECG (DE AMBROGGI ET AL. 1997). ARVD patients have more QT dispersion than control subjects (BENN ET AL. 1999, FAGUNDES ET AL. 2000, TURRINI ET AL. 2001). One study reported normal QT dispersion, however, but noted prolonged QTc intervals (>440 ms) in half of the studied ARVD patients (KAZMIERCZAK ET AL. 1998). Turrini with colleagues reported that QT dispersion was the strongest independent predictive marker of sudden death in ARVD patients (TURRINI ET AL. 2001). They further noted that the maximum QT intervals were found in the right precordial leads.

Autonomic nervous system. ARVD patients have abnormal cardiac sympathetic innervation as determined by scintigraphic methods (LERCH ET AL. 1993, WICHTER ET AL. 1994, WICHTER ET AL. 2000). Moreover, ARVD patients have decreased HRV that appears to correlate with the extent of the disease (FOLINO ET AL. 2002). Symptoms are usually associated with physical or mental stress, and it has been shown that the arrhythmias can be induced by isoproterenol infusion (HAISSAGUERRE ET AL. 1990) and suppressed by drugs with antiadrenergic properties (WICHTER ET AL. 1992). These findings indicate that the activity of the autonomic nervous system may contribute to the genesis of arrhythmia in ARVD patients.

2.4.3 Brugada syndrome

The Brugada syndrome (BRUGADA AND BRUGADA 1992) is characterized by marked ST-elevation in the right precordial ECG leads and a high incidence of sudden arrhythmic death. Loss-of-function SCN5A mutations are associated with this disorder, causing attenuated I_{Na} (CHEN ET AL. 1998) as opposed to the augmented I_{Na} observed in LQT3. Reduced I_{Na} causes partial or complete loss of the AP dome during phase 2 in RV epicardium where I_{to} is prominent, but not in endocardium where I_{to} is weak. This gives rise to a transmural voltage gradient that explains the ST elevation observed in ECG leads placed over the RV (YAN AND ANTZELEVITCH 1999, KURITA ET AL. 2002) and creates a substrate for re-entry (ANTZELEVITCH 2001). Consequently, sodium channel blockers are valuable in the diagnosis of the disease, by unmasking the abnormal ECG pattern (HONG ET AL. 2004). Recently, loss-of-function mutations of $I_{Ca(L)}$ have also been found to cause the Brugada phenotype (ANTZELEVITCH ET AL. 2007).

In Brugada patients, QTc intervals are generally not prolonged in any other leads than V1-V3 (where the ST-elevation hampers QT measurements). However, TPE duration, TPE dispersion and the presence of prolonged QTc in lead V2 have been shown to correlate with arrhythmic events (CASTRO HEVIA ET AL. 2006). QT dispersion (IKEDA ET AL. 2001, NANKE ET AL. 2002) and T wave alternans (IKEDA ET AL. 2001) has been reported not to be significantly different between Brugada patients and healthy controls. BSPM mapping has shown depolarization and repolarization abnormalities especially over the RV outflow tract (HISAMATSU ET AL. 2004). Decreased QTpeak/RR and QTend/RR slopes and impaired QT prolongation in response to slowing of HR have been described in patients with Brugada-like ECG and a history of idiopathic ventricular fibrillation (FUJIKI ET AL. 2004).

Scintigraphic findings indicative of presynaptic myocardial sympathetic dysfunction have been reported (WICHTER ET AL. 2002). Higher vagal and lower sympathetic activity in symptomatic Brugada patients than in controls was suggested from HRV observations (NAKAZAWA ET AL. 2003). The ST elevation in Brugada syndrome is augmented by α -adrenergic stimulation, but is attenuated by β -adrenergic stimulation (MIYAZAKI ET AL. 1996). These previous findings indicate that although the arrhythmogenic substrate is related to local repolarization abnormalities, sympathetic stimulation appears not to be an important precipitator of arrhythmic events in the Brugada syndrome.

2.4.4 Catecholaminergic polymorphic ventricular tachycardia

Familial polymorphic ventricular tachycardia is characterized by salvos of bidirectional and polymorphic ventricular tachycardias, occurring typically during adrenergic stimulation or intense physical exercise (LEENHARDT ET AL. 1995, SWAN ET AL. 1999b). The incidence of sudden cardiac death at early age is very high. Mutations in the cardiac ryanodine receptor gene (LAITINEN ET AL. 2001, PRIORI ET AL. 2001) or the calsequestrin 2 gene (LAHAT ET AL. 2001) resulting in abnormal intracellular calcium handling have been identified as causes for the disorder. QTc intervals of the patient populations studied have been normal or only slightly prolonged at rest (LEENHARDT ET AL. 1995, SWAN ET

AL. 1999b). In a canine LV wedge model of this syndrome, it was observed that the epicardium was a frequent source of ectopic beats during sympathetic stimulation (NAM ET AL. 2005). The reversed activation sequence of epicardial ectopic beats markedly amplified TDR, thus providing a substrate for arrhythmia.

2.4.5 Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a familial cardiac disease with an autosomal-dominant pattern of inheritance, presenting clinically with LV hypertrophy. A vast number of different mutations have been identified (FUNG ET AL. 1999). It has been recognized as one of the most common causes of sudden death in otherwise healthy young individuals, thought to be caused by ventricular arrhythmias in most cases.

Repolarization abnormalities (e.g., prolonged QTc intervals, increased QT dispersion and increased complexity of T waves) are frequently described in these patients (ZAIDI ET AL. 1996, SVELIEVA ET AL. 1998a, YI ET AL. 1998, JOUVEN ET AL. 2002, BARLETTA ET AL. 2004). No differences in QT/RR slopes or QT dispersion responses were observed between patients and healthy controls during exercise testing (YI ET AL. 2000). However, increased QT variability has been noted in patients with hypertrophic cardiomyopathy, particularly in those with history of syncope, suggesting that an altered control of repolarization could be related to arrhythmia in this disorder (CUOMO ET AL. 2004).

Scintigraphic studies have suggested impaired sympathetic cardiac innervation (LEFROY ET AL. 1993, SCHAFERS ET AL. 1998). HRV studies have shown both decreased sympathetic regulation (FEI ET AL. 1995, LIMBRUNO ET AL. 1998) as well as decreased parasympathetic regulation (MORNER ET AL. 2005). Also, selective impairments of the HR responses to deep breathing and Valsalva have been reported, indicating impaired parasympathetic control (GILLIGAN ET AL. 1993).

3. Aims of the study

The studies reported in this thesis were designed to investigate the effects of standardized cardiovascular autonomic function tests on body surface measurements of ventricular repolarization and its homogeneity, especially in patients prone to ventricular arrhythmias associated with sudden changes in autonomic activity. The specific aims of the substudies were:

1. To outline the effects of abrupt changes in autonomic activity on QT intervals and spatial QT dispersion in healthy patients.
2. To examine the dynamics of QT intervals and spatial QT dispersion in the multichannel MCG in healthy patients.
3. To explore the effects of standardized cardiovascular autonomic function tests on QT intervals in patients with LQT1 subtype of LQTS.
4. To study the effects of the cardiovascular autonomic function tests on interventricular ECG dispersion of repolarization in LQT1 patients.
5. To explore the effects of cardiovascular autonomic function tests on ECG ventricular repolarization and its interventricular dispersion in ARVD patients.

4. Patients and methods

4.1 Study patients

Studies I-II: Ten healthy male volunteers (age 27 ± 6 years) without history or signs of cardiovascular disorders participated. They were all non-smokers, had a normal 12-lead ECG and took no medications.

Studies III-IV: Nine LQT1 patients (age 41 ± 12 , seven women) coming from eight different families were studied. All of them carried the same missense C-terminal KCNQ1 mutation (G589D), a common founder mutation in Finland (PIIPPO ET AL. 2001). They were all asymptomatic, but everyone had at least one symptomatic family member. Eight healthy control subjects (age 44 ± 10 , six women) served as controls. None of the patients or healthy control subjects took any medications. They had no signs of coronary artery disease on exercise testing or structural heart disease on cardiac magnetic resonance imaging. On baseline ECG, the asymptomatic LQT1 patients had normal T wave morphology and normal or only mildly prolonged QTc intervals (mean 445 ± 21 ms, range 407–469 ms). All control subjects had normal QTc intervals (mean 405 ± 21 ms, range 375–432 ms).

Study V: Nine unrelated patients with ARVD (age 53 ± 7 , five women) were recruited from a national database. Patients had to fulfil the international diagnostic criteria (MCKENNA ET AL. 1994) and not to have complete right bundle branch block, pacemaker or a cardioverter-defibrillator. All ARVD patients had structural abnormalities of the RV but normal LV function on echocardiography, magnetic resonance imaging or cine-angiography. They all had a history of arrhythmic symptoms and documented arrhythmia of RV origin, and sustained ventricular arrhythmia was induced during electrophysiological study in all patients. Therefore, their medications were not discontinued: 7 ARVD patients were on β -antiadrenergic drugs (sotalol in two cases) and one patient was on amiodarone. Nine healthy volunteers served as controls (age 44 ± 10 , six women). All of them had normal exercise tests and cardiac magnetic resonance imaging.

In all studies, patients and control subjects refrained from coffee, tea and cola drinks, and heavy meals for 6 hours, and alcohol and extreme physical activity for 24 hours before the study.

