Traces of Repolarization
Inhomogeneity in the ECG

MILOS KESEK
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**Abstract**


Repolarization inhomogeneity is arrhythmogenic. QT dispersion (QTD) is an easily accessible ECG-variable, related to the repolarization and shown to carry prognostic information. It was originally thought to reflect repolarization inhomogeneity. Lately, arguments have been risen against this hypothesis. Other measures of inhomogeneity are being investigated, such as nondipolar components from principal component analysis (PCA) of the T-wave. In all here described populations, continuous 12-lead ECG was collected during the initial hours of observation and secondary parameters used for description of a large number of ECG-recordings.

Paper I studied QTD in 548 patients with chest pain with a median number of 985 ECG-recordings per patient. Paper II explored a spatial aspect of QTD in 276 patients with unstable coronary artery disease. QTD and a derived localized ECG-parameter were compared to angiographical measures. QTD, expressed as the mean value during the observation was a powerful marker of risk. It was however not effective in identifying high-risk patients. Variations in QTD contained no additional prognostic information. In unstable coronary artery disease, QTD was increased by a mechanism unrelated to localization of the disease.

Two relevant conditions for observing repolarization inhomogeneity might occur with conduction disturbances and during initial course of ST-elevation myocardial infarction (STEMI). Paper III compared the PCA-parameters of the T-wave in 135 patients with chest pain and conduction disturbance to 665 patients with normal conduction. Nondipolar components were quantified by medians of the nondipolar residue (TWRabsMedian) and ratio of this residue to the total power of the T-wave (TWRrelMedian). Paper IV described the changes in the nondipolar components of the T-wave in 211 patients with thrombolyzed STEMI. TWRabsMedian increased with increasing conduction disturbance and contained a moderate amount of prognostic information. In thrombolyzed STEMI, TWRabsMedian was elevated and has an increased variability. A greater decrease in absolute TWR during initial observation was seen in patients with early ST-resolution. Nondipolar components do however not reflect identical ECG-properties as the ST-elevation and their change does not occur at the same time.

**Keywords:** cardiology, repolarization, ECG, QT dispersion, nondipolar components, T-wave, principal component analysis, repolarization inhomogeneity

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Picasso was riding in a train compartment with a stranger, who, recognizing Picasso, asked him why he didn’t paint pictures of people “the way they really are.” Picasso asked the man what he meant by “the way they really are.” The man pulled out of his wallet a snapshot of his wife and said, “That’s my wife.” Picasso responded: “Isn’t she rather small and flat?”

Cited by Heinz Pagels (page 163) in “The dreams of reason”.
The present thesis is based on the following original papers, which will be referred to by their Roman numerals.


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<th>Definition</th>
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<tbody>
<tr>
<td>APD</td>
<td>action potential duration (computed for example from MAP)</td>
</tr>
<tr>
<td>ARI</td>
<td>activation-recovery interval, see page 22</td>
</tr>
<tr>
<td>AT</td>
<td>activation time, a MAP-measure of the impulse propagation</td>
</tr>
<tr>
<td>BSM</td>
<td>body surface mapping, see page 18</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CASS</td>
<td>Coronary Artery Surgery Study</td>
</tr>
<tr>
<td>CUSUM</td>
<td>method of cumulative sums. See Appendix A, page 73.</td>
</tr>
<tr>
<td>CV</td>
<td>coefficient of variance, standard deviation/mean*100 (%)</td>
</tr>
<tr>
<td>CQV</td>
<td>coefficient of quartile variance (nonparametrical), see page 47</td>
</tr>
<tr>
<td>ERP</td>
<td>effective refractory period</td>
</tr>
<tr>
<td>HW-score</td>
<td>hemodynamically weighted score of coronary pathology (defined in the present work). See page 52.</td>
</tr>
<tr>
<td>ICD</td>
<td>Implantable cardioverter-defibrillator</td>
</tr>
<tr>
<td>LAD</td>
<td>left anterior descending coronary artery</td>
</tr>
<tr>
<td>LAH</td>
<td>left anterior hemiblock</td>
</tr>
<tr>
<td>LBBB</td>
<td>left bundle branch block</td>
</tr>
<tr>
<td>LCX</td>
<td>left circumflex coronary artery</td>
</tr>
<tr>
<td>LQTS</td>
<td>long QT-syndrome, see page 26</td>
</tr>
<tr>
<td>MAP</td>
<td>monophasic action potential, see page 22</td>
</tr>
<tr>
<td>PCA</td>
<td>principal component analysis. See Appendix A, page 73.</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>QTd</td>
<td>QT-dispersion, the difference between longest and shortest QT obtained from different leads of an ECG</td>
</tr>
<tr>
<td>RBBB</td>
<td>right bundle branch block</td>
</tr>
<tr>
<td>RCA</td>
<td>right coronary artery</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristic curve</td>
</tr>
<tr>
<td>RT</td>
<td>repolarization time obtained from MAP-recordings, sum of activation time and action potential duration</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>TCRT</td>
<td>total cosine between R and T, cosine of the three-dimensional angle between depolarization and repolarization vectors</td>
</tr>
<tr>
<td>TWRabs</td>
<td>absolute T-wave residue. See page 39.</td>
</tr>
<tr>
<td>TWRrel</td>
<td>relative T-wave residue. See page 39.</td>
</tr>
<tr>
<td>TIMI grade</td>
<td>angiographical scoring of the flow in the coronary vessels, used in the Thrombolysis In Myocardial Infarction studies</td>
</tr>
<tr>
<td>VT</td>
<td>ventricular tachycardia</td>
</tr>
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</table>
Introduction

Sudden death due to assumed malignant ventricular arrhythmia is known to cause about 50% of the cardiovascular deaths (3). About 40-50% of the deaths late after myocardial infarction have earlier been described as caused by sudden death (4, 5). More recently, the proportion of mortality late after a myocardial infarction that is due to cardiac causes, seems to have decreased. The relative number of arrhythmic deaths may, however, have remained constant. In a recently described series of 675 patients, the total mortality during follow-up of 43 months was 15.0%. The cardiac mortality was 8.7 % and included 3.3% of patients suffering sudden cardiac death (6).

With the advent of implantable defibrillators (ICD), sudden arrhythmic death has become treatable (7). The therapy is, however, prone to complications (8) and expensive. ICD implantation in an unselected population of patients is not considered as a realistic strategy (9, 10). Means are needed for selection of high-risk groups where the benefits will outweigh the adverse effects and balance the cost.

Repolarization inhomogeneity

Inhomogeneous repolarization is one factor behind the potentially fatal arrhythmias (12). The resulting electrical gradients and differences in refractoriness constitute a substrate for arrhythmia and a risk for the individual patient. For a review of electrical inhomogeneity in the normal and diseased myocardium see Wolk et al (14). The clinical research has concentrated on easily obtainable markers that may reflect the repolarization inhomogeneity and carry an adverse prognosis. Various parameters derived from the T-wave of the ECG have been evaluated. QT-dispersion (QTd) is probably the most extensively studied of these measures during the last decade. Lately, research has been conducted on other possible ECG-measures of repolarization inhomogeneity, such as the nondipolar components of the T-wave (15).

During the first hours after occlusion of a coronary artery, dramatic biochemical and electrical gradients arise between the affected myocardium and the surrounding tissue (16, 17). Reperfusion will initially further contribute to this state (18). Increased arrhythmogeneity is observed during the early phase of a myocardial infarction as well as during reperfusion. The initial course of a ST-elevation myocardial infarction (STEMI) might therefore
provide a useful clinical condition for observing parameters associated with repolarization inhomogeneity. It is known that patients with left bundle branch block (LBBB) have a high incidence of sudden death and long-term mortality (19-22). This risk is at least partially due to arrhythmogenic factors that may be linked to repolarization inhomogeneity and there is a need for markers for estimation of the long-term prognosis in patients with bundle branch block. The present work focused on the properties of repolarization parameters, derived from a large number of automatically collected ECG-recordings in several populations that can be assumed to exhibit repolarization disturbances. The approach with repeated sampling and computerized measurement aimed at reducing the influence of measurement error and allowed for computation of measures of variations in the parameters. The intentions were

- To examine whether QTd, measured automatically in a large number of ECG-recordings and its variations during observation time of patients with chest pain contain prognostic information
- To identify a hypothetical localized factor in QTd and investigate its relation to known localized pathology
- To investigate the nondipolar components of the T-wave and their relation to conduction disturbance
- To explore the changes in the nondipolar components of the T-wave during initial course of a ST-elevation myocardial infarction
Background

The ECG and models of the source of the myocardial electrical field

The action potentials produced by the various myocardial fibers interfere in producing a common electrical field. This field spreads through the surrounding tissues and can be detected on the body surface. The myocardial source of the field can be described at several different levels of complexity (23):

- The microscopic, cellular level, investigated by microelectrodes
- The macroscopic level of fields within the myocardium, investigated by methods in close contact with the myocardium: MAP-catheters, electrode arrays and endocardial basket electrodes
- The level of remote observation, investigated by methods used by clinical electrocardiography: 12-lead standard ECG, vectorcardiography and body surface mapping (BSM)

Due to cancellation effects, caused by diverging wavefronts within the source, only a minor part of the electrical fields generated by the fibers can be recorded at a remote position. It has been estimated that at most 4% of the time-voltage product of the source is recorded by the ECG (Schaefer and Haas 1962, page 358) (24).

From a description of an electrical source and the surrounding medium, one can compute the potentials generated at a distance from the source; this so-called forward problem has a unique solution. The so-called inverse problem of determining the source from the observed distant potentials does on the contrary not have a unique solution (Helmholtz, 1853). There is thus an infinite number of possible myocardial sources that can reproduce a given potential distribution at the surface. If only the latter is known, it is not theoretically possible to give any unique description of the source (23, 25). Only after the basic properties of the source have been hypothesized, one can compute the parameters describing the source.

Attempts to describe the source have resulted in a multitude of models. The "doom on the inverse problem" (23) makes it problematic to decide in favor of any of these. The description of the source should, however, be physio-
logically relevant. Depolarization and repolarization should be considered separately when the validity of the models is discussed.

The passive electrical properties of the medium
The properties of the electrical field generated by the myocardium are determined by the source, as well as the surrounding medium. The medium surrounding the heart is neither homogenous nor of a regular and geometrically simple surface. The resistivity differs greatly between the various tissues. The intracavitary blood mass has approximately ten times lower resistivity than the surrounding tissue. In measurements on dogs (26), the resistivity of the lung was 2200 ohm-cm and that of the fat tissue 2500 ohm-cm. The passive resistivity of skeletal muscle, as well as that of myocardium, was anisotropic i.e. it depended on the direction of measurement. The resistivity of the skeletal muscle varied between 200 – 1900 ohm-cm, depending on the direction. In the left ventricular wall, the resistivity varied between 250 and 560 ohm-cm when measured in different directions. (It should be noted that this anisotropy of the medium is not the same property as the anisotropies of the impulse propagation velocity and action potential duration within the muscle, see page 25.

Theoretically, the impedance properties of the tissue may contribute to distortion of the electrical field generated by the myocardium: If tissue impedance apart from a resistive component also should include a capacitive component, then the signal would be subject to a phase shift between heart and body surface. The electrical capacity of various tissues surrounding the heart has been investigated in living dogs (27). The ratio of the capacitive to resistive current component was found to be smaller than 0.1 for frequencies up to one kHz. These results and resistivity data from other measurements on body tissues show that the electrical properties of body tissues are primarily resistive.