4.2 Cardiovascular autonomic function tests

In studies I and II, the subjects underwent a series of cardiovascular autonomic function tests as follows:

1. *Quiet breathing*: Breathing frequency was cued with a metronome at 12 cycles/minute.
2. *Mental stress*: A verbal mental arithmetic test with serial subtraction of 13 or 17 from a four-digit number, with loud metronome beeps at 120/min used as a distraction.
3. *Valsalva manoeuvre*: An expiration pressure of 40 mmHg, determined with an aneroid manometer, was sustained for 15 seconds.
4. *Sustained handgrip*: Squeezing of a dynamometer at 30% of predetermined maximal handgrip strength, for five minutes or until fatigue. Breathing frequency was cued at 12 cycles/minute to avoid performing a Valsalva-strain.
5. *Deep breathing*: Breathing at maximal tidal volume, 6 breathing cycles/minute.
6. *Hyperventilation*: Deep breathing was continued for five minutes, to cause acute respiratory alkalosis.
7. *Cold pressor test*: Immersion of the left hand in +4° C iced water for two minutes. Breathing was cued at 12 cycles/minute.

In studies III-V, the function test series was slightly different:

1. *Quiet breathing*: Baseline measurement for 5 minutes during spontaneous quiet breathing
2. *Deep breathing*: 4 deep breaths to subjective maximal vital capacity, with expiration and inspiration cued at 6 seconds each
3. *Valsalva manoeuvre*: An expiration pressure of 40 mmHg, determined with an aneroid manometer, was sustained for 15 seconds.
4. *Mental stress*: A verbal mental arithmetic test with serial subtraction of 13 or 17 from a four-digit number for 3 minutes. The subjects were periodically urged to count faster.
5. *Sustained handgrip*: Squeezing of a dynamometer at 30% of predetermined maximal handgrip strength, for 3 minutes. Care was taken to avoid a Valsalva manoeuvre.
6. *Supine bicycle exercise*: A 10-minute supine exercise test.

A 1-minute baseline recording preceded each test, and recovery was monitored for 1 minute, except for 10 minutes after exercise. There was sufficient rest between each test to allow for stabilization of basic physiologic state.

4.3 Signal acquisition

All tests were performed in the supine position, in a magnetically shielded low-noise environment.

Studies I-II: Breathing phase was monitored measuring air pressure changes in a tube placed around the caudal part of the thorax. All leads of a standard 12-lead ECG were recorded simultaneously. In Study II, MCG was recorded with a 67-channel cardiomagnetometer (Neuromag Ltd., Helsinki, Finland), consisting of 7 co-axial and 60 planar dc-SQUID (Superconducting QUantum Interference Device) gradiometers arranged in a hexagonal pattern, immersed in liquid helium inside a cylindrical dewar. The surface of the dewar (diameter 30 cm) was positioned 15 cm caudally from the jugular notch and 5 cm to the left, as close to the patient's chest as possible. All signals were band-pass filtered at 0.03-100 Hz and analog-to-digital converted at 1000 Hz. Both the planar (unit pT/cm) and the axial (unit pT) MCG signals were converted off-line to 33 co-axial signals (unit pT) with an interpolation method based on mathematical modelling of the source current distribution (NUMMINEN ET AL. 1995), allowing for better direct comparison between ECG and MCG.

Studies III-V: BSPM was recorded with three limb leads and 25 unipolar chest leads. Adhesive flexible plastic strips with Ag/AgCl electrodes at 5 cm intervals were placed on the anterior chest, from the right parasternal area to the left anterior axillary line (Figure 3). The simultaneously recorded signals were band-pass filtered at 0.03-300 Hz and analog-to-digital converted at 1000 Hz.

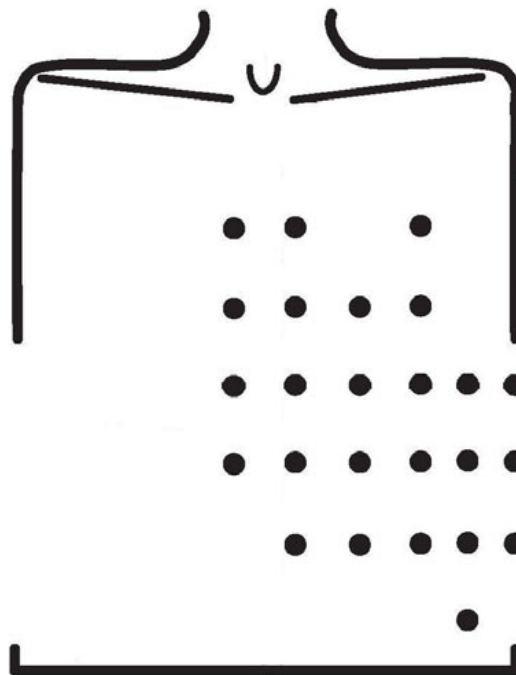


Figure 3. *Electrode layout of the 25 unipolar BSPM chest leads in Studies III-V.*

4.4 Signal processing and QT interval measurements

Studies I-II: QT measurements were performed on manually selected single beats. The effect of breathing phase was explored by selecting beats from end-inspiration and end-expiration during quiet and deep breathing. Otherwise, representative beats at fixed time intervals (at end-expiration) as well as at HR extremes were selected.

For a given beat, earliest QRS onset in any channel was identified and this same QRS onset was used in all channels. The intervals from QRS onset to the end and to the peak of the T wave (QT_{end} and QT_{peak}, respectively) were determined with an automatic computer-based method. First, a baseline was identified within user-defined limits in the T-P interval; with linear interpolation between two successive intervals in case of baseline drift. A second-degree polynomial was then fitted on the T wave. T wave peak was defined as the point where the first numerical derivative reached zero, and T wave end was defined as the intersection of the maximum slope tangent and the baseline. In more complex T waves, the second derivative of the signal was used to detect discontinuities after the T wave apex (OIKARINEN ET AL. 1998), and U waves were excluded according to the principles outlined by Lepeschkin and Surawicz (LEPESCHKIN AND SURAWICZ 1952). Channels with excessive noise, low-amplitude T waves (< 20 μ V or 600 fT) or clearly misinterpreted time points for other reasons (e.g., unclear baseline, indeterminate T wave apex, biphasic T wave), were excluded.

Studies III-V: Signals were triggered to the steepest upward slope of the R wave on a high-amplitude ECG channel. A fitted spline baseline was subtracted to negate baseline drift. Noise levels were reduced with continuous averaging over five successive QRS complexes, except during deep breathing and Valsalva where changes in HR and QT intervals were expected to be more rapid. The trigger point (i.e., start of the R wave) rather than Q wave was used as reference point in beat-to-beat QT measurements, as this approach is less sensitive to measurement errors caused by noise due to movement during the interventions. QT_{peak} and QT_{end} were then automatically determined for every heart beat with a modification of the algorithm used in Studies I and II. An example of the beat-to-beat measurements plotted against time is presented in Figure 4a. Noisy channels and clearly misinterpreted intervals were manually excluded. Excessive noise precluded reliable QT interval measurements during supine exercise, therefore only the recovery phase was analysed.

4.5 Definitions and statistical analyses

Study I: Instantaneous HR was generally calculated from 3 successive R-R intervals. When comparing breathing phases only the previous R-R interval was used. The mean QT_{peak} and QT_{end} values of all accepted leads were calculated and defined as global QT_{peak} and QT_{end} intervals, respectively. Spatial QT dispersion was defined as the maximum difference in QT duration between any leads. Interlead variation of QT

intervals was also explored by calculating the standard deviation of the measured QT intervals.

Study II: HR and global QTpeak and QTend intervals and their dispersion were measured as in Study I. However, the MCG channels with the longest and the shortest QT interval were omitted before QT dispersion assessment in order to reduce the effects of outliers. In addition, the TPE interval was measured as QTend - QTpeak and TPE dispersion as maximum TPE - minimum TPE.

Study III: HR extremes and global QTpeak and QTend intervals were defined as in Studies I and II. The mean TPE over all channels was defined as the global TPE interval. QTc values were calculated for the 5-minute resting period only, otherwise only the measured intervals were used.

Averages over defined time periods were calculated to facilitate statistical comparisons of the beat-to-beat recordings: 5- and 10-second periods during Valsalva, and 30-second periods during mental stress, handgrip and recovery from exercise. Using these time periods, changes compared with baseline values were calculated (Δ HR, Δ QTpeak, Δ QTend and Δ TPE) and explored by plotting them against time (Figure 4b). Changes in the time intervals were also plotted against Δ HR (Figure 4c).

Beat-to-beat QT interval adaptation to HR change was assessed by plotting global QTpeak and QTend intervals against the preceding R-R interval and instantaneous HR (Figure 4d). Slopes of the linear regression lines and correlation coefficients were computed for comparisons between study groups. QT/HR relationships were also studied by plotting the averaged QT interval and HR values over the defined time periods.

Deep breathing difference was calculated as the mean difference between maximum HR during inspiration and minimum HR during expiration. From the HR responses to the Valsalva manoeuvre, the Valsalva ratio (longest R-R interval shortly after strain/shortest R-R interval during strain) and the tachycardia ratio (shortest R-R interval during strain/longest R-R interval before strain) were calculated.