The dipolar concept and the fixed-location dipolar model
Much of the work around the dipolar concept of the electrical field generated by the myocardium was done before 1970 and the properties and limitations of this model are well established. A great deal of the ECG-parameters that are supposed to reflect the repolarization inhomogeneity are expressed either in terms of the single dipole or in terms of the difference between this dipole and the actual measurement, i.e. the nondipolar content of the signal. The physiological analogy between the single vector of the model and the heart in the real situation is obviously poor. It is thus important to review the properties of the dipolar concept before a discussion about the generation of QT-dispersion and about measurements of the nondipolar part of the ECG-signal.
The simple concept of Einthoven triangle is still useful as a practical description of the myocardial electrical field, as recorded in 12-lead ECG.

*Figure 1. The Einthoven triangle*

The underlying model describes the field source as dipole located at the center of an equilateral triangle with parallel conducting laminae and the electrodes L, R and F in the corners of the triangle (28). A more accurate vectorial model approximates the heart with a dipolar source placed in a spherical conductor of homogenous conductivity. The electrical fields generated by the myocytes are vectorially summed to a single resultant with the origin at the center of the dipole. The physical size of the dipole is negligible compared to the conducting sphere. The dipole rotates and the difference in electrical charge between its two poles changes. In each moment, three parameters are needed to describe the (electrical) magnitude and direction of the vector. Additional three parameters describe the (geometrical) position of the dipole. In the simple model, the dipole center is viewed as fixed centrally in the homogenous sphere and the geometrical parameters will be constant. In an extension of the model the dipole center is allowed to move, see below. The electrodes L, R and F are located at the boundary of the sphere and in
the same plane as the central dipole. Potential differences between the electrodes may be regarded as projections of the heart vector on the so-called lead line. If the lead lines and the projections are known, we may therefore reconstruct the heart vector (i.e. the field source in this model). For a unipolar lead (V1–V6 and the modified unipolar leads aVL, aVR, aVF), the lead line is the straight line between the exploring electrode (Schaefer and Haas 1962, page 327) (24) and the dipole center. For bipolar extremity leads the lead line is the straight line connecting the two electrodes.

Vectorcardiography

The dipolar model forms the basis of vectorcardiography in classical as well as in the more recent applications in ischemia monitoring. (Signal averaged ECG in the current form also assumes the dipolar model.) A vectorcardiogram can be recorded from specialized electrode positions or derived from a conventional 12-lead ECG (29, 30). The vectorcardiogram contains principally the same information as a conventional scalar ECG (as opposed to body surface maps, see page 18). The vector presentation is however better suited to illustrate some relations not easily quantified in a scalar ECG.

Limitations of the dipolar model

The model results in simple equations describing the recorded potentials as functions of a central dipole (Schaefer and Haas 1962, page 326) (24). Describing the real conditions as a central dipole in a large homogeneous sphere is however a rather crude approximation at the level of clinical electrocardiography, the latter itself being very remote from the source, i.e. the electrochemical processes in the cell membrane. When relating the ECG signal to the source in the myocardium, two types of limitations of the dipolar model can be seen (Schaefer and Haas 1962, page 333) (24):

- The inaccuracy in the source representation, i.e. how precisely can the potentials from the myocytes be represented by a single resultant vector that changes direction and magnitude. The discrepancy in anatomical terms is obvious. The source in the model is small but in reality, the dimension of the heart is significant in comparison to the thoracic cavity. For a recording electrode, the myocardial fibers in remote parts will appear under a much smaller (solid) angle than those close to the electrode (Schaefer and Haas 1962, page 326) (24). This difference can account for proximity potentials that will appear as nondipolar components in the signal. These can occur to varying degree during depolarization and repolarization.
The inaccuracy due to the volume conductor, i.e. how precisely can the spread of the field in the body be approximated by simple projections of the vector onto the boundary of a homogeneous sphere. A simple global vectorial addition of individual fibers’ dipole moments onto surface projections of a heart vector would be strictly valid only in the ideal case. In reality, the heart is placed somewhat eccentrically in a thoracic cavity and the inhomogeneous resistivity and passive anisotropy of the thoracic media (see page 14) result in complicated lead lines and distort the projection of the single vector (Schaefer and Haas 1962, pages 333, 337) (24).

Other source models
The error in the single dipole concept can be lessened if the dipole position is allowed to shift during the cardiac cycle. A further extension describes the cardiac source as several moving dipoles. Such a multipolar model offers a slightly better description of the field than the simple dipolar model. The correspondence to the anatomical and physiological properties of the heart is, however, even poorer, with no clear meaning attached to the individual components of the model.

More physiological models of the myocardial field source have been developed, such as the uniform double layer (UDL, described already by Wilson in 1933 (31)) and equivalent double layer models (EDL). These represent the source as a moving wavefront consisting of elementary dipoles distributed across the heart surface. Experimental verification of the UDL-model has been attempted by direct measurements by plunge electrodes on the surface of a canine heart mounted in a fluid-filled cylinder and measurement of the distant potentials observed on the wall of the cylinder. The latter were then compared to values predicted by forward computations (see page 13) based on UDL and shown to differ. Other experiments seemed to result in higher values of anisotropy than the UDL-model could account for. Both these problems may, however, have been caused by erroneous assumptions underlying the forward computation and the derived data describing the anisotropy. For review of the models see van Oosterom (23, 32).

The conductor
The modeling of the volume conductor is a separate concern that has to be observed in the assumptions, such as in the concept of dipolar source in a homogeneous sphere. More complicated models consist of cylinders, homogeneous torsos and torsos that may be specifically designed from individual anatomy (inhomogeneous, anisotropic, dynamic) (33).
Body surface maps

Recordings of signal from multiple (60-220) electrodes placed on the torso allow a precise mapping of the potentials generated by the myocardial source and present on the body surface. If the dipolar concept (see pages 15, 20, 37 and 39) offered a complete description, than recordings from multiple sites would be unnecessary. The body surface maps (BSM), however, contain more physiological information than the conventional 12-lead ECG. At brief thought this may seem strange, in light of the proven applicability of the dipolar concept of the ECG and the relatively small nondipolar content, not accounted for by this concept (see page 20). However, even if the signal found in 12-lead ECG largely can be represented by a dipolar model, this does not mean that the surface potential distribution is dipolar, not to mention the source itself. The 12-lead ECG defines global electrophysiology (34). The ECG can be used for construction of an accurate dipolar model and can subsequently be reconstructed from it. This model is however only accurate to the ECG and not primarily to the real source. Nondipolar patterns from the real source can still be present somewhere on the surface, without being reflected in the 12-lead ECG. (The global nature of 12-lead ECG is only seemingly contradicted by the well-known ability to localize a STEMI from the ST-elevations in 12-lead ECG. See further page 21.)

The BSM-data can be displayed as a sequence of isopotential maps with contours connecting the surface positions with the same potential. In normal subjects, a precordial maximum (positivity) and dorsal minimum move over the body surface during the QRS-interval (35, 36). During ST-T interval, one precordial maximum and one right clavicular minimum is seen (36, 37). In an early observation, Taccardi associated a nondipolar pattern during repolarization with pathologic conditions (a patient with angina and hypertension) (37).

The potential recorded in each electrode can be integrated over a defined time interval to an area, i.e. one numerical value in each measurement point. A single isointegral contour map for the QRS-, T- or QRST-area can then be drawn. The QRST-area map (ventricular gradient map (36)) is regarded as representing local repolarization properties (see page 35).

In an isochrone map, sites that are activated at the same time are connected by a contour. A departure map can be constructed from any of the above maps by computing the difference between the current recording and a defined reference material. For a review of BSM see Taccardi et al (25) and Medvegy et al (36).
The nondipolar content (QRS- and T-waves)

Nondipolar components in the signal do not contribute to the global QRS- or T-vector (15). They are thus reflected in the difference between actual recordings and a simple dipolar source model. Several ways have been explored in assessing this difference. For the significance that has been attributed to the nondipolar components of the T-wave see pages 39 and 65.

The cancellation technique

Frank used the signal cancellation technique (described by Duchosal & Sulzer 1949) to find points on the thoracal surface with mirror patterns that exhibit same waveform but opposite polarity (38). Existence of mirror patterns is evidently not a proof of the heart being a dipole (39) (see page 13). Instead, the cancellation technique gave a quantitative measure of the degree to which the fixed-location dipole hypothesis is applicable to humans. Directly measured and amplified maximum instantaneous potential difference between two nearly exact mirror patterns was typically 0.05 to 0.1 mV, while the QRS complexes themselves ranged from about 1 to 5 mV. Approximately 95% of the QRS complex could thus be attributed to a fixed-location dipole (38). From these findings, Frank drew the conclusion that a normal QRS-complex is not generated by a local mechanism (proximity potential, see page 16).

Inspection of isopotential body surface maps

Some nondipolarities in isopotential maps (see page 18) can be noted on inspection of the map. If more than one potential maximum and one potential minimum are found on the conductor surface then the corresponding source is regarded as nondipolar. In principle, a detection of multiple extrema at the surface does not necessarily imply that the source is nondipolar (25). However, in experimental models where dipolar field sources were introduced in the thoracic cavity, no nondipolar patterns could be detected on the surface (2). This was interpreted as indicating that any nondipolar patterns observed on the surface correspond to a nondipolar source. (On the other side, nondipolarity can be present even with one potential maximum and one potential minimum on the surface (40).) By processing of BSM, QRST-area maps can be derived (see above). Their nondipolarity has a somewhat different interpretation, see page 35.
Comparison of measurements with values derived from a dipolar model

Frank (41) recorded potentials from a human subject, computed the anatomical location of the fixed dipole by the cancellation technique and entered the result in a computation that used properties of a homogenous torso model. He placed an artificial dipole in the corresponding position in the torso model and recorded the signals from the surface. The difference between the human and the model recordings was about 15%, expressing the error from the assumption of a fixed dipole in a simplified conductor model.

A single moving dipole source model can be defined from an actual BSM by an inverse procedure (see page 13). A theoretical dipolar map can then be computed by a forward procedure. The nondipolar content in the signal can then be identified as the difference between the actual distribution and the theoretical dipolar map (36). This approach was described by Okamoto and used for comparison between actual measurements in a BSM and an optimal (instantaneously computed) approximation by a dipole with shifting position (42, 43). In each moment, a relative residue not attributable to the dipolar model was computed. See page 39.

Principal component analysis

The nondipolar content of the ECG-signal can be quantified by principal component analysis (PCA), a multivariate statistical method that can separate out the algebraically independent components from multiple partially related variables. The method (44) was developed by Pearson 1901 and, independently, by Hotelling 1933. A related procedure, known as factor analysis proper, was developed by Spearman (1904, 1926). PCA is most useful when all the original variables are measured in same units, as in the ECG-recording (and opposed to the more complicated situations appearing for example in psychology, where the original parameters often use different metric). See Appendix A, page 73.

PCA, space and dipolarity

The dipolar concept describes the electrical field as originating from a single vectorial source in a three-dimensional space. The magnitude and direction of the vector can in each moment be characterized by three orthogonal components. When the ECG-signal is processed by PCA, the resulting three largest principal components will with necessity (due to their orthogonality) be a description of this single vector in three-dimensional space. All the components of higher order (the nondipolar components) describe the part of the signal that cannot be explained by the single vector of the model, i.e. the nondipolar content.
Scher et al (45) analyzed ECG-recordings from normal subjects with factor analysis. In their analysis, 96.3-99.9% of all information in the QRS-complex was retrieved in the first three (i.e. dipolar) factors. An early analysis of BSM by the PCA was done by Horan et al (1). When QRS was resynthesized from three principal factors, a close resemblance to the original waveform was obtained. A significant percentage (8%) of information was however located in the factors 4-8. For PCA of the T-wave see page 37.

**How can we localize a myocardial infarction if the ECG just mirrors a global dipole?**

A STEMI can be localized by position of the ST-elevations in the 12-lead ECG, in spite of the small amount of local (nondipolar) information in the signal. This is possible due to changes in the global vector following the local process. The 12-lead ECG still predominantly reflects a single global dipole, fixed at the center of a spherical conduction medium. The ST-elevations are not caused by local changes in the electric field. The direction and magnitude of the vector are however changed by the STEMI. As observed by Abildskov, our ability to localize the STEMI from the pattern of ST-elevations depends on the global property of a normal conduction and is greatly attenuated by a bundle branch block (34). (It may be noted here, that the ST-elevation observed in STEMI is at least partially due to a virtual effect, where the T-P interval - normally an "electrically silent" segment of the electrogram that serves as a reference level - is depressed, due to a diastolic injury current (46, 47).)

**Other measurement methods of interest**

**Magnetocardiography**

Electrical currents originating in the active myocardium generate a magnetic field. The latter can be used in investigations of the myocardial source, in analogy to the electrical field and BSM. A magnetocardiographic map has a better spatial resolution than a BSM. Magnetocardiographic signal is less affected by the medium surrounding the myocardial source than the ECG-signal. A considerable technological challenge is involved in the measurement: The field to be detected is around $1/10^6$ of the magnetic field of the earth. This weak field is distorted by the electromagnetic noise generated by the multitude of electrical equipment in the environment (48). Earlier magnetometers had a small number of channels and required a magnetically shielded room for acceptable signal quality. The current multichannel instruments use superconducting magnetometers (SQUID magnetometers, immersed in liquid helium) and can record signal in unshielded rooms. The
magnetocardiogram is morphologically similar to ECG and same time-intervals can be defined in both types of recordings.

Monophasic action potentials

The regional differences in repolarization that give rise to the T-wave can be measured in recordings of monophasic action potentials (MAP). The method can be applied experimentally, as well as clinically. Originally, the technique used a suction electrode catheter (Korsgren et al 1966, Olsson et al 1971) (49). Later, a contact electrode catheter was developed. The information obtained by the MAP-technique is local (representing a few hundred cells (50) from an area of around 5 mm in diameter). The MAP reproduces closely a transmembrane action potential. It is often recorded from a few sites on the ventricular endocardium. Commonly measured parameters are the local activation time (AT, time from start of QRS to the upstroke of the MAP), action potential duration (APD, represented by the time from upstroke of the MAP to 90% repolarization) and repolarization time (RT, sum of AT and APD) (50, 51). The method is regarded as gold standard for measurement of local activation time and action potential duration (52). Both experimentally (53) and in human in vivo studies, sites with short activation time have long action potential duration (50, 54). The action potential duration in right ventricle is usually longer than that in left ventricle (55). The dispersion in the entire repolarization time is smaller than just the dispersion of action potential duration. This may have a protective effect against reentrant arrhythmias (56). The transmural gradient of repolarization seems to have the opposite direction to that of depolarization, resulting in a T-wave concordant with the QRS-complex. In experimental, as well as clinical studies of repolarization by the MAP-technique, a link has been established between increased dispersion of MAP duration and arrhythmogenenity (12, 57).

Activation-recovery intervals

The local action potential duration can be estimated from an extracellular recording obtained from insulated unipolar electrode that is kept in close contact with the myocardial surface or introduced into the myocardium. From the electrogram, the activation-recovery interval (ARI) is computed as the interval between the \(dV/dt_{\text{min}}\) (steepest downward deflection) of the local "QRS" and \(dV/dt_{\text{max}}\) (steepest upward deflection) of the local "T-wave". Measurements of ARI are correlated to the action potential duration, determined by intracellular technique. The method has been used in experimental conditions (55, 58, 59), as well as in a clinical setting during coronary artery surgery (60).
Recovery of excitability

The effective refractory period (ERP), measured over a wide range of driving cycle lengths is closely related to the action potential duration, measured by MAP at the same site (61). The finding has been verified in recordings of ARI (58, 59). Ischemia and other known arrhythmogenic factors have in experiments with canine heart in situ been shown to greatly increase local differences in refractory periods (62). Experimentally, the refractory period has anisotropic properties and changes depending on the underlying activation sequence, presumably due to electrotonic interaction (63). Difference in refractory periods between different myocardial sites has been used as an indirect measure of local repolarization differences (53, 64).

Optical mapping

Methods based on fast voltage-sensitive dyes for monitoring of rapid changes in membrane action potential activity have been adapted for use in experimental cardiac electrophysiology. Their use offers several advantages, such as possibilities of recording the activity from cells too small for conventional recording techniques, absence of artifacts caused by electrical stimulation and possibilities of studying propagation patterns in cardiac tissue (65).
The T-wave of the ECG and its measures

The T wave is the result of repolarization gradients across the ventricular myocardium (66) and contains thus information about repolarization inhomogeneity. Indeed, the normal T-wave in itself represents a normal dispersion of repolarization (67, 68), as a result of electrical heterogeneity at the cellular level in the normal heart (see page 33).

The concept of primary and secondary T-wave

The shape of the T-wave is determined by both the activation sequence and local repolarization characteristics. The T-wave has been described as a sum of two components that express these two properties (69-71): If all the ventricular muscle was excited simultaneously, then the observed T-wave would not depend on any activation sequence and reflect only intrinsic properties of ventricular recovery. This hypothetical T-wave component has been called the primary T-wave. On the other hand, if the ventricular recovery properties were uniform, then the resulting T-wave would be determined only by the ventricular activation sequence. This component has been named the secondary T-wave. See also page 35.

Dependence of repolarization duration on the activation sequence

The above described two components of the T-wave are in reality not mutually independent. Experimental studies have shown that the local duration of the repolarization is affected by the activation sequence (34, 50). It seems to depend on whether the propagation is parallel or transverse to the orientation of myocardial fibers (64). (In another study, this interdependence seems to be relatively small and vary between different parts of the myocardium (72).) Electrotonical interaction from surrounding myocardium (73) is the probable mechanism underlying the dependence. A further challenge to the simple concept of primary and secondary T-wave is posed by the phenomenon of cardiac memory (56): When an initially aberrant impulse propagation reverts to normal (after termination of a period of ventricular pacing or after ablation of an accessory pathway), residual T-wave changes are observed with the T-vector being similar to the QRS-
vector during the initial, abnormal condition. The local repolarization properties are thus influenced by the properties of the present, as well as the past propagation.

Propagation velocity and its anisotropy
The propagation velocity of the depolarization wave in the myocardium is anisotropic, i.e. dependent on the direction of propagation. No simple relation exists between the velocity of the impulse propagation through the myocardium and the local properties of the action potential. Increased velocity is associated with increased peak depolarizing current (represented by \( dV/dt_{\text{max}} \), the steepest upward deflection of the action potential) and tissues with slow propagation velocity (such as AV node) often have low \( dV/dt_{\text{max}} \) of the action potential. However, in measurements in anisotropic situations where the excitation was changed from longitudinal to transverse, a decrease in propagation velocity was associated with an increase of \( dV/dt_{\text{max}} \) (74).

Gap junctions
The myocardial cells are elongated and grouped at several levels, separated by a thin interstitial space. The impulse propagation is dependent on the cellular coupling by gap junctions. A typical myocyte is connected to 9-11 adjacent myocytes by around 100 gap junctions (14). These act as intercellular bridges with low resistivity and mediate the depolarizing current (75, 76) and the electrotonical coupling between the cells (77). The channels are unselectively permeable to organic ions and small molecules. The essential protein subunit of the myocardial gap junction, connexin 43, has a rapid turnover, with a half-life estimated to 1-2 hours. Experimentally, after a period of pacing, a cellular redistribution of connexin 43 was seen together with the changes of the T-wave attributable to the cardiac memory (78). No pathology was detected in conventional light microscopy.

A normal anisotropy, seen in tissue from children and young adults, is caused by the geometrical factors and uneven distribution of the gap junctions. In aging or diseased tissue, microfibrosis or edema causes a loss of lateral connections. The differences in propagation increase further and a pattern of "nonuniform anisotropy" emerges (74, 79).

QT-interval
The QT-interval in the 12-lead ECG reflects global repolarization duration. QT-interval decreases with increased heart rate and should be adjusted for the frequency (as opposed to the QT-dispersion, see below).
A multitude of correction formulas have been employed, among these the well-known Bazett’s formula:

\[ QT_c = \frac{QT}{\sqrt{RR \text{(seconds)}}} \]

The corrected QT-values still show a dependence on the heart rate (80), implying that the correction is not complete. Neither does any of the other suggested formulas achieve a full correction. The heart rate dependence is altered by several factors such as autonomic tone and temperature. The QT-RR relation is furthermore highly individual and can not be expressed by any generally valid formula (81).

A correlation exists between the duration of QT and action potential duration measured by MAP from right ventricle (82) (see page 22). QT is, however just a crude measure of arrhythmogeneity due to repolarization inhomogeneity. It is influenced by the QRS duration, as well as by the duration of ST-T. An increased ST-T duration may be caused by a uniformly prolonged repolarization, as well as by asynchronous repolarization, i.e. increased differences in action potential duration. Some conditions with a uniform prolongation of repolarization (hypocalcemia and steady-state hypothermia) seem not to be arrhythmogenic (83). Prolonged action potential duration could nevertheless be arrhythmogenic without associated increased inhomogeneity, by promoting repetitive afterdepolarizations (84).

A prolonged repolarization is also related to increased inhomogeneity of repolarization. In the inherited long QT-syndrome (LQTS), prolonged QT-interval is associated with arrhythmias and sudden death. LQTS has been used as a clinical model of repolarization disturbances. The disease complex is caused by defects in the cardiac ionic channels, involved in repolarization. LQTS is associated with prolonged ventricular repolarization and increased transmural inhomogeneity, probably due to changes in the properties of the M-cells (58, 85, 86) (see page 33). In an animal model of LQTS, bradycardia dependent repolarization inhomogeneity between different parts of the epicardium has been shown to create a substrate for conduction block and promote inducibility of tachycardia (87). The authors assume an interplay, where afterdepolarizations act on a substrate of marked spatial dispersion of repolarization. The latter probably is associated with impaired cellular coupling (see page 25) and decreased electrotonical interaction, that otherwise tends to diminish the dispersion.

Acute ischemia, associated with anginal pain does not seem to affect rate corrected QT-interval duration (88). In ischemic disease, there is an association between QT-prolongation and mortality. It is however, weak and QT-prolongation does not seem to be a true risk marker (83, 84).
**QT-dispersion**

QT dispersion (QTd) is an easily accessible clinical ECG-variable that is related to the repolarization process. It is commonly defined as the difference between the longest and the shortest QT-interval across all available leads in the 12-lead ECG. An increased QTd can thus be caused by a prolongation of the longest QT (QTₘₐₓ) or shortening of the shortest QT (QTₘᵢₙ). Other measurement approaches use the range computed from the precordial leads only or replace the range with the standard deviation of QT-intervals in all the measured leads. None of these alternatives has however been shown to be superior to the first definition.

The existence of the difference was noted around 1985 in BSM (89, 90). Cowan et al described in 1988 an increased interlead variation in QT in 12-lead ECG of patients with myocardial infarction (91). The term QT dispersion was coined by Day et al in 1990 (92). Increased QTd, (together with uncorrected, as well as rate corrected QT prolongation) was a risk factor for total and cardiovascular mortality in an epidemiological study in 3781 subjects, followed for 13 years. The risk was confined to the subgroup with cardiovascular disease (150 deaths / 821 subjects) (80). QTd (computed automatically, as well as manually) has been linked to prognosis in several other studies (93-97). In patients with LQTS (see page 26), automatically computed QTd is increased (80 ms vs. 38 ms in the controls) (98).