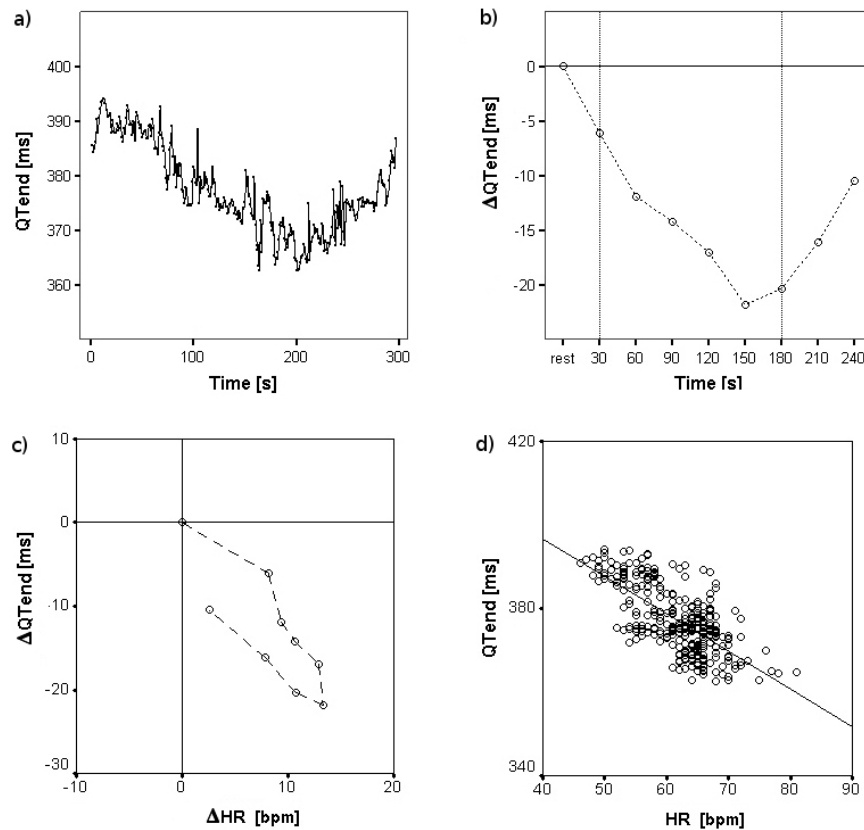


Figure 4. Demonstration of the methods used for QT interval analyses in Studies III-V, using data from an unaffected healthy subject during mental stress testing: a) QTend interval plotted against time, b) change in QTend interval ($\Delta QTend$) plotted against time, c) $\Delta QTend$ plotted against change in heart rate (ΔHR) and d) QTend interval plotted against instantaneous heart rate (HR), with regression line.

Studies IV-V: HR and global QT intervals were measured and time periods defined as in study III. QTc values were determined for the 5-minute resting period only. ECG leads were further grouped in LV type and RV type leads, according to QRS morphology. Leads showing QRS complexes with R wave amplitude of more than 2/3 of total QRS amplitude were classified as LV leads whereas those with R wave amplitude of less than 1/3 of total QRS amplitude were classified as RV leads. All measured intervals were then averaged for LV and RV leads separately, using the defined time periods. As an index of interventricular dispersion of repolarization, intervals measured from RV were subtracted from corresponding intervals measured from LV, and defined as interventricular QTpeak, QTend and TPE dispersion, respectively.

Reproducibility of QT measurements. The reproducibility of the QT interval and QT dispersion measurements in studies I and II was tested by repeating the procedure on a sample of ECGs from the Valsalva and deep breathing tests (778 beats): The mean relative differences $((A-B)/(A+B)/2)$ of both QTpeak and QTend measurements were

0.1%, whereas it ranged from 0.5% to 0.8% for the QT dispersion indices. For the method of beat-to-beat measurement of global QT_{peak} and QT_{end} intervals, the coefficient of variation had been determined as 0.8% and 0.6%, respectively, in earlier resting measurements (HEKKALA ET AL. 2006).

Statistics. Continuous values were presented as mean \pm SD, except in the figures of studies III-V where mean \pm SEM was used. Parametric tests were used for data having a normal distribution (assessed with the Kolmogorov-Smirnov test), otherwise nonparametric tests were used. In Studies I and II, analysis of variance for repeated measurements, the Friedman test or the paired t-test was used when comparing changes between different phases during autonomic testing. In Studies III-V, between-group comparisons were made with Student's t-test or Mann-Whitney U-test. Within-group changes from baseline were assessed with the paired t-test or Wilcoxon signed rank test. Pearson's or Spearman's correlation coefficients (R) were used to test the strength of the linear relationship between continuous variables. A two-tailed P value $<$ 0.05 was considered statistically significant.

5. Results of the studies

5.1 Heart rate responses

Single-beat studies (I-II). Significant ($P < 0.001$) HR increases occurred during all autonomic function tests: The maximum HRs reached were 103 ± 14 bpm during Valsalva, 100 ± 16 bpm during mental stress, 73 ± 7 bpm during sustained handgrip, 75 ± 8 bpm during hyperventilation and 77 ± 12 bpm during the cold pressor test.

LQT1 patients (III-IV). Resting HR was 62 ± 5 bpm in the LQT1 group and 64 ± 10 bpm in the control group ($P = \text{NS}$). HR increased significantly ($P < 0.001$) during all tests in both study groups. LQT1 patients showed smaller HR increases than control subjects in response to the Valsalva manoeuvre, mental stress, and sustained handgrip, whereas the HR deceleration after the Valsalva strain and the deep breathing difference were similar (Figure 5). There were no significant differences in the Valsalva or tachycardia ratios (1.71 ± 0.29 vs. 1.77 ± 0.25 , $P = 0.35$ and 0.65 ± 0.09 vs. 0.60 ± 0.09 , $P = 0.12$) between LQT1 patients and controls. In a maximal bicycle exercise test performed as a part of the screening process before the study, the maximum HRs were 160 ± 11 bpm in LQT1 patients and 180 ± 8 bpm in controls ($P < 0.001$).

ARVD patients (V). Resting HR was 58 ± 15 bpm in ARVD patients and 64 ± 9 bpm in controls ($P = \text{NS}$). In ARVD patients HR increased to a maximum of 78 ± 23 bpm during Valsalva, 70 ± 20 bpm during mental stress and 65 ± 19 bpm during handgrip ($P < 0.01$ compared to baseline for all). In controls the corresponding maximum HRs reached were 95 ± 14 bpm, 88 ± 9 bpm and 79 ± 13 bpm, respectively ($P < 0.001$ compared to baseline). At cessation of exercise, HR was 105 ± 22 bpm in ARVD patients and 112 ± 9 bpm in controls. ARVD patients had smaller deep breathing difference than controls (9 ± 4 vs. 18 ± 5 beats, $P = 0.002$). In response to the Valsalva manoeuvre, ARVD patients had slightly higher tachycardia ratios than controls (0.73 ± 0.10 vs. 0.61 ± 0.08 , $P = 0.01$), whereas the Valsalva- and bradycardia ratios were not significantly different (1.58 ± 0.34 vs. 1.77 ± 0.24 , $P = 0.19$ and 1.15 ± 0.16 vs. 1.16 ± 0.09 , $P = 0.97$, respectively).

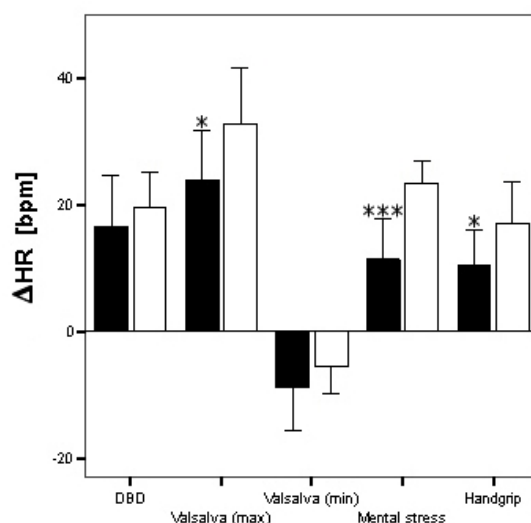


Figure 5. Maximum changes in heart rate (ΔHR) during the tachycardia (max) and bradycardia (min) phases of the Valsalva manoeuvre, mental stress and sustained handgrip in LQTI patients (closed bars) and controls (open bars). DBD = deep breathing difference. * $P < 0.05$ and *** $P < 0.001$ LQTI vs. controls (Study III).

5.2 QT intervals

Single-beat studies (I-II). ECG QTpeak intervals shortened significantly ($P < 0.01$) during the autonomic tests: from 315 ± 22 to 293 ± 16 ms during Valsalva, from 301 ± 23 to 280 ± 29 ms during mental stress, from 310 ± 20 to 290 ± 20 ms during sustained handgrip, from 315 ± 24 to 299 ± 21 ms during cold pressor testing, and from 311 ± 22 to 291 ± 21 ms during hyperventilation. Corresponding QTend changes were from 388 ± 22 to 366 ± 15 ms, from 374 ± 24 to 351 ± 28 ms, from 383 ± 23 to 358 ± 23 ms, from 386 ± 27 to 370 ± 22 ms, and from 383 ± 25 to 356 ± 24 , respectively ($P < 0.01$ for all). Quiet breathing did not change the QT intervals significantly when comparing end-expiration with end-inspiration in ECG and MCG measurements. During deep breathing, however, QTpeak and QTend intervals were longer during expiration compared with inspiration (Table 4). MCG recordings showed on average slightly longer QT intervals than ECG, but ECG and MCG measurements showed a close correlation during the autonomic tests ($r = 0.91$ for QTpeak and $r = 0.93$ for QTend).

Table 4. *Effects of deep breathing phase on QT intervals in ECG and MCG recordings (Studies I-II).*

	<i>Inspiration ECG</i>	<i>Expiration ECG</i>	<i>Inspiration MCG</i>	<i>Expiration MCG</i>
<i>R-R interval</i>	795 ± 118	1047 ± 151***		
<i>QTpeak</i>	305 ± 19	311 ± 24	305 ± 24	316 ± 23**
<i>QTend</i>	375 ± 21	383 ± 26*	380 ± 26	393 ± 27**

Values are mean ± SD, in milliseconds. * P < 0.05, ** P < 0.01 and *** P < 0.001 inspiration vs. expiration.

LQT1 patients (III-IV). QTend intervals shortened less in LQT1 patients than in controls during the autonomic tests (Figure 6). Plotting Δ QTend against Δ HR shows the changes in QTend relative to the changes in HR, forming a loop during the autonomic tests and a line during the recovery phase of supine exercise (Figure 7). Valsalva manoeuvre induced the widest loops in both study groups. LQT1 patients showed smaller loops than controls during mental stress and handgrip.

In the recovery phases of the tests, LQT1 patients showed an overshoot of QTend intervals to longer values than they were at baseline (Figures 6 and 7). The number of tests with such an overshoot was 2.4 ± 1.7 in LQT1 patients and 0.8 ± 0.7 in controls (P = 0.02), with the most distinctive overshoot occurring in response to the Valsalva manoeuvre.

QTend/HR slopes were steeper in LQT1 patients than in controls during deep breathing, Valsalva and sustained handgrip (Table 5). QT rate adaptation during recovery of exercise was biphasic, which prevented the assessment of linear slopes. However, at 1 minute after exercise, QTend values had already recovered to $91 \pm 5\%$ of baseline value in LQT1 patients compared with only $82 \pm 5\%$ in controls (P = 0.005).

Table 5. *QTend/HR slopes during autonomic tests in LQT1 patients and controls.*

	<i>LQT1</i>	<i>Controls</i>
<i>Deep breathing</i>	-1.17 ± 0.45*	-0.71 ± 0.37
<i>Valsalva</i>	-0.74 ± 0.33*	-0.47 ± 0.20
<i>Mental stress</i>	-0.84 ± 0.58	-0.73 ± 0.26
<i>Handgrip</i>	-1.15 ± 0.46*	-0.67 ± 0.38

Values are mean ± SD, in milliseconds/minute. * P < 0.05 LQT1 vs. controls.

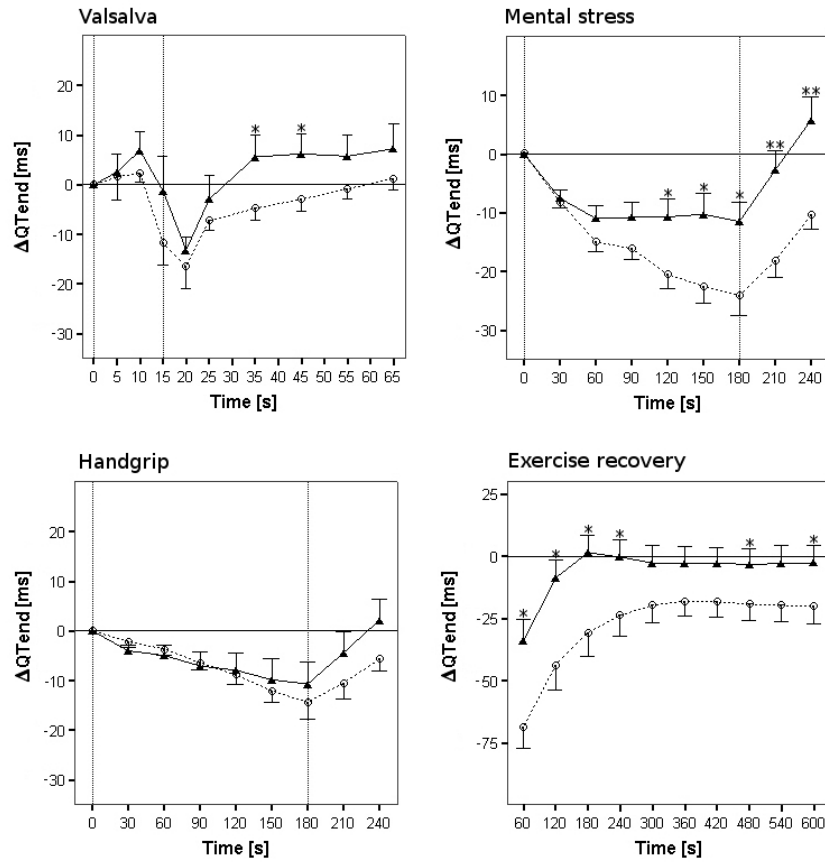


Figure 6. *Global QTend interval change (ΔQT_{end}) plotted against time during Valsalva, mental stress, handgrip and recovery after exercise in LQTI patients (closed symbols) and controls (open symbols). The second vertical lines indicate the beginning of the recovery phases of Valsalva, mental stress and handgrip. * $P < 0.05$ and ** $P < 0.01$ LQTI vs. controls (Study III).*

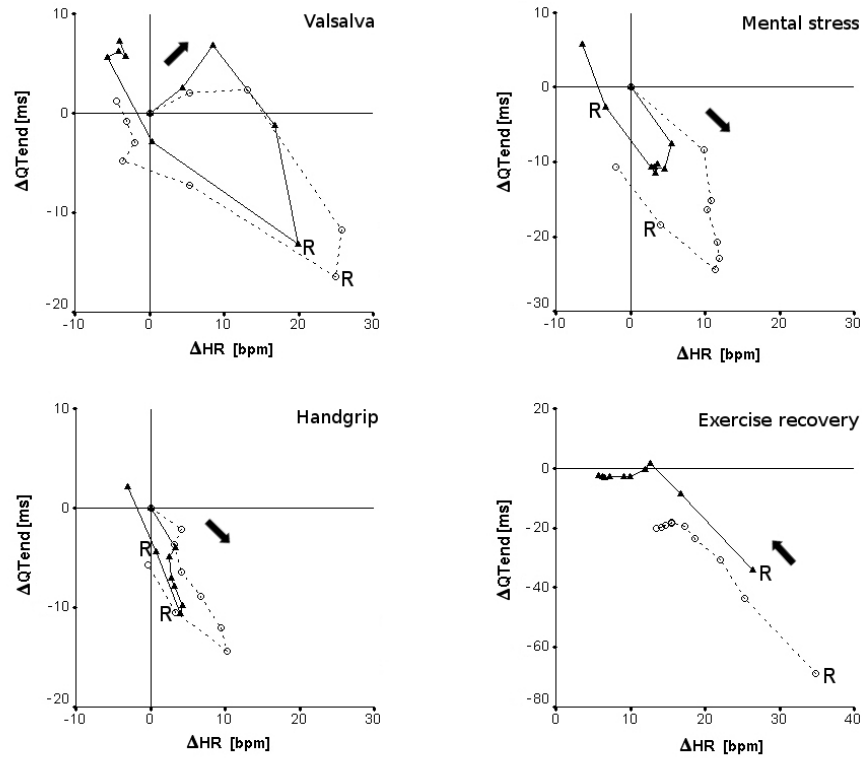


Figure 7. Global QT_{end} interval change (ΔQT_{end}) plotted against HR change (ΔHR) during Valsalva, mental stress, handgrip and recovery from exercise in LQTI patients (closed symbols) and controls (open symbols). Arrows show the direction of the loops and line whereas R indicates the start of the recovery phase (Study III).

ARVD patients (V). Rate corrected baseline QT_{peak} (327 ± 18 ms vs. 308 ± 33 ms, $P = 0.09$) and QT_{end} intervals (398 ± 14 ms vs. 381 ± 39 ms, $P = 0.24$) tended to be slightly longer in ARVD patients than in controls. ΔQT_{end} plotted against ΔHR formed similar but clearly smaller loops in ARVD patients during mental stress and handgrip, indicating less change in both QT_{end} and HR during these tests in ARVD than in controls (Figure 8). During the Valsalva manoeuvre, the corresponding loops had a different shape between the two study groups.