**Rate correction of QTd**

Several authors have used heart rate correction of QTd by Bazett’s formula (97, 99-104). An experimental MAP-study by Zabel et al indicates that this is not necessary (105). No relation is found between QTd and the heart rate in the materials of Elming et al (80) and Oikarinen et al (106). An illustrative example (107) shows, how a correction instead may introduce an error by contaminating the original parameter with prognostic information from the heart rate: In a database with acute myocardial infarction data, the authors confirm a correlation between the heart rate and long-term survival (a general relation, for another example see Elming et al (80)). They subsequently analyze the number of letters in the patients surname and find this parameter to be unrelated to the survival. Ultimately, they construct a new parameter by correcting the number of letters for heart rate by Bazett’s formula and show that this corrected parameter is correlated to survival (p=0.0145). A correction of a variable by heart rate that is known to contain prognostic information might thus introduce a powerful artifact.

**Correlation to arrhythmia and sudden death**

Glancy et al compare the QTd, measured on two occasions in patients dying up to 5 years after myocardial infarction to that in matched survivors (103).
QTd (uncorrected and rate-corrected) on day 3 of the infarction does not correlate to survival. Late QTd (measured four weeks or later after the event) is unchanged in the patients who later died, but decreased in the survivors. QTd (rate corrected) is a risk factor for sudden death in a population with ischemic heart disease (94). Post myocardial infarction patients that suffer from ventricular fibrillation or monomorphic ventricular tachycardia have a greater QTd than patients without arrhythmia (100, 106). QTd is increased in patients with ischemic heart disease and sustained ventricular tachyarrhythmias (108) and in patients with inducible ventricular tachycardia (109). In the latter study QTd is measured as dispersion of the QT_peak interval in precordial leads; for discussion of T_peak see also below and page 33. Patients with dilated cardiomyopathy of mixed origin and left ventricular dysfunction exhibit greater QTd (and longer QT) than controls. The studied patients that suffer from ventricular tachyarrhythmia or sudden death have greater QTd than the patients dying from pump failure, acute myocardial infarction and the controls (110). In 280 infarct survivors, Zabel et al evaluate QTd as a prospective marker for the composite endpoint death, VT or resuscitated VF after two years (104). QTd does not discriminate between the groups; neither do the other tested measures of repolarization (T_peak-T_end interval, T-area and late T-area).

Ischemia

QTd increases in several conditions with myocardial ischemia (111, 118). Atrial pacing in patients with coronary three-vessel disease increases the QTd. Simultaneous measurements of myocardial lactate extraction show a correlation to the QTd (r=0.76) (101). QTd increases during PCI (112-114). After a successful PCI in patients with one-vessel disease, QTd decreases from 60 to 23 ms. In a subgroup with late restenosis, QTd increases to 56ms (115). In a study of QTd and myocardial viability assessed by positron emission tomography before and after revascularization of patients with a history of Q-wave infarction and coronary stenosis, QTd is lower if viable myocardium is present in the infarction area (102).

Correlation to thrombolysis and coronary blood flow

QTd, measured ten days after thrombolysed STEMI, is lower in the patients with higher coronary flow (estimated angiographically by the TIMI-grade) (116). The patients with occlusions of LAD have a higher QTd, compared to the patients with LCX- or RCA occlusions. In a comparison study, the (rate corrected) QTd is higher in patients with myocardial infarction than in a group with unstable angina. In a few patients that have developed ventricular fibrillation, the QTd is further increased. No difference is found between anterior and inferior infarctions. (99).
Components of QTd

The QTpeak interval has a dispersion that exhibits a relatively modest correlation with QTd ($r=0.45$) (117). Mänttäri et al compares the dispersion of the QTpeak interval with QTd for victims of fatal myocardial infarction or sudden death drawn from a large study population and matched controls (96). Increased dispersion of the QTpeak interval in an earlier recorded ECG is associated with increased risk for sudden death while conventional QTd does not predict sudden death. Victims of fatal infarction do not differ from controls. In study on post myocardial infarction patients, Oikarinen et al finds, that QTd, as well as dispersion of QTpeak is greater in a group with ventricular tachycardia; no difference is seen between patients without arrhythmia and patients with ventricular fibrillation (106).

The increase of QTd in ischemia is mainly caused by shortened QTmin in viable tissue (112, 119). Myocardial scar tissue does not seem to influence the parameter (120). Somewhat different pattern has been described in acute myocardial infarction. Higham et al (99) investigated the QTmin and QTmax underlying the (rate corrected) QTd and similar measures defined for Tpeak. A prolonged QTmax was responsible for the increased QTd in patients with acute myocardial infarction. The increased dispersion of the QTpeak interval seen in infarction was mainly due to a shortened QTpeak minimum. These disparate patterns are an expression for a morphological alteration of the T-wave. Regarding $T_{peak}$, $T_{peak}$-$T_{end}$ interval and T-wave morphology see page 33.

Problems of manual measurement

Manual measurements of QTd suffer from operator dependency and poor reproducibility (121, 122). The Qonset can be defined either individually for each lead or at a common point for all leads. In the latter case, the measurement error is increased by approximately four ms, due to the existence of a Qonset dispersion (52, 123). The end of the T-wave ($T_{end}$) is not well-defined and may be very difficult to identify, especially in leads with low T-wave amplitude. An exclusion of these leads greatly decreases the QTd (124). The measurement is significantly affected by the amplifier gain and the recording paper speed (125). Correction formulas for number of excluded leads have been defined (52) but a correction itself affects the QTd-value (126). A safer approach involves reporting the data on the number of the analyzed leads. In the materials, that report the number of valid leads, the conclusions are based on ECG-recordings with at minimum 7-10 valid leads and average number of valid leads around 10.3 (80, 99, 104, 108, 113).

U-wave

The U-wave should be considered separately, since the mechanism underlying the U-wave seems to be different from that of the T-wave, at least in
some cases (52). U-wave is possibly caused by mechanoelectrical feedback, due to activation of mechanosensitive ion channels, that are activated by stretch during mechanical diastole (127). Delimitation of the QT-interval is uncertain, when a U-wave is present. The T<sub>end</sub> in presence of a U-wave is often defined as the nadir between T and U-waves. A nadir is however often not present. If the difficult leads are excluded from the analysis then the resulting QTd might turn out falsely low (121). A recent study in patients undergoing PCI confirms earlier findings of increased QTd during ischemia after inflation of the PCI balloon. However, when the U-wave is included and QU-dispersion is calculated, the increase is eliminated and no significant difference is found between basal conditions and ischemia (114).

**Automatic methods**

In an attempt to overcome some of the limitations of QTd, automatic measurement methods have been developed. The results obtained by automatic methods depend heavily on the algorithm used for detection of the T<sub>end</sub> (52) and the relation between manual and automatic measurements is weak (124, 128, 129). Different approaches have been tested for the detection of the T<sub>end</sub>, based on amplitude thresholds, T-wave area, derivatives of the T-wave and their intersection of the isoelectrical line. The QTd data in the present work were based on T<sub>end</sub> computations with the LSI-algorithm, that uses the intersection of a least-square fitted line to the maximum downslope of the T-wave and the isoelectrical line (130). A problem of reproducibility remains with the automatic methods (121, 124). It tends to diminish somewhat when QTd is computed by averaging a few (2-5) automatic measurements (129, 131). (See Aims of the present work, page 42.) The short- and long-term reproducibilities of QTd-measurements by a commercial automatic system of interest for the present work (QT-Guard, GE Medical Information Technology, Milwaukee, Wisconsin) have been evaluated by Gang et al (131). Multiple registrations of 12-lead ECG were performed in healthy subjects. The measurements were repeated after 8 days. QTd was computed from a common Q<sub>onset</sub> and the T<sub>end</sub> in each lead as defined by the LSI-algorithm, briefly described above. The short-term reproducibility was measured by the coefficient of variance (CV) for the repeated measurements and shown to be 20-40%, compared to 1-5% for conventional ECG-parameters (QRS-duration, QT) registered at the same occasion. The long-term reproducibility was evaluated by calculating the relative error for the means at the two registration occasions, A and B:

\[ E_r = \frac{|A - B|}{(A + B)/2} \]
The relative error was around 30% (compared to <8% for the conventional ECG-parameters, registered at the same occasion).

Estimates of temporal variation in QTd
QTd may have a component exhibiting temporal variability (see Aims of the present work, page 42). QTd increases during spontaneous anginal episodes (132), in patients scheduled for PCI (115, 133) and during ischemia induced by atrial pacing (101, 134), exercise testing (119, 135) or inflation of a PCI-balloon (112-114). In patients with acute myocardial infarction, QTd on admission is significantly greater than QTd 24 hours later (99). Successful thrombolysis decreases QTd (116, 136). Molnar et al finds a circadian variation in automatically computed QTd from 24 hour two-channel Holter recordings of healthy subjects. In survivors of sudden cardiac death, QTd is greater and the circadian variation is blunted (137).

Normal values
There is a large overlap between normal and pathological values and no general consensus regarding reference values has been established. QTd in normal subjects is approximately 30 to 45 ms. In acute myocardial infarction values of approximately 60 ms have been reported (111). In a large population-based study (80), values above 80 ms are associated with a relative risk of 4.4 for cardiovascular mortality. One recommendation is that only greatly prolonged values above 100 ms should be interpreted as sign of significantly abnormal repolarization (52).

Generation of QTd, local hypothesis
QTd has been linked to changes in ionic environment of the myocardium (138-141). Originally, QTd was thought to reflect the local repolarization inhomogeneity (92). This so called local hypothesis (68) for generation of QTd has been supported by studies correlating QTd to measurements of monophasic action potentials (MAP, see page 22). In a Langendorff model, variables in surface-ECG and MAP-variables were measured while the repolarization was manipulated by altering pacing intervals and adding d-sotalol to the perfusate. The dispersion of action potential duration (APD, see page 22) was compared to the model equivalents of ECG variables QTd, Tpeak-Tend interval (a measure of dispersion of repolarization, possibly due to the transmural dispersion, see page 33), T-area (a measure of repolarization sequence, see page 35) and late T area (area of the T-wave during Tpeak-Tend interval). QTd correlated significantly with the dispersion of APD (Pearson r=0.6). The Tpeak-Tend interval, T-area and late T area exhibited an even higher correlation to the dispersion of APD, with r values of 0.8 (142). (These parameters were subsequently tested as clinical risk markers with a negative result, see page 28.) An analysis of data available from
human measurements exhibited similar correlations between QTd and the dispersion of the repolarization time (the MAP-parameter RT) (143). Even relatively recent works refer to the local hypothesis as explanation of QTd (144, 145). It has also been proposed that in pathological conditions, a local factor might be involved in the generation of the T-wave, as opposed to a normal situation where the global dipole dominates (68, 146).

Within the frame of the local hypothesis, the spatial distribution of the ECG-factors responsible for the QT dispersion (147) would influence the arrhythmogenic potential. The latter should be greater if QTd arises from adjacent regions, compared to differences between regions remote from each other. The difference in QT measured over adjacent areas of the myocardium would thus reflect repolarization inhomogeneity. This assumed local factor is not reflected in the conventional definition of QT-dispersion. Attempts have been made to quantify the localized differences in QT, measured in multiple channels by magnetocardiography (see page 21) (148, 149).

See Aims of the present work, page 42.

Recent view on QTd, global hypothesis

The local hypothesis is not compatible with the dipolar model of the myocardial source, that can account for the dominating part of the signal in a 12-lead ECG (see page 15). Plausible arguments have been risen against the local hypothesis (15, 123, 150-153). An experimental investigation finds no correlation between the dispersion of ARI and the QTd in the ECG (59). In a scintigraphic study, the regional variability in sympathetic innervation of the heart does not correlate to QTd (145). Twelve-lead ECG recordings synthesized from orthogonal 3-lead recordings exhibit larger QTd than the original recordings (154). After a transformation of the 12-lead ECG to an orthogonal 3-lead recording and back to 12-lead ECG (thus eliminating any nondipolar components), QTd remains mainly unchanged (155).