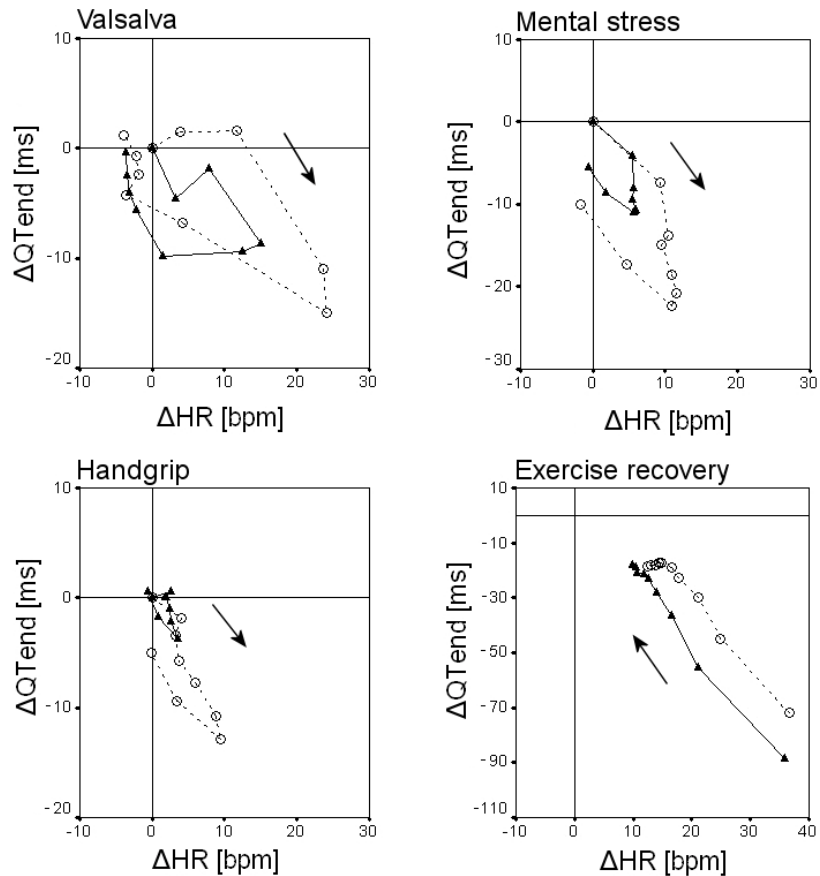


Figure 8. Global QT_{end} interval change (ΔQT_{end}) plotted against HR change (ΔHR) during Valsalva, mental stress, handgrip and recovery from exercise in ARVD patients (closed symbols) and controls (open symbols). Arrows show the direction of the loops and line (Study V).

5.3 TPE intervals

LQT1 patients (III). At baseline resting conditions, LQT1 patients and controls showed similar global TPE intervals (78 ± 3 ms vs. 75 ± 10 ms, $P = NS$). TPE intervals remained unchanged in both LQT1 patients and in controls in response to mental stress and sustained handgrip. During the strain phase of the Valsalva manoeuvre, however, TPE intervals prolonged in LQT1 patients whereas they did not change significantly in controls (Figure 9). TPE intervals also tended to prolong in LQT1 patients after supine exercise (Figure 9).

ARVD patients (V). Although global TPE intervals were similar at baseline, ARVD patients had longer TPE intervals than control subjects in RV leads (73 ± 9 ms vs. 64 ± 7 ms, $P < 0.05$). ARVD patients showed opposite change in global TPE intervals compared with controls during sustained handgrip (Figure 10), whereas it behaved similarly in both study groups during the other tests.

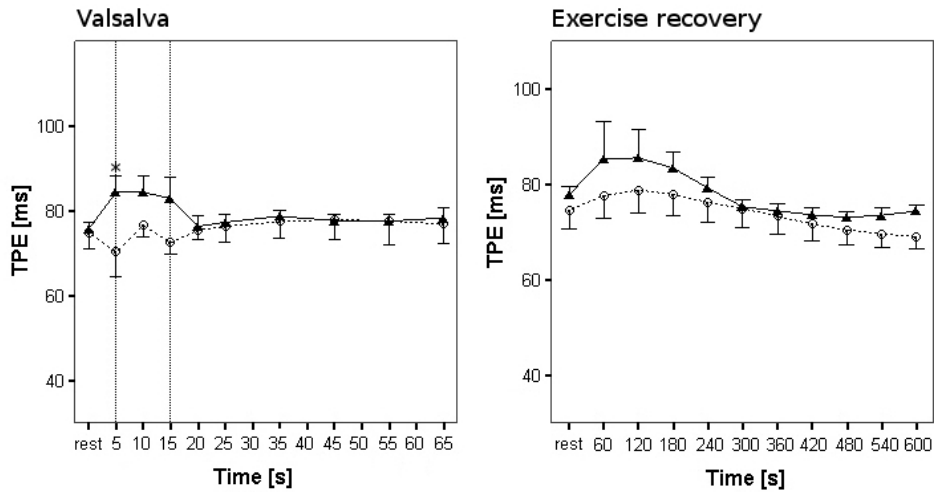


Figure 9. Global T wave peak to T wave end (TPE) intervals in LQTI patients (closed symbols) and controls (open symbols) during Valsalva manoeuvre and exercise recovery. * $P < 0.05$ LQTI vs. controls (Study III).

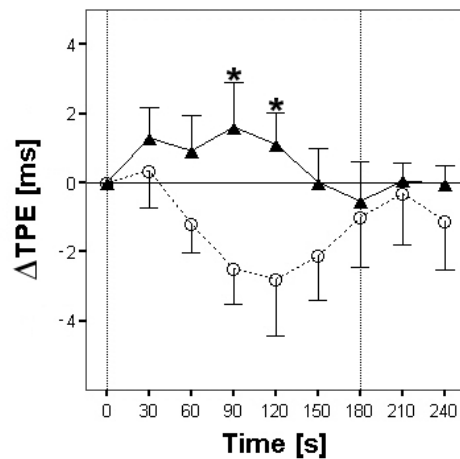


Figure 10. Change in global TPE interval (ΔTPE) in ARVD patients (closed symbols) and controls (open symbols) during sustained handgrip. * $P < 0.05$ ARVD vs. controls (Study V).

5.4 Spatial QT dispersion

Single-beat studies (I-II). Sympathetic activation induced by mental stress, sustained handgrip or cold pressor testing did not modulate dispersion of QTpeak or QTend intervals. However, deep breathing (Table 6) and Valsalva manoeuvre induced changes in spatial QT dispersion. In the ECG recordings, QTpeak dispersion was amplified during deep expiration compared with deep inspiration, whereas dispersion measurements

showed an opposite behaviour in MCG. In ECG, QTend dispersion decreased from 45 ± 23 ms to 35 ± 21 ms ($P < 0.05$) during the strain phase of the Valsalva manoeuvre. In MCG measurements, however, QTend dispersion increased from a baseline value of 55 ± 26 ms to 76 ± 29 ms ($P < 0.05$) during the bradycardia phase of the manoeuvre. Although QTpeak and QTend intervals measured from ECG and MCG correlated closely ($r = 0.93$ and $r = 0.91$, respectively), there was no significant correlation between ECG and MCG measures of QTpeak and QTend dispersion (see also Figure 1 in Study II).

Table 6. *Effects of deep breathing phase on spatial QT dispersion in ECG and MCG (Studies I and II).*

	<i>Inspiration ECG</i>	<i>Expiration ECG</i>	<i>Inspiration MCG</i>	<i>Expiration MCG</i>
<i>QTpeak dispersion</i>	39 ± 15	$52 \pm 23^*$	74 ± 20	56 ± 25
<i>SD QTpeak</i>	13 ± 5	$16 \pm 7^*$	17 ± 4	14 ± 6
<i>QTend dispersion</i>	41 ± 18	49 ± 30	96 ± 19	$73 \pm 27^*$
<i>SD QTend</i>	12 ± 5	15 ± 8	20 ± 5	16 ± 5

Values are mean \pm SD, in milliseconds. SD denotes standard deviation of the measured intervals. * $P < 0.05$ inspiration vs. expiration.

LQT1 patients (unpublished results). LQT1 patients showed more QTpeak dispersion than controls. QTpeak dispersion remained greater in LQT1 patients than in controls also during mental stress, handgrip and the late phase of exercise recovery. In the LQT1 patients it diminished compared with baseline during mental stress and the early phase of exercise recovery (Figure 11). LQT1 patients and controls showed an opposite behaviour of QTpeak dispersion during the Valsalva manoeuvre, the former exhibiting a slight increase in dispersion at the beginning of strain (Figure 11). In LQT1 patients spatial QTpeak dispersion correlated with global TPE ($R = 0.30$, $P < 0.001$) during the autonomic function tests, whereas no such correlation was observed in controls.

QTend dispersion was similar in LQT1 patients and controls. In the LQT1 group, QTend dispersion increased from 42 ± 12 ms to a maximum of 49 ± 15 ms ($P = 0.003$) during mental stress and from 48 ± 11 ms to 54 ± 10 ms ($P = 0.050$) during sustained handgrip, but the absolute values reached were not significantly different from those of unaffected subjects.

ARVD patients (unpublished results). In resting measurements, ARVD patients showed more QTpeak and QTend interval dispersion than controls (Table 7). QTend dispersion decreased from a baseline value of 48 ± 20 ms to a minimum of 32 ± 17 ms ($P = 0.0001$) during the strain phase of the Valsalva manoeuvre, and from 57 ± 17 s to a

minimum of 42 ± 9 s ($P = 0.03$) during the first minute of recovery after supine exercise, increasing gradually back to resting level. QTpeak dispersion behaved similarly. Neither measure of dispersion changed during mental stress or handgrip, but both remained greater in ARVD patients than in controls throughout the tests. Controls exhibited no significant changes in QT dispersion during any of the tests.

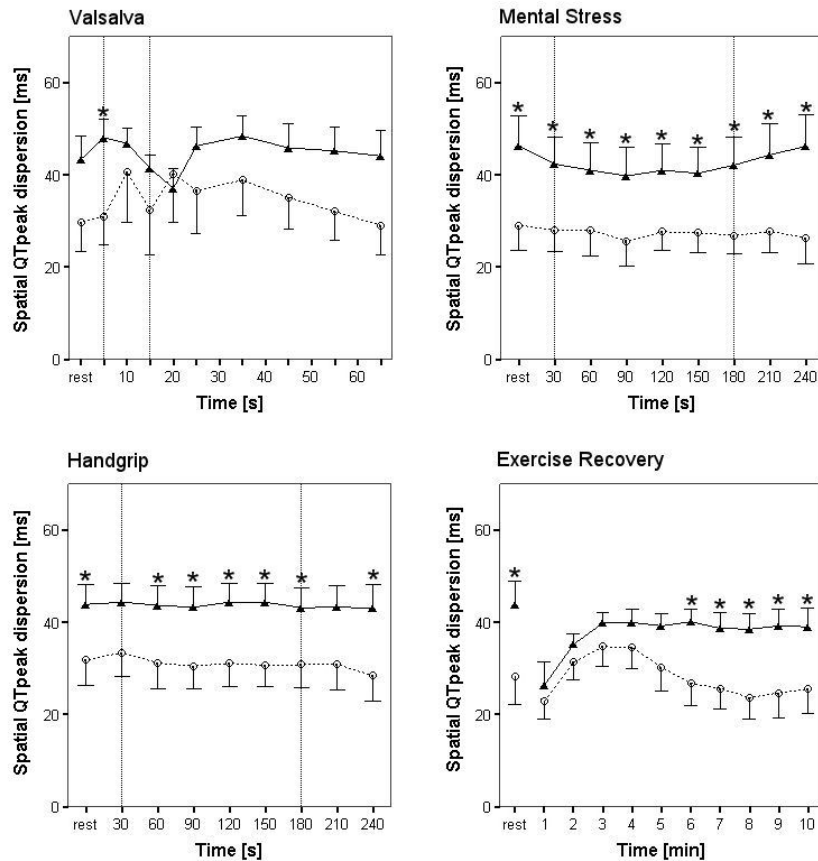


Figure 11. Spatial QTpeak dispersion in LQT1 (closed symbols) and controls (open symbols) during Valsalva, mental stress, sustained handgrip and recovery from supine exercise (unpublished results). Values after the second vertical line represent the recovery phases of Valsalva, mental stress and handgrip, respectively. * $P < 0.05$ LQT1 vs. controls.

Table 7. *QT interval dispersion in ARVD-patients and controls at rest (unpublished results).*

	<i>ARVD</i>	<i>Control</i>	<i>P-value</i>
<i>QTpeak dispersion</i>	50 ± 22	33 ± 17	0.08
<i>SD QTpeak</i>	15 ± 8	9 ± 4	0.05
<i>QTend dispersion</i>	55 ± 18	40 ± 11	0.04
<i>SD QTend</i>	16 ± 6	11 ± 3	0.02

Values are mean ± SD, in milliseconds. SD denotes standard deviation of the measured intervals.

5.5 Interventricular QT dispersion

LQT1 patients (IV). Table 8 shows the resting QTpeak, QTend and TPE intervals in LV and in RV type leads in the study groups. LQT1 patients had significantly longer QTpeak and QTend intervals in LV than in RV, whereas controls exhibited only a similar trend. On the other hand, TPE intervals were longer in RV than in LV in LQT1 patients. Interventricular QTpeak dispersion was greater in LQT1 patients than in controls (13 ± 9 ms vs. 4 ± 4 ms, $P = 0.03$) whereas the interventricular dispersion of QTend and interventricular difference of TPE were similar in both study groups.

Responses of interventricular QTpeak dispersion to the autonomic tests are presented in Figure 12. Interventricular QTpeak dispersion was greater in LQT1 patients than in controls during Valsalva and mental stress. It remained unchanged during mental stress and sustained handgrip but decreased to the same level as in controls during recovery from exercise and showed an opposite behaviour to that of controls during the Valsalva manoeuvre. During the Valsalva manoeuvre, the behaviour of interventricular QTpeak dispersion was similar to that of both TPE interval duration and spatial QTpeak dispersion; all three parameters showed a transient increase in the strain phase (Figure 13). When assessed from all the tests, interventricular QTpeak dispersion correlated with spatial QTpeak dispersion ($R = 0.44$, $P < 0.001$) and weakly with TPE ($R = 0.17$, $P < 0.01$) in LQT1 patients, whereas no significant correlation was observed in controls. Interventricular QTend dispersion was similar in LQT1 patients and controls and remained virtually unchanged during the autonomic tests.

Table 8. *QT intervals from left ventricular type and right ventricular type leads in LQT1 patients and controls at rest (Study IV).*

	<i>LQT1 (ms)</i>	<i>Controls (ms)</i>	<i>P-value (LQT1 vs. Controls)</i>
<i>QTc peak in LV type leads</i>	359 ± 24	325 ± 16	0.008
<i>QTc peak in RV type leads</i>	346 ± 30**	321 ± 18	0.09
<i>QTc end in LV type leads</i>	435 ± 24	398 ± 19	0.007
<i>QTc end in RV type leads</i>	426 ± 31*	389 ± 23	0.03
<i>TPE in LV type leads</i>	74 ± 4	70 ± 5	0.14
<i>TPE in RV type leads</i>	78 ± 4*	65 ± 7	0.001

QTc = rate corrected QT intervals (Bazett, $QT/RR^{1/2}$). * $P < 0.05$ and ** $P < 0.01$ compared with corresponding intervals in LV type leads.

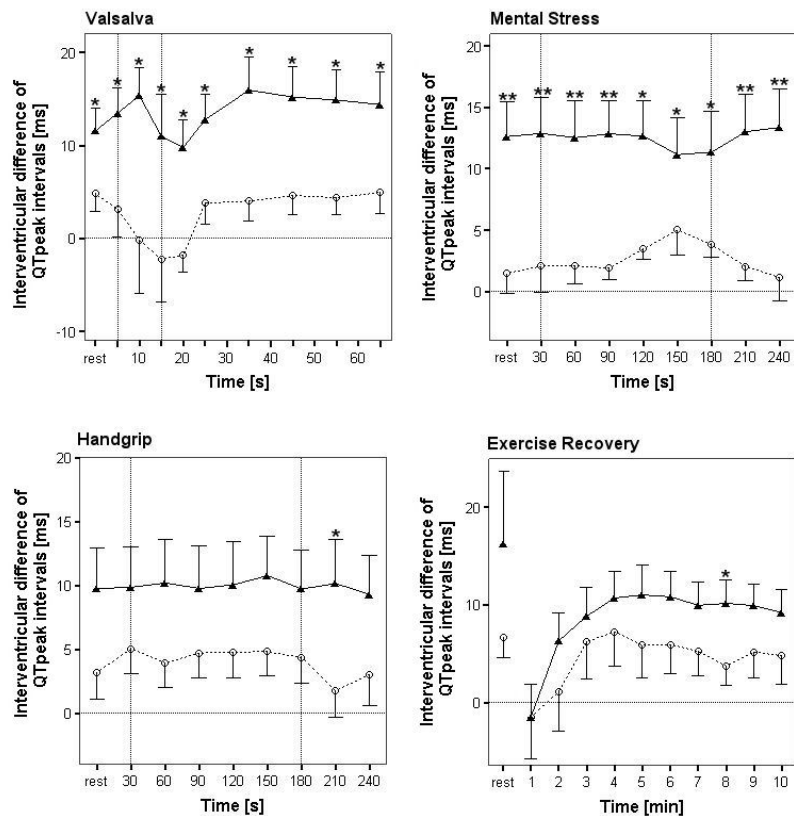


Figure 12. *Interventricular difference of QTpeak intervals in LQT1 (closed symbols) and controls (open symbols) during cardiovascular autonomic function tests. Values after the second vertical line represent the recovery phases of Valsalva, mental stress and handgrip, respectively. * $P < 0.05$, ** $P < 0.01$ LQT1 vs. controls (Study IV).*

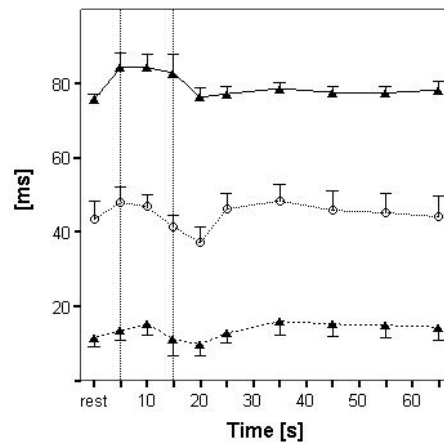


Figure 13. *T wave peak to T wave end intervals (closed symbols, solid line), spatial QTpeak dispersion (open symbols, dotted line) and interventricular QTpeak dispersion (closed symbols, dotted line) in LQT1 patients during Valsalva manoeuvre. Values between the vertical dotted lines represent the strain phase of the manoeuvre.*

ARVD patients (V). Table 9 presents the resting QTpeak, QTend and TPE intervals in LV and in RV type leads in ARVD patients and controls. Controls had longer QT intervals in LV than in RV type leads. Of the 9 ARVD patients, however, 6 had longer QTend intervals in RV than in LV ($P < 0.01$). Interventricular QTend dispersion was -5 ± 13 ms in ARVD patients and 7 ± 5 ms in controls ($P = 0.012$), showing an opposite repolarization gradient in the two study groups. The corresponding values of interventricular TPE difference were -6 ± 4 ms vs. 3 ± 6 ms ($P = 0.005$). During mental stress, handgrip and exercise recovery this difference in interventricular QTend dispersion between ARVD patients and controls remained unaltered, being -7 ± 13 ms vs. 6 ± 5 ms ($P = 0.016$), -6 ± 14 ms vs. 8 ± 8 ms ($P = 0.012$), and -4 ± 10 ms vs. 10 ± 11 ms ($P = 0.007$), respectively. Valsalva strain transiently reversed this interventricular gradient, due to an abrupt abbreviation of QTend intervals in the RV leads (Figure 14). Interventricular TPE difference behaved similarly. There were no significant differences in interventricular QTpeak dispersion between the study groups.