In survivors of acute myocardial infarction, QTd (rate corrected) is not associated to nondipolarity in the QRST-area map (156) (see page 35). After principal component analysis of the T-wave signal (15), information is mainly found in three dimensions, corresponding to the global T-wave dipole (see pages 15, 37 and 39). The nondipolar content of the signal that may correspond to local repolarization inhomogeneity accounts in normal subjects for 0.03% of the total information and exhibits a weak correlation to QTd (r=0.2). Global geometrical factors have therefore been suggested as a cause of QTd. Projections of the T- vector onto the scalar ECG-leads result in different QT-durations and can thus generate QTd (153-155, 157, 158). A significant part of QTd can be explained by the measurement error of QT in different leads (in its turn related to the T-wave amplitude in the measured lead) (123).
T<sub>peak</sub> and the T<sub>peak</sub>-T<sub>end</sub> interval

While the T<sub>end</sub> represents the end of measurable repolarization potential differences, the T<sub>peak</sub> occurs at moment with maximal potential differences during phase 3 of the repolarization (159). The T<sub>peak</sub>-T<sub>end</sub> interval may thus be a rough estimate of the maximum dispersion of repolarization (83, 159). Practically, in most cases, T<sub>peak</sub> is easier to identify than T<sub>end</sub>. The QT<sub>peak</sub> interval correlates strongly to QT measured conventionally between Q onset and T<sub>end</sub> (122, 159). The correlation between dispersion of the QT<sub>peak</sub> interval and conventional QTd is however weak (122). A large limitation in using T<sub>peak</sub> as a repolarization parameter is due to biphasic T-waves, that create a dramatic shift in the localization of T<sub>peak</sub>.

The concept of transmural repolarization inhomogeneity

Ventricular myocardium is composed of cells with different properties. The M-cells, present in the deep myocardial layers, have electrophysiological properties similar to Purkinje cells and make up about 40% of the left ventricular free wall of the canine heart. The M-cells exhibit a more prominent prolongation of action potential duration at slow heart rates than the epicardial and endocardial cells (14, 160). A transmural repolarization inhomogeneity during slow heart rate has been confirmed in measurements of ARI from the ventricular wall in animal experiments (58).

According to Antzelevitch et al, the epicardial repolarization is completed at the peak of the T-wave (55, 147). The endocardial repolarization corresponds to the descending limb of the T-wave. The M-region repolarizes at last and full repolarization corresponds to the end of T-wave. The T<sub>peak</sub>-T<sub>end</sub> interval (measured in precordial leads only) is supposed to be related to the transmural dispersion of repolarization (73, 161). Conflicting opinions however exist with respect to this proposition.

The T<sub>peak</sub>-T<sub>end</sub> interval (measured in Holter recordings) is increased in patients with LQTS (162) and patients with ischemic heart disease and ventricular arrhythmia (163). The T<sub>peak</sub>-T<sub>end</sub> interval, measured in magnetocardiogram from 33 positions, was significantly prolonged in patients with dilated cardiomyopathy (DCMP) and history of ventricular arrhythmia, compared to DCMP-patients without arrhythmia (164). The magnetocardiographically measured QTd did not differ between the groups. The same technique, applied to post myocardial infarction patients, showed a greater T<sub>peak</sub>-T<sub>end</sub> interval in a group with ventricular tachycardia (VT) (165). The study compared MCG fQRS (a magnetocardiographical measure of intraventricular conduction disturbance, analogous to a finding of late potentials in signal averaged ECG), to the magnetocardiographically measured T<sub>peak</sub>-T<sub>end</sub> interval. Interestingly, the T<sub>peak</sub>-T<sub>end</sub> interval was only
correlated to MCG fQRS in the patients without VT. A possible interpretation of the findings is that the repolarization inhomogeneity in these patients without arrhythmia is related to the activation sequence, while the inhomogeneity in the patients with VT might be related to the local repolarization duration. These two groups should thus exhibit different QRST-area maps. See pages 24 and 35.

Doubts have, however, been expressed regarding the relation of the Tpeak-Tend interval to repolarization inhomogeneity. The Tpeak-Tend interval (measured in Holter recordings) in patients with a history of myocardial infarction and taking amiodarone was longer than in similar patients on placebo (166). The victims of arrhythmic death in the placebo group had a longer Tpeak-Tend interval than the survivors. In the amiodarone group, the Tpeak-Tend interval duration did not differ between the victims of arrhythmic death and the survivors. The authors conclude that if the Tpeak-Tend interval reflects transmural repolarization inhomogeneity then the latter is increased by amiodarone, which they question. The Tpeak-Tend interval did not predict mortality in the study on survivors of myocardial infarction by Zabel et al (104), see page 28. The transmural dispersion in itself may be greater in experimental settings than clinically (56), where it can be counterbalanced by electrotonic influences. In an operative setting, Taggart et al could not confirm the existence of a transmural dispersion of repolarization by direct measurements of unipolar activation recovery intervals (see page 22) at various depths of the myocardium during pacing in patients undergoing CABG (60).

Aspects on the T-wave morphology

Merri et al performed a descriptive study of 11 variables describing various aspects of the T-wave morphology in normal subjects. After a principal component analysis (see pages 20 and 73), seven of the variables were selected as mutually relatively independent and expressing the major part of the information (167). Among those was the Tpeak-Tend interval, Send-Tpeak interval, T-area, symmetry ratio (the ratio of the initial to the terminal T-wave area, i.e. area during T onset-Tpeak / area during Tpeak-Tend interval) and standard deviation of Send-Tpeak interval in precordial leads (inhomogeneity of early repolarization duration). In the analysis, the QT interval did not remain as independent descriptor among the more specific investigated parameters. Neither QTd, nor any variable describing the T-dipole were among the analyzed variables. In a population-based study, Kors et al showed that a simple classification of the T-vector carries a prognostic information with respect to cardiovascular mortality (168). In a model experiment by di Bernardo and Murray, an increased dispersion of repolarization was associated with a symmetrical T-wave and the symmetry ratio was interpreted as an expression for the dispersion (66, 169).
T-wave alternans

Visible alternations in T-wave amplitude every other heart beat can occasionally be observed in the ECG. The rare phenomenon has for a long time been known to be associated with arrhythmias and high long term mortality. More recently, a microvolt-level T-wave alternans, not visible on plain inspection of the ECG, has attracted considerable interest. In brief, the parameter is quantified by a frequency analysis of multiple series of voltage measurements. The series are derived from a sequence of consecutive ECG-complexes and each series consists of samples from a fixed instant within the T-wave. After subsequent processing by fast Fourier transform, the peak at 0.5 cycles/heart beat in the frequency spectrum will quantify the alternations in the signal that occur every other beat. T-wave alternans is caused by alternations of repolarization at the level of the single cell, presumably associated with intracellular calcium regulation. Clinically, the measurements are obtained at increased heart rate during a low-level exercise test and a T-wave alternans that appears at rates below 110 bpm is considered significant. The parameter has been shown to contain prognostic information (170, 171). In a prospective trial it however failed to predict subsequent mortality (172).

The ventricular gradient and the QRST-area

The QRST-area in a lead is considered to reflect the local repolarization of the underlying myocardium (as opposed to the activation sequence). This interpretation is based on the concept of ventricular gradient introduced by Wilson (173), according to following reasoning: If the entire ventricular muscle was excited simultaneously, then the area of QRS would be zero. The signal would not be influenced by any activation sequence and the T-area would be determined by the repolarization sequence. (The sum of QRS and T-area would thus in this hypothetical case equal the T-area.) Wilson then assumed, that the sum of QRS- and T-area represents the repolarization sequence also in the real case with an activation sequence present and QRS-area greater than zero (34, 70). The ventricular gradient is formally expressed as a vector, composed of the QRST-areas in three orthogonal leads (174).

The concept of ventricular gradient forms the basis of the T-wave model of Harumi (175), with its hypothesis that the QRS- and T-wave areas would be equal and of opposite direction, if all the action potentials had the same form and duration. Since the action potentials are of nonuniform duration, the T-area is not equal to the QRS-area, i.e. a gradient exists. Under the above assumptions, the QRST-area should be independent of the activation sequence (176) and the concept opened a possibility to separate the activation
sequence from the local repolarization. Absolute independence could however not be shown experimentally (177), which seemingly flawed the concept. It has later been shown that the activation sequence influences local repolarization duration by electrotonus (see page 24).

Ventricular gradient has been applied in studies of body surface distributions of QRST-areas, where the QRS-, T- and QRST-areas are assumed to represent the ventricular activation sequence, repolarization sequence and pattern of local repolarization. The QRST-area in a site is strongly related to the refractoriness in the same site (176) (the latter being a measure of repolarization duration, see page 23). No relation was found between QRST-area and the refractoriness for different sites; sites with same refractoriness could have very different QRST-areas. Localized changes in refractoriness by warming changed the QRST-area, in contrast to global changes induced by changing the pacing cycle length (177). These findings imply that, rather than reflecting the repolarization duration itself, the QRST-area in a lead is a measure of differences in repolarization duration (between the sampled site and more distant locations).

Nondipolar content of the QRST-area map
The QRST-area map is normally dipolar. Nondipolarities have been described in subjects with history of coronary artery disease and ventricular arrhythmias (34, 43).

QRST-area maps can be analyzed by a statistical approach where the QRST-areas from multiple patients are processed with PCA. The nondipolarity detected in a single patient by this method will be a descriptive entity dependent on the patient set (34). It does not have the same physiological interpretation as the nondipolarity detected in a sequence of ECG- or BSM-recordings (see page 18 and papers III, IV) or in a single QRST-area map. The QRST-area nondipolarity derived with reference to an entire set of patients however shows an association to the nondipolarity in a single QRST-area map (156).

TCRT
TCRT (total cosine between R and T) is a quantification of the difference between the directions of the propagations of depolarization and repolarization wavefronts. The variable expresses similar properties of the repolarization as the ventricular gradient. It is computed as the cosine of the three-dimensional angle between depolarization and repolarization vectors (the long-axes of the QRS- and T-loops that have been reconstructed from the three virtual orthogonal leads obtained by singular value decomposition of the ECG-signal). A large angle between the two vectors corresponds to a low (or negative) TCRT value (174). With increased heart rate, TCRT decreases towards zero, implying an increased angle between depolarization and repolarization wavefronts (178). In healthy subjects, TCRT is significantly higher
in women than in men (0.63 vs. 0.29). A morning peak is seen in TCRT and
the authors draw an analogy to the well-known morning peak in cardiovas-
cular and arrhythmic events (179). A low TCRT-value is associated with
increased mortality in groups with cardiovascular disease (180) and follow-
ing a myocardial infarction (181, 182).

PCA-analysis of the T-wave
For a short general description of PCA see pages 20 and 73. In the PCA of
the T-wave of the 12-lead ECG, the parameters are computed from the eight
independent leads over the entire duration of the T-wave. They do not con-
vey any time-domain related information and they are insensitive to errors in
localization of any critical instant during the repolarization. The principal
components can be said to express the complexity of the T-wave in the
sense, that a larger number of principal components is needed for an ade-
quate description of a more complex T-wave.