Table 9. *QT intervals from left ventricular type and right ventricular type leads in ARVD patients and controls at rest (Study V).*

	<i>ARVD</i>	<i>Controls</i>	<i>P-value (ARVD vs. Controls)</i>
<i>QTc peak in LV type leads</i>	330 ± 23	320 ± 16	0.36
<i>QTc peak in RV type leads</i>	329 ± 18	316 ± 17*	0.16
<i>QTc end in LV type leads</i>	395 ± 18	390 ± 21	0.61
<i>QTc end in RV type leads</i>	400 ± 14	383 ± 23**	0.09
<i>TPE in LV type leads</i>	67 ± 8	68 ± 7	0.94
<i>TPE in RV type leads</i>	73 ± 9**	64 ± 7	0.047

Abbreviations and symbols as in Table 8.

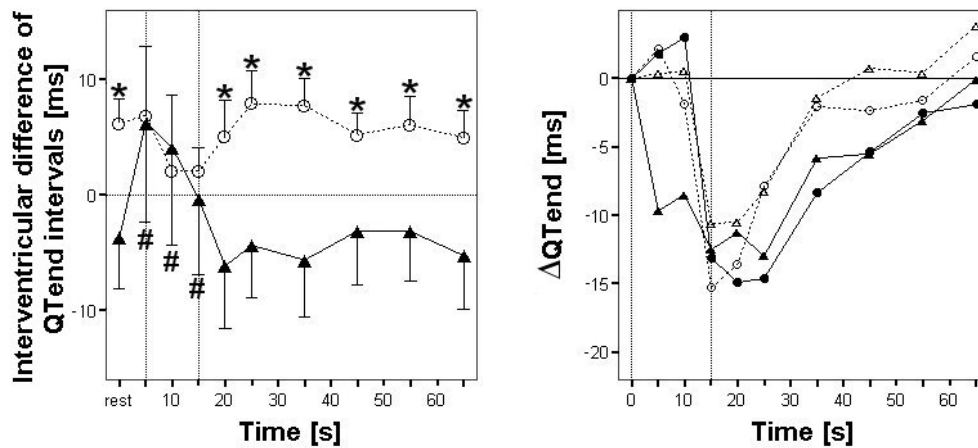


Figure 14. *Interventricular difference of QTend intervals and changes of QTend intervals ($\Delta QTend$) during Valsalva manoeuvre in ARVD patients (closed symbols) and controls (open symbols). In the right panel, circles represent LV leads and triangles RV leads. * $P < 0.05$ ARVD vs. controls, # $P < 0.05$ vs. rest (left panel).*

6. Discussion

6.1 Main findings

Global QT interval measurements from ECG and MCG showed a good correlation. Autonomic interventions involving deep respiratory effort or intrathoracic volume and pressure changes influenced ECG and MCG spatial QT dispersion differently. Furthermore, spatial QT dispersion measures from ECG and MCG recordings showed no correlation.

The responses of QT and TPE intervals to autonomic function tests differed between asymptomatic LQT1 patients and healthy controls. LQT1 patients showed impaired shortening of QTpeak and QTend intervals during autonomic tests and exaggerated prolongation of these intervals during the recovery phases. In addition, LQT1 patients showed TPE prolongation during Valsalva strain and the early phase of recovery from exercise. The acceleration response of the sinus node to adrenergic stimulation was impaired in LQT1 patients, whereas the responses to vagal stimuli appeared normal.

LQT1 patients had greater interventricular QTpeak dispersion than controls, and this interventricular repolarization gradient was transiently augmented by Valsalva strain. Spatial QTpeak dispersion correlated with both interventricular QTpeak dispersion and TPE in LQT1 patients but not in controls. Interventricular QTpeak dispersion correlated weakly with TPE in LQT1 patients.

ARVD patients showed an interventricular repolarization gradient from RV to LV, which was opposite to that of healthy controls. Valsalva strain transiently reversed this gradient, indicating abnormal behaviour of repolarization to abrupt sympathetic activation and preload change in the diseased RV. ARVD patients showed greater ECG transmural dispersion of repolarization in RV than in LV. TPE intervals increased during sustained sympathetic strain and showed interventricular lability during Valsalva.

6.2 Relation to previous studies

6.2.1 Cardiovascular autonomic function testing in healthy subjects

QT intervals in ECG and MCG. This was the first study reporting a direct comparison between simultaneous ECG and MCG recordings in QT interval measurements, showing a good correlation during autonomic function testing. Breathing has been observed to cause variation in the QT interval also in previous ECG studies (KRUPIENICZ ET AL. 1997, EMORI AND OHE 1999), but this was the first such study where the breathing phase was

actually monitored directly ensuring that QT intervals were compared at exactly the same phases of inspiration and expiration. There are no previous reports on the effects of cardiovascular autonomic function testing on MCG recordings.

Spatial QT dispersion. QT dispersion was a hot topic at the time when the first two studies of this thesis were conducted, with a vast number of reports being published on its usefulness as a non-invasive marker of arrhythmia risk in many disease states. Given the importance of autonomic activity as a determinant of QT interval duration, it was surprising that direct autonomic effects on QT dispersion had not been thoroughly evaluated before attempting to adopt it as a clinical tool. Only one previous study had at the time addressed the matter, observing no effects of reflex parasympathetic activation on QT dispersion. In agreement with the observations presented in Studies I-II, subsequent studies have reported a lack of autonomic effects on QT dispersion in healthy subjects (GHURAN ET AL. 2000, VAN HUYSDUYNEN ET AL. 2004). Others have observed augmentation of QT dispersion during catecholamine infusion (LOWE ET AL. 2001, LEE ET AL. 2003) and orthostatic stress (NAKAGAWA ET AL. 1999). One previous study had observed effects of breathing phase that were at variance with the present observations (KRUPIENICZ ET AL. 1997), but this might be attributable to methodological differences. There were only two previous studies reporting QT dispersion from MCG recordings (OIKARINEN ET AL. 1998, HAILER ET AL. 1999); both were clinical studies on patients with coronary artery disease. One of these involved a pharmacologic stress test with nonselective β -adrenoceptor agonist arbutamine, which did not change QT dispersion, however (HAILER ET AL. 1999).

6.2.2 Cardiovascular autonomic function testing in LQT1 patients

QT and TPE intervals. The association between sympathetic activation and occurrence of arrhythmia in LQTS patients has long been recognized. However, most previous studies exploring the usefulness of non-invasive autonomic function testing in diagnosing or risk-stratifying LQTS patients were conducted on non-genotyped patient populations. Moreover, only QTc intervals have generally been reported, making it difficult to interpret the true behaviour of QT intervals during autonomic challenge. The present work was the first study to follow the QT interval responses beat-to-beat during autonomic challenge in LQT1 patients. Previous experimental studies have suggested (SHIMIZU AND ANTZELEVITCH 2000) and clinical studies on genotyped patients later on have confirmed that catecholamine infusion (TANABE ET AL. 2001) or physical exercise (TAKENAKA ET AL. 2003) unmask or aggravates repolarization abnormalities in LQT1, seen especially as an increase in TDR. In accordance with these previous observations, transient prolongations of QTend and TPE intervals were observed during the strain phase of the Valsalva manoeuvre. The impaired shortening of QT intervals observed during autonomic tests is in agreement with previous interpretations of QT interval behaviour at different HRs in ambulatory recordings (VIITASALO ET AL. 2002b). An exaggerated prolongation of QT intervals compared with controls during the recovery from

sympathetic challenge had earlier been observed after exercise testing (SWAN ET AL. 1999a). The presently described overshoot of QTend intervals occurring during HR deceleration in the recovery phases of the autonomic tests might be related to increase in vagal activity, because similar phenomena have been observed after intracoronary acetylcholine (AIZAWA ET AL. 1996) and face immersion in non-genotyped LQTS patients (YOSHINAGA ET AL. 1999). It is tempting to ascribe this to direct vagal AP prolonging effects, perhaps amplified by elevated levels of circulating adrenaline.