The dipolar components of the T-wave
The three largest components S₁, S₂, S₃ and the corresponding (orthogonal)
eigenvectors match the three-dimensional space. If the T-wave in the 12-lead
ECG would be completely explained by a single T-vector (a global dipole)
that changes amplitude and direction in the three-dimensional space (thereby
depicting the T-loop of the vectorcardiogram), then the three largest (dipolar)
principal components would contain all the information in the T-wave
and the (nondipolar) principal components S₄ to S₈ would all be zero.
The components S₁ and S₂ can be seen as measures of the length and the
width of the T-loop. The S₂/S₁ ratio is an expression for the relation of the
width to the length of the T-vector loop, the “fatness” of the T-loop (13, 130,
153). The term S₂/S₁ ratio will be used for this entity throughout this work.
The ratio has also been named “complexity ratio” (98), PCA-ratio (183,
184), PCA₂ (185), eigenvalue ratio E₂/E₁ (152), TWC (186). It has been de-
scribed as an expression for the ”complexity of the repolarization”. The
name “complexity ratio” has also been used for the slightly different ratio
(181):

\[
\frac{S_2}{\sqrt{S_1^2 + S_2^2 + \ldots + S_8^2}}
\]

This expression would result in marginally smaller values than the S₂/S₁
ratio in the same patients. Another group used the parameter Teigenv (113,
187) (quotient between the largest and the second largest eigenvalue obtained from PCA of the T-wave, i.e. inverse of the $S_2/S_1$ ratio).

Clinical studies related to the dipolar components of the T-wave

Al Abdulla et al showed that the T-loop is rounder in subjects with ischemic heart disease than in normals (11). A widening of the T-loop during exercise in patients with ischemic heart disease was shown to be associated with adverse prognosis (188). In an early work using PCA, Draper et al computed the $S_2/S_1$ ratio for the T-loop in normal subjects without conduction disturbance to $0.17 \pm 0.13$ (13). Increased roundness of the T-loop has been observed in patients with LQTS and patients with a history of myocardial infarction (189) and during PCI-induced ischemia (113). In LQTS, the $S_2/S_1$ ratio, measured as mean of hourly recordings during 24 hours, as well as one value (the first) is increased in comparison to normal subjects (34% vs. 13% and 30% vs. 12%) (98).

In a comparison between patients with arrhythmogenic right ventricular dysplasia and healthy subjects, De Ambroggi et al (190) evaluated QRST-area maps (see page 35) and also analyzed the consecutively sampled ST-T interval with PCA (see pages 20 and 73). The nine patients with a history of ventricular tachycardia exhibited a low value of $S_1$ in relation to the total information (64% vs. 80%). This corresponds to a relatively greater proportion of information in $S_2$ and thus increased $S_2/S_1$ ratio (30% vs. 16%, as computed here post hoc from the published data). The authors also provided strong indirect information that the nondipolar components were increased in the patients with a history of ventricular tachycardia: The first 3 principal components represented markedly less of the total power in the signal (see page 73) in the patients with a history of ventricular tachycardia than in the normal controls and in the patients without previous arrhythmia (90% vs. 97%).

In an evaluation of PCA variables by Yi et al (using the QT-Guard software, GE Medical Systems, Information Technologies), the mean $S_2/S_1$ ratio in patients with hypertrophic obstructive cardiomyopathy was significantly higher than in normal subjects (24% vs. 16%) (183). $S_2/S_1$ ratio was higher in the patients with a history of syncope (29% vs. 22%). No significant increase was found in the patients with nonsustained VT on Holter or in the 6 patients with a history of ventricular fibrillation. The $S_2/S_1$ ratio did not correlate to the maximum thickness of the left ventricular wall, as measured by echocardiography.

Okin et al (184) studied the $S_2/S_1$ ratio (computed by the QT-Guard software) as a predictor of cardiovascular mortality in a population-based study of American Indians. The $S_2/S_1$ ratio was a significant predictor of cardiovascular mortality both univariately and in a multivariate model.
In a population of consecutive post-myocardial infarction patients studied by Zabel et al (181), the complexity ratio (see page 37) did not differ significantly between the groups with and without arrhythmic event.

The nondipolar components of the T-wave

Nontrivial assumptions are underlying the approximation of the myocardial electrical field by a single dipole (see page 15). Their validity in the case of T-wave can be examined by PCA. The T-wave cannot be adequately represented by a single global dipole if the principal components of higher order than S3 (the nondipolar components) contain any information, i.e. are needed for explaining a part of the power of the T-wave (for formal definition of power see page 73). It shows that the nondipolar components normally constitute just a small fraction of the total T-wave power (see page 40).

BSM

Tsunakawa et al investigated the dipolarity in isopotential maps from BSM of entire QRS and ST-T intervals (see also page 18) in normal subjects (42). The nondipolar content was computed as a residue not represented by a single dipole. The nondipolar content during QRS showed two peaks, at the beginning and end of the QRS. The dipole of the T-wave was almost fixed (in contrast to that of the QRS). The residue during repolarization was stable and lower than during QRS. In the normal population, the repolarization process thus appears to be dipolar to a higher degree than depolarization. Other studies in normal subjects and in experimental settings in isolated, perfused rabbit hearts also indicate that the T-wave can be to a very high degree described by a single dipole (43, 191). The data from BSM in subjects with old myocardial infarction, however, showed nondipolarity in the T-wave (43). When repolarization is manipulated by premature stimuli and d-sotalol in a Langendorff preparation of rabbit heart, the level of the nondipolar content in (the second half of) the T-wave shows a moderate correlation to the Tpeak-Tend interval (see page 33) (67).

12-lead ECG

The nondipolar components have been assumed to reflect a local repolarization inhomogeneity (181). The power contained in the nondipolar components of the T-wave in the 12-lead ECG can be quantified by the absolute and relative T-wave residue (TWR) (15, 180, 181).
Absolute TWR is computed as the sum of the squares of the principal components S₄ to S₈:

\[ TWR_{abs} = S_4^2 + S_5^2 + \ldots + S_8^2 \]

It can be viewed as a quantification of the error that arises from the dipolar approximation of the T-wave. The relative TWR is defined as the ratio of the absolute TWR to the total power of the T-wave:

\[ TWR_{rel} = \frac{TWR_{abs}}{S_1^2 + S_2^2 + S_3^2 + \ldots + S_8^2} \]

A similar variable that mirrors the size of the nondipolar components is nondipolar voltage, computed as the square root of the sum of the principal components S₄ to S₈ (152):

\[ NDPV = \sqrt{S_4 + S_5 + \ldots + S_8} \]

Clinical studies of nondipolar components
The nondipolar components of the T-wave in 12-lead ECG have been investigated in a few studies.
In a study, designed primarily to explore the mechanism generating QTd, Malik et al (15) obtained 10 ECG recordings/subject in patients with hypertrophic obstructive cardiomyopathy, patients with dilated cardiomyopathy, survivors of acute myocardial infarction and normal controls. The principal components S₁ to S₈ were computed and the absolute and relative TWR determined. The authors remarked that the T-wave of the ECG contained less nondipolar signal than the QRS-complex, an observation in line with earlier experience from BSM, mentioned above (42). The relative TWR differed significantly between the groups, ranging from the lowest value of approximately 0.03% in the controls to the highest value of approximately 0.18% in the survivors of acute myocardial infarction and the cardiomyopathies in an intermediate position. The QT-Guard software was used for automatic determination of QTd. The correlation coefficients between QTd and the relative TWR were between 0.22-0.30 (see also page 32). Of concern was the fact that the calculations of TWR were based on signals of low magnitude. The authors addressed the issue of measurement stability by computing the coefficient of variance (CV) from repeated recordings in a single patient. The mean CV was 28%, 24%, 30% and 35% in the normal subjects, hyper-
trophic cardiomyopathies, dilated cardiomyopathies and acute myocardial infarctions, respectively.

Zabel et al (180) investigated the PCA-derived parameters (and TCRT, see page 36) as markers for total mortality in a retrospectively assembled cohort of 813 men with cardiovascular disease and a follow-up time of 10 years. The mean absolute and relative TWR and the mean S₂/S₁ ratio were significantly higher in the 252 patients that subsequently died than in the survivors (112 000 vs. 86 000, 0.43% vs. 0.33% and 25% vs. 23%, respectively). Values in the upper median in all three variables indicated a significantly increased mortality risk. Cox regression in a multivariate model showed that either the relative or the absolute TWR, dichotomized by the median, remained as risk factors independent of age, ejection fraction and presence of left ventricular hypertrophy, with adjusted risk ratios 1.37 and 1.47. The S₂/S₁ ratio and the other repolarization parameters were not independent risk factors in the model.

In two studies, that also investigated TCRT (see page 36), Smetana et al (178, 179) described a morning peak in relative TWR and an association between an increase in relative TWR and increased heart rate.

In a study on subjects recruited from an ECG-database, Rautaharju (152) compared the S₂/S₁ ratio and nondipolar voltage to QTd, computed automatically by the QT-Guard software. In a group with clinical evidence of coronary heart disease, QTd, S₂/S₁ ratio and nondipolar voltage were significantly greater than in the other subjects (40 vs. 33 ms, 19 vs. 14% and 12 vs. 11 uV). The author found a low correlation between the two PCA-derived variables and QTd (r=0.25 and 0.27 respectively).
Aims of the present work

The present work was undertaken with following aims:

- To examine the prognostic information in QTd measured automatically in a large number of ECG-recordings and compare it to QTd obtained from a single ECG-recording.
- To study the variation in QTd during the observation time.
- To examine if QTd in ischemic heart disease could be associated to the extent of the disease and if a QTd-related parameter that could be localized to a specific region would have a relation to the regional coronary pathology. This should be the case, if QTd were generated by local differences between various regions of the myocardium.
- To study whether the nondipolar components are increased in patients with conduction disturbance. This should be the case, if the nondipolar components of the T-wave were associated with repolarization inhomogeneity and if the latter were increased in conduction disturbances.
- To quantify the changes in the nondipolar components of the T-wave during initial course of a ST-elevation myocardial infarction and relate them to the evolution of the ST-elevation.
Subjects and methods

Populations

The population A consisted of patients admitted to the coronary care unit at the Akademiska hospital, Uppsala for chest pain, with an ECG nondiagnostic of acute myocardial infarction (the FAST study) (192). The discharge diagnosis, according to the ICD-10 code, was used for subsequent classification of the index event into acute myocardial infarction, angina pectoris or other types of ischemic heart disease and other diagnoses.

Figure 2. Population A. AF=atrial fibrillation
Patients eligible for FRISC II study
n=3489
FRISC II study
(invasive vs. noninvasive treatment)
n=2457
58 centers

Patients with continuous recording of 12-lead ECG
n=318
7 centers

**B**
*In paper II*
Sinus, no conduction disturbance, continuous ECG-registration with satisfactory ECG recordings (QTd)
n=276
Invasive strategy n=106
Noninvasive strategy n=170

**B (sub)**
Coronary angiogram
n=174
Invasive strategy n=106
Noninvasive strategy+clinical indication n=68

Figure 3. Population B.

The population B consisted of patients in Scandinavian multicenter FRISC-II trial (193), monitored by continuous 12-lead ECG.

The population C was recruited from the two multicenter trials on thrombolytic agents, ASSENT-2 (194) and ASSENT-PLUS (195). The population consisted of a subgroup from these trials, which was monitored by continuous 12-lead ECG.

For summary see also table I, page 46.
ECG-recordings

In all three populations, the 12-lead ECG-recordings were collected continuously during the initial hours of observation after admission to the coronary care unit. Sampling of the ECG signal started immediately after admission. Each minute, signals from the 12 conventional scalar ECG-leads were collected for a length of ten seconds at 240 samples per second by a commercial system (ST-Guard system, GE Medical Information Technology, Milwau-kee, Wisconsin). The signal was digitized by a 16 bit A/D converter. Within the ten-second window, the ECG-complexes with dominating morphology were chosen by a template matching method that compared the incoming beat with the most frequent beat and rejected the former when the difference was larger than 10% of the template. A median ECG-complex was subsequently computed for each lead.
<table>
<thead>
<tr>
<th>Population In paper</th>
<th>Nr of patients</th>
<th>Age (years) (range)</th>
<th>Male (%)</th>
<th>DM (%)</th>
<th>HT (%)</th>
<th>Prev AMI (%)</th>
<th>Nr of ECG-recordings (range)</th>
<th>Monitoring time (h) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A III</td>
<td>800</td>
<td>70 (58-77)</td>
<td>59</td>
<td>17</td>
<td>40</td>
<td>34</td>
<td>955 (622-1258)</td>
<td>17 (12-23)</td>
</tr>
<tr>
<td>A (sub) I</td>
<td>548</td>
<td>67 (55-76)</td>
<td>58</td>
<td>16</td>
<td>37</td>
<td>28</td>
<td>985 (682-1258)</td>
<td>17 (12-23)</td>
</tr>
<tr>
<td>A (sub2) IV</td>
<td>127</td>
<td>57 (49-68)</td>
<td>67</td>
<td>12</td>
<td>28</td>
<td>15</td>
<td>708 (460-961)</td>
<td>12 (8-18)</td>
</tr>
<tr>
<td>FAST with clinical data</td>
<td>893</td>
<td>70 (58-78)</td>
<td>60</td>
<td>18</td>
<td>40</td>
<td>34</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B II</td>
<td>276</td>
<td>66 (59-73)</td>
<td>72</td>
<td>14</td>
<td>32</td>
<td>26</td>
<td>1514 (1294-1980)</td>
<td>27 (23-36)</td>
</tr>
<tr>
<td>B (sub) II</td>
<td>174</td>
<td>64 (58-71)</td>
<td>70</td>
<td>15</td>
<td>36</td>
<td>24</td>
<td>1512 (1293-2038)</td>
<td>27 (23-37)</td>
</tr>
<tr>
<td>FRISC-II Scandinavia</td>
<td>2457</td>
<td>66 (58-72)</td>
<td>70</td>
<td>12</td>
<td>30</td>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C IV</td>
<td>211</td>
<td>68 (59-74)</td>
<td>71</td>
<td>12</td>
<td>35</td>
<td>19</td>
<td>1681 (1413-2291)</td>
<td>29 (25-41)</td>
</tr>
<tr>
<td>C (sub) IV</td>
<td>177</td>
<td>68 (59-74)</td>
<td>71</td>
<td>12</td>
<td>36</td>
<td>19</td>
<td>1743 (1452-2353)</td>
<td>30 (25-41)</td>
</tr>
<tr>
<td>ASSENT-2</td>
<td>16949</td>
<td>61 (52-70)</td>
<td>77</td>
<td>16</td>
<td>38</td>
<td>16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ASSENT-PLUS</td>
<td>439</td>
<td>64 (56-74)</td>
<td>70</td>
<td>12</td>
<td>32</td>
<td>14</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table I. The characteristics of the populations targeted in the present work and their originating study populations. DM = diabetes mellitus; HT = hypertension; AMI = acute myocardial infarction; h = hours.
Parameters derived from the ECG

The QTd-measurements (papers I, II, III) were performed with commercial software using an algorithm that has been acceptably validated (QT-Guard, GE Medical Systems, Information Technologies, Milwaukee, Wisconsin, U.S.A.) (131). The program excluded ECG-leads with noisy signal, very low T-wave amplitude or undetermined T-wave shape from the QTd computation and reported the number of valid leads. The principal component analysis (papers III, IV) was done with QT-Guard 1.3, custom modified by its author (J Xue, GE Medical Information Technology, co-author of papers III and IV).

Computation of secondary parameters that summarize the QTd and the variables from PCA in each patient was done by custom software developed in Pascal (Delphi 3, Borland Software Corporation, Scotts Valley, California, U.S.A.) by the author of this thesis. The calculations of PCA-derived parameters used all available ECG-recordings in each patient. In the computation of QTd-derived parameters, only ECG-recordings with ≥10 valid leads were used.

Statistics

Secondary parameters summarizing the ECG-recordings in each patient

QTd in each patient was described by the arithmetic mean of the measurements from the ECG-recordings with ≥10 valid leads (papers I, II and III). The PCA-derived parameters (S₂/S₁ ratio, absolute TWR and relative TWR) were described by medians of the measurements from all ECG-recordings in each patient (papers III and IV). Variability of the primary PCA-parameters in a patient was quantified by the coefficient of quartile variation (CQV, %) (196, 197):

$$CQV = 100 \times \frac{(Q_3 - Q_1)}{(Q_3 + Q_1)}$$

Groupwise descriptions of secondary parameters

Rank based methods were used. The central tendency and the spread were described by the median and the interquartile range. Differences between materials were tested with nonparametric methods (two-tailed Mann-Whitney and Kruskal-Wallis tests). χ²-test and Fisher exact test were used for testing differences in proportions. Spearman ρ was computed for correlation between continuous variables. Kappa statistics was used for estimating agreement between categories (paper II). The agreement is expressed by κ, with values ranging from +1 (perfect agreement) via 0 (no agreement above that expected by chance) to -1 (complete disagreement). For follow-up, Kaplan-Meier curves were constructed and differences between dichotomized groups were evaluated by log rank test. Cox regression analysis was used for
calculation of adjusted relative risk ratios (paper I). Prognostic content in a variable was assessed by constructing a ROC-curve (198) and computing area under curve (papers I and III).

**Repeatability**

Repeatability of the primary PCA-parameters (papers III and IV) was assessed by splitting of each patient’s array of parameter values into two mutually interposed arrays that consist of all odd and all even samples from the original array. The absolute error in each pair of samples (A, B) from the two arrays was calculated as the absolute value of their difference \(|A-B|\). The relative error was subsequently calculated as absolute error/mean value of the pair, \((A-B)/(A+B)/2\). For each patient, the median of the relative error was calculated.

**Changes in the PCA-parameters**

The data were analyzed for changes during the first 24 hours of the monitoring time (paper IV). The primary data sequence was filtered for extreme outliers. These were defined as values outside Tukey’s outer fences, computed from the quartiles as \(Q_3 - 3*(Q_3 - Q_1)\) and \(Q_3 + 3*(Q_3 - Q_1)\) (199). The outliers were replaced by the running median of 20 previous values. This filtered primary data sequence was used for computation of median values of absolute TWR and relative TWR for each recorded hour. The filtered primary sequence was subsequently processed to a median averaged sequence, where each point of the latter was computed as the running median of 20 previous values in the former. This median averaged sequence was divided into an early and late time window, 0-10 respectively 11-24 hours after start of the ECG-monitoring. In each time window, the dominant change (positive or negative) could be localized by a procedure using cumulative sums (CUSUM, see Appendix A, page 73).

Commonly, CUSUM is used in quality control monitoring of real-time processes. In such an application, the design has to take into account the problem of false detections (identified retrospectively). Presence of a change in the series, important enough to be detected, is defined in the CUSUM-computation from a threshold, based on the mean and standard deviation of the series. In the present off-line analysis, the entire data series was available at the time of evaluation. The consideration regarding false real-time detections was of no importance. Therefore, the threshold was chosen to be very small, resulting in detection and localization of a change in virtually every data sequence. In a second step, the size of the dominant change and thus the relevance of the detected changepoint was estimated by computing a relative difference in the medians before and after the detected changepoint as

\[
\frac{\text{median value during 60 minutes after changepoint} - \text{median value during 60 minutes before changepoint}}{\text{median value during 60 minutes before changepoint}}
\]
**QT-dispersion (papers I, II)**

**Paper I** investigated the prognostic information of automatically measured QTd in a large number of 12-lead ECG-recordings from each patient. The approach with repeated sampling and computerized measurement of QTd aimed at reducing the influence of measurement error. Furthermore, in repeated measurements the geometrical factors determining QTd (the size and shape of the myocardial source and the torso) would remain constant. The influence of repolarization on QTd can on the other hand be assumed to vary. In addition to the central measure (QTdMean), the variations in QTd were therefore quantified by several different approaches.

From the population A, 548 patients in sinus rhythm without bundle branch block were selected. The sampling started in median 5.6 h after the onset of symptoms. The median number of ECG-recordings was 985 per patient. The yield of satisfactory recordings, defined as the median ratio of recordings with ≥10 valid leads out of total number of recordings in each patient, was 0.65. In median 435 recordings per patient were satisfactory. The mean number of valid leads in the satisfactory recordings was 10.6 (this result is presented here only).

In each patient, QTd was quantified as the mean value of automatically measured QTd (QTdMean), computed from the satisfactory ECG recordings (with ≥10 valid leads) during the observation time. QTdMean was analyzed as a marker for outcome during follow-up. The variations of the QTd were expressed by the standard deviation, the 90th and 99th percentile of QTd in all satisfactory ECG recordings during the registration time, the qQTd-ratio (based on a cut-off value of 80 ms, with shown prognostic impact (80)):

\[
qQTd = \frac{\text{Number of recordings with } QTd > 80 \text{ ms}}{\text{Number of satisfactory recordings}}
\]

the root of mean of squared successive differences computed for m pairs of QTd-measurements:

\[
RMSSD_{QTd} = \sqrt{\frac{1}{m} \sum_{n=1}^{m} (QTdn+1 - QTdn)^2}
\]

and the Pearson correlation coefficient for the Poincaré plot of successive QTd measurements (QTd\(_{n+1}\) vs. QTd\(_n\)).
Paper II explored a possible anatomical aspect of QTd in a well-defined population with unstable coronary artery disease (population B). The 276 patients were in sinus rhythm, included at seven centers with facilities for continuous recording of 12-lead ECG. QTd and a localized ECG-parameter (QTdiff, computed by a method similar to previously published approaches (108, 200)) were compared to angiographical measures of coronary artery disease in an attempt to directly associate QTd with an anatomical substrate and possibly identify a local difference in QT.

In median, 1514 ECG recordings were recorded during a median observation time of 27 hours in each patient. The yield of satisfactory recordings (defined as the median ratio of recordings with ≥10 valid leads out of total number of recordings in each patient) was 0.59 (this result is presented here only). In median, 824 of the recordings were satisfactory. In each satisfactory ECG-recording, QTdiff was computed as the maximal difference in QT between two adjacent ECG-leads (the precordial leads and the extremity leads, ordered in Cabrera sequence). QTdiff was localized to one of three electrocardiographic regions: anterior when the maximal difference was found in V1-V2, V2-V3, V3-V4 or I-avR; lateral (V4-V5, V5-V6 or avL-I) and inferior (avR-II, II-avF or avF-III). In each patient, QTdiffMean was computed as the mean value of QTdiff and the most common regional localization of QTdiff was taken as the localization of QTdiffMean. QTdMean was computed for each patient as above (paper I).
In 174 of the patients, a prospectively analyzed coronary angiography was available. The classification was based on a subdivision of the coronary artery tree into 15 segments and five degrees of stenotic changes in each segment. In the present work, the severity and localization of the coronary pathology was quantified from this classification by two scoring approaches, adapted from previously published tools: A CASS-score (201), equaling the number of central coronary vessels (LAD, LCX, RCA) with stenoses of >70% and a hemodynamically weighted score (HW-score), constructed for the current purpose by multiplying the hemodynamical weight in each segment with a stenosis coefficient.

Each of the scores was computed regionally for the anterior (LAD-), lateral (LCX-) and inferior (RCA-) region and summarized to a global score for the patient. Possible ranges for the CASS-score and the HW-score were 0-3 and 0-82, respectively. The region with the highest score was considered as the region of dominating coronary pathology.