Spatial and interventricular dispersion. In the present study, spatial QTpeak dispersion diminished during sympathetic activation. This finding is in line with the observations made by Hirao and co-workers, who noted that rapid atrial pacing reduced the dispersion of MAPs both before and after adrenaline infusion in LQTS patients (HIRAO ET AL. 1996). Previously, adrenaline infusion has been reported to increase QT dispersion in LQTS (SUN ET AL. 1998, TANABE ET AL. 2001). Although it has been observed in experimental LQTS models that increased interventricular dispersion of repolarization is associated with TdP (VERDUYN ET AL. 1997b) and that the RV may act as part of the re-entrant circuit (CHINUSHI ET AL. 2001), no previous clinical studies have attempted to quantify interventricular dispersion or its dynamics in LQTS patients. One previous MCG study reported that the origin of abnormal repolarization was the LV in LQT1 patients (KANDORI ET AL. 2002), a finding that is in agreement with the present observation of an augmented interventricular repolarization gradient in LQT1. In the present study it was further observed that spatial QT dispersion correlated with both interventricular and transmural ECG dispersion of repolarization.

HR responses. It had earlier been noted that LQT1 patients show diminished HR responses during maximal exercise testing (SWAN ET AL. 1999a) and lower HRs in ambulatory ECG recordings (EXTRAMIANA ET AL. 2005). The present study showed that an impaired sympathetic sinus nodal response is evident even in asymptomatic LQT1 mutation carriers during relatively mild adrenergic challenge. Combined, these observations underscore the functional importance of I_{Ks} during sympathetic activation also in the sinus node.

6.2.3 Cardiovascular autonomic function testing in ARVD patients

Previous studies have reported anatomical (WICHTER ET AL. 2000) and functional (FOLINO ET AL. 2002) abnormalities of the cardiovascular autonomic nervous system in ARVD patients, as well as repolarization abnormalities localizing in the RV (PEETERS ET AL. 1997, DE AMBROGGI ET AL. 1997, BOULOS ET AL. 2001). However, Study V is the first to describe the effects of autonomic adaptation on repolarization in ARVD patients. Moreover, abnormal interventricular repolarization gradients, prolonged local TPE intervals over the RV and dynamics of QT dispersion are described for the first time.

6.3 Methodological considerations

Study patients. A limitation common to all five studies of this thesis was the relatively small number of patients and controls. In Studies I-IV this was a necessary restriction owing to the labour-intensive processing of data when introducing new methods of assessing repolarization under dynamic conditions. The routines developed during these experiments have nevertheless paved the way for future studies enrolling larger patient populations. Importantly, the developed methods were accurate enough to detect significant changes between patients groups despite the limited number of patients.

Patient selections in the substudies also imposed some restrictions regarding the generalizability of the present findings. Studies I-II encompassed only healthy young men, leaving possible gender differences unaccounted for. In Studies III-IV, all LQT1 patients carried the same C-terminal KCNQ1 mutation, meaning that the observed results may not be universal for the LQT1 subtype of LQTS. However, a homogeneous population in respect to the underlying mutation has the advantage of limiting variability caused by genotype-specific factors. In Study V, a potential confounder was the use of β -blockers and class III antiarrhythmic drugs. All enrolled ARVD patients were symptomatic prior to treatment and had documented clinical or induced serious ventricular arrhythmias. Therefore discontinuation of treatment merely for the purposes of this study was considered unethical. The use of β -blockers definitely explained the blunted HR responses and partly the diminished QT responses to sympathetic challenge in these patients. However, exclusion of the three patients with class III antiarrhythmic drugs did not change the main results, indicating that these drugs had only a minor confounding influence. Another possible source of bias was the slight but non-significant difference in age between ARVD patients and their controls, as well as the presence of mild co-morbidities in the patient group but not in the controls.

Autonomic mechanisms. Significant changes in HR and QT intervals were observed during the autonomic function tests, indicating that the tests caused adequate reflex autonomic stimulation. However, it is not possible to verify the exact autonomic mechanisms for a given change, considering that similar responses can be elicited both by sympathetic activation and parasympathetic withdrawal. This is especially true during the Valsalva manoeuvre, where mechanoelectric feedback further complicates the picture. It is also likely that autonomic tests differ in the degree of direct neural as opposed to humoral adrenergic activation, which may influence repolarization differently. Moreover, rebound parasympathetic activation may occur simultaneously with persisting sympathetic activation, as is probably the case during the early phases of recovery from sympathetic challenge. Although these combined responses limit the inferences that can be made regarding the extent of direct sympathetic and parasympathetic effects on repolarization, such response patterns closely resemble those encountered in daily living.

QT interval and QT dispersion measurements. Automated QT interval measurement eliminates observer bias, but remains vulnerable to constant and systematic error. There have been concerns regarding the reliability of automated QT interval and QT dispersion assessment (McLAUGHLIN ET AL. 1995, GLANCY ET AL. 1996a), especially in the presence

of abnormal T waves. The QT-algorithms employed in the present studies showed high reproducibility both in single beat (Study I) and beat-to-beat (HEKKALA ET AL. 2006) measurements, facilitated partly by the relatively normal T waves encountered in the study patients. Moreover, leads with excessive noise or ambiguous T waves were carefully excluded from the analyses. Exclusion of leads potentially affects QT dispersion, but has nevertheless been a common practice in QT dispersion studies. Assessment of a global QT interval, encompassing the mean value over all measurable leads, provided a robust measure of autonomic influences on ventricular repolarization. Moreover, the averaging of 30-second beat-to-beat periods reduced the effects of outliers resulting from measurement error, the elimination of which is of importance especially in dispersion assessments.

ECG markers of transmural and interventricular dispersion. TPE interval has been widely adopted as the ECG counterpart of TDR. Some authors have questioned this assumption, based on the lack of direct in vivo validation (OPTHOF ET AL. 2007) and the fact that any given ECG lead records not only local events but also a weighted average of more widespread electrical gradients. However, the good agreement between experimental models and clinical observations (see 2.3.6) strongly supports the relevance of TPE as a marker of TDR especially in LQTS. This is further underscored by the recent observation that TPE was the best ECG predictor of TdP in patients with acquired bradyarrhythmias (TOPILSKI ET AL. 2007).

Possible limitations in the ability of a lead or group of leads to detect local events apply also to the proposed new ECG marker of interventricular dispersion of repolarization. However, the combined observations in healthy controls, LQT1 patients and ARVD patients follow nicely the inferences made from previous studies (HLAING ET AL. 2005, KANDORI ET AL. 2002, PEETERS ET AL. 1997), emphasizing that LQTS is a primarily LV disease while ARVD is – by definition – primarily a RV disease. It can be argued that the proposed RV type leads based on QRS morphology reflect also basal and septal repolarization. This would be expected to reduce rather than amplify the observed differences in the patient groups, however. Technical restrictions at the time of study limited the BSPM electrode layout to only 25 precordial leads; it remains possible that a more extensive spatial sampling would provide an even better detection of local repolarization abnormalities.

6.4 Practical implications

The present studies have outlined physiological conditions that need to be controlled when assessing spatial QT dispersion. In the wake of more recent findings, the whole concept of spatial QT dispersion has fallen into disrepute. Nevertheless, the present observations indicate that spatial QT dispersion might reflect the basic underlying dispersion of repolarization at least in the presence of defective I_{Ks} , suggesting that earlier reports on spatial QT dispersion in LQT1 patients need not be completely disregarded.

Even in the era of genetic testing, a need remains for non-invasive and simple diagnostic assessment of patients with known or suspected LQTS. Autonomic testing unmasks the abnormal repolarization in asymptomatic KCNQ1 mutation carriers, emphasizing on one hand the pivotal role of autonomic reflexes and on the other hand, the limited value of a mere resting QTc interval in the LQT1 subtype of LQTS. Even though a larger study is needed to address the diagnostic power of autonomic testing, the present work outlines new methods to deal with the complex relation between HR and QT responses encountered during such a setting. Combined, the present findings may provide a possible explanation for why symptoms in LQT1 patients commonly occur during swimming, where a Valsalva-like strain may happen during vagal activation elicited by the exposure of the face to cold water.

A method to assess interventricular dispersion of repolarization is presented. Exploring its dynamics may provide new insight to possible underlying arrhythmogenic substrates, especially in ARVD.

Finally, the Valsalva manoeuvre appears to be the most useful autonomic test to explore repolarization abnormalities. Easily performed and standardized, it could be used along with exercise testing and ambulatory recordings in outpatient clinics, to aid in the immediate management and counselling of patients with a known or suspected arrhythmogenic disorder such as LQTS or ARVD.

7. Conclusions

- QT intervals measured from ECG and MCG recordings show a close correlation.
- Breathing movements influence the measurement of regional QT intervals in ECG and MCG differently.
- Recovery phases of standard cardiovascular autonomic function tests and the Valsalva manoeuvre expose the abnormal repolarization in asymptomatic LQT1 mutation carriers having nearly normal resting QT intervals.
- Spatial QT dispersion correlates with interventricular QT dispersion and TPE in LQT1 patients but not in healthy controls.
- ECG manifestations of defective I_{Ks} are more evident in the left than in the right ventricle. Abrupt autonomic adaptation amplifies the resulting interventricular repolarization gradient, further underscoring the labile nature of the underlying repolarization abnormality in LQT1.
- ARVD patients exhibit an abnormal ECG interventricular repolarization gradient and increased transmural dispersion of repolarization in the right ventricle. Valsalva strain transiently reverses the interventricular repolarization gradient in ARVD patients.
- Valsalva manoeuvre appears especially useful in revealing repolarization abnormalities both in LQT1 and ARVD patients.

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