Figure 6. Example of computation of QTd and QTdiff. From paper II.
The prognostic value of a CASS score is well established (202). The here described HW-score merits further consideration. It summarizes the degrees of stenosis and the hemodynamical importance of the stenosed vessels: For each of the 15 segments (203), the degree of stenosis (0-4, modified after Sullivan (204)), is multiplied by the hemodynamic weight of the affected vessel (0.5-5, modified after Gensini (205)). Among the 174 patients with angiography, four patients died and 29 patients encountered a combined endpoint of death or acute myocardial infarction within 1 year. The median HW-score was 14 in the 170 survivors and 29 in the four dead, (p=0.03, Mann-Whitney). Similarly, the median HW-score was 12 in the 145 patients with eventfree survival at one year and 26 in the 29 patients that encountered the combined endpoint, p=0.008 (these results are presented here only).

In the regional analysis, the electrocardiographic region of QTdiffMean and the region of dominating coronary pathology (computed by the two approaches above) were tested for agreement in individual patients. In the global analysis, QTdMean was compared to the severity of the coronary
pathology measured by the two global scores and to the QTdMean in a population with chest pain and nondiagnostic ECG on admission (population A).

Principal component analysis of the T-wave (papers III, IV)

Conduction disturbances primarily result in regional differences in activation time. They presumably also cause inhomogeneous repolarization and may thus create an arrhythmogenic substrate. The T-wave parameters derived from PCA (see pages 20 and 73) are more robust and relevant measures of repolarization inhomogeneity than QTd. They can be used for description of the entire T-wave and quantification of the information that is not expressed by a dipolar source model (see page 15).

In paper III, the PCA-parameters of the T-wave ($S_2/S_1$ ratio, TWRabs and TWRrel) in patients with various conduction disturbances were studied in a single-center material of 800 patients with chest pain and nondiagnostic ECG on admission (population A). The admission 12-lead ECG recordings were manually interpreted according to a prespecified protocol. The 135 patients with conduction disturbances were classified into groups with left anterior hemiblock (LAH, 43 patients), left bundle branch block (LBBB, 59 patients) and right bundle branch block (RBBB) with or without LAH (6 and 27 patients, respectively). The 665 patients without conduction abnormalities were divided into three mutually exclusive comparison groups; those with normal QRST-morphology (286 patients), those with ST-T changes (343 patients) and those with pathological Q-waves or R-wave progression (36 patients).

In median 955 ECG-recordings were obtained for each patient during a median observation time of 17 hours. In each ECG-recording, the nondipolar content was quantified by TWRabs (the absolute TWR, the residue that summarizes the eigenvalues $S_4$ to $S_8$) and TWRrel (the relative TWR, the ratio of this residue to the total power of the T-wave). See page 39. In addition, the $S_2/S_1$ ratio was computed (the ratio of the two largest eigenvalues, a dipolar measure expressing the relation of the width to the length of the T-vector loop, see page 37). The QTd and the number of leads excluded from the QTd-computation were automatically computed by the same procedure as described above.

For each patient, the median values during the observation time $S_2/S_1$, TWRabsMedian and TWRrelMedian were derived from all ECG-recordings. From the ECG-recordings with $\geq 10$ leads valid for QTd-computation, QTdMean was computed as above (paper I). These parameters were subsequently used in comparisons between the four patient groups with
conduction disturbances and the three groups without conduction abnormalities. In the patients with conduction disturbance, the relation between the $S_2/S_1$Median, TWRabsMedian, TWRrelMedian and QTdMean was studied. The prognostic value of the three PCA-parameters was evaluated with ROC-curves at 6, 24 and 35 months after inclusion.

In paper IV, the ECG-recordings from 211 patients with thrombolyzed acute myocardial infarction with ST-elevation (population C) were used to describe the changes in the nondipolar content of the T-wave, expressed by TWRabs and TWRrel. In median, 1681 ECG-recordings were collected during 29 hours. The proportion of filtered outliers was <5% in the computation of both TWRabs and TWRrel. The monitoring time was at least 10 hours in 93% and at least 24 hours in 72% of the cases. In 177 of the STEMI-patients, a core laboratory ECG-analysis with respect to the ST-segment resolution was available. Serial ECG-recordings were used to assess the time to 50% ST-segment resolution, compared to the maximal ST-elevation. The ST-elevation at 60 min after start of monitoring was classified as <50% ST-segment resolution or ≥50% ST-segment resolution. An attempt was made to relate this time to the time of the dominant changes in the filtered and median averaged sequences of TWRabs and TWRrel, localized by the CUSUM procedure (see Statistics, above and Appendix A, page 73). The results were compared to those in a group of 127 patients with chest pain and a normal ECG, monitored with continuous 12-lead ECG and subsequently discharged with diagnosis of unspecific chest pain (recruited from population A).
Results

Mean of QTd as a marker for cardiac events during follow-up (paper I)

The median QTdMean of the 548 patients (population A) was 40 ms. By 30 days, 11 (2%) patients had died and the triple endpoint (death, myocardial infarction or revascularization) was reached in 79 (14%) patients. During the continued follow-up time, 24 (4%) patients died and the triple endpoint was reached in 117 (21%) patients. The patients that died during follow-up had a significantly greater QTdMean than the survivors, 52 vs. 40 ms, p = 0.02. Among the patients reaching the triple endpoint during follow-up, the QTdMean was 49 ms, compared to 37 ms among patients with eventfree survival, p < 0.001.

The studied population was dichotomized with respect to QTdMean. In the group of 277 patients with QTdMean ≥ 40 ms, 10 patients died during the initial 30 days. One patient died among the 271 patients with QTdMean < 40 ms (p = 0.07). During continued follow-up (median 6 months), 19 and 5 deaths were observed in the same groups (p = 0.03). The figures for the triple endpoint death/myocardial infarction/revascularization were 52 vs. 27 events during the initial 30 days (p = 0.018) and 76 vs. 41 events during follow-up (p = 0.003). ROC-curves for QTdMean, constructed from total mortality and triple endpoint at 30 days, exhibited areas under curve of 0.706 and 0.625.

QTdMean dichotomized at 40 ms contributed significantly to the prediction of total mortality and triple endpoint in a multivariate model with clinical covariables (age, history of diabetes, previous myocardial infarction and previous clinical episode of cardiac insufficiency). QTdMean did not contribute to the prediction in a model with covariables retrieved from the admission ECG (heart rate, T-wave inversion and ST-segment depression ≥0.1 mV in any lead).
Figure 8. Kaplan-Meier curves for QTdMean, dichotomized at the median. Total mortality in upper panel, triple endpoint events in lower panel. From paper I.

Automatically computed QTd from only the first ECG-recording with ≥10 valid leads did not predict new cardiac events. No further prognostic information was found in the variations of the QTd, as expressed by the standard deviation, the 90th and 99th percentile of all valid QTd values during the registration time, the qQTd-ratio, the Pearson correlation coefficient for the Poincaré plot of QTd and the root of mean of squared successive differences computed for pairs of QTd-measurements.
QTd and its relation to coronary angiogram in unstable coronary artery disease (paper II)

In the 276 patients with unstable coronary artery disease (population B), QTdMean was in median 55 ms. The electrocardiographically localizable measure QTdiffMean correlated strongly with QTdMean (Spearman ρ = 0.93, p < 0.001) and accounted for three fourth of the latter (medians 42 and 55 ms, respectively). The most common localization of QTdiffMean was V1 - V2, being responsible for the maximal local difference of QT in 95 cases. The lead V1 was the most prevalent lead with the shortest QT-interval (the most common localization in 28% of the patients). The most prevalent lead with the longest QT-interval was V2 (the most common localization in 24% of the patients). (These results are presented here only.)

The QTdMean of the group (population B, 276 patients) was significantly greater than that of a group with unselected chest pain (548 patients from population A, see above), 55 vs. 40 ms (p < 0.001, Mann-Whitney for the comparison). The population B had a higher proportion of men; otherwise the two groups were comparable with respect to clinical variables (see table I, page 46). The mortality was 3% in the population B (complete follow-up at 1 year), compared to 4% in the group from population A (median follow-up 6 months).

In the 174 patients with coronary angiograms, no relation could be shown between the region with dominating coronary pathology as localized by the two regional angiographical scoring tools and the regional localization of QTdiffMean (absolute value of κ < 0.1, p = n.s.). No difference in QTdMean was detected between patients grouped according to their CASS-score. No correlation was shown between QTdMean and the global HW-score.

A subgroup analysis was done in 84 patients with major coronary pathology confined to one region (with CASS score 1) and in 68 patients with clinically aggressive coronary artery disease (patients initially randomized to the non-invasive strategy but undergoing coronary angiography due to clinical indication). No relation between the region with dominating coronary pathology and the regional localization of QTdiffMean could be shown for these two subgroups.

Nondipolar content of the T-wave is increased in conduction disturbance (paper III)

In the 800 patients with chest pain and nondiagnostic ECG (from population A), the median of TWRabsMedian was 19 000 uV. The medians of TWRrelMedian and S2/S1Median were 0.17% and 26%.
The 135 patients, pooled from the four groups with conduction disturbances had a higher TWRabsMedian than the 665 patients without conduction disturbances, 32 100 vs. 17 500 uV4 (p < 0.0005, Mann-Whitney). The corresponding comparisons for TWRrelMedian and S2/S1Median showed no significance (0.17 vs. 0.18% and 26 vs. 27% in patients with vs. without a conduction disturbance). Within the subpopulation with conduction disturbance, differences between the groups with various conduction pathologies were detected in both the dipolar parameter S2/S1Median and the nondipolar parameters TWRabsMedian and TWRrelMedian.

The nondipolar parameter TWRabsMedian increased successively in the groups with RBBB, LAH, LBBB and LAH & RBBB (compared to the group with normal QRST). The group with ST-T pathology exhibited a smaller elevation while the level in the group with pathological Q-waves or R-wave progression (QRS-pathology) was comparable to that of the normal QRST group.

Figure 9. TWRabsMedian in patients with conduction disturbances and the comparison groups. From paper III.

The dipolar parameter S2/S1Median was elevated in the groups with conduction disturbances, compared to the normal QRST group. No obvious relation between the type of conduction disturbance and S2/S1Median could be
observed. The highest values of this parameter were seen in the comparison group with ST-T pathology. In the 135 patients with conduction disturbances, S2/S1Median, TWRabsMedian and TWRrelMedian showed a modest correlation with QTdMean (Spearman $\rho = 0.56, 0.28$ and $0.40$). The patients with conduction disturbances had an increased long-term mortality. Of the tested variables only TWRabsMedian showed a borderline significance in discrimination between the 101 survivors and the 34 deceased patients after 24 months ($28 \text{ 600 vs. } 42 \text{ 100 uV}^4$, $p = 0.05$). TWRabsMedian contained a moderate amount of prognostic information at 6 and 24 months after the index event, with the ROC-curves exhibiting area under curve of 0.66 and 0.65, respectively. No information was found in the variable regarding prognosis after 35 months.

**Nondipolar content of the T-wave decreases in thrombolyzed STEMI (paper IV)**

In the 211 patients with STEMI (population C), TWRabsMedian (summarizing the entire monitoring period) was in median 25 000 uV$^4$, as opposed to 13 500 uV$^4$ in the 127 comparison cases, recruited from population A ($p < 0.0005$). The variability during the observation time, measured by CQV of the filtered primary dataset sequence was 36% in the STEMI-group vs. 30% in the comparison group ($p<0.0005$).

In STEMI, the hour median of TWRabs for hour 2 was significantly lower than that for hour 1 ($28 \text{ 800 vs. } 36 \text{ 500 uV}^4$, $p = 0.002$), as opposed to the comparison group ($12 \text{ 500 vs. } 13 \text{ 300 uV}^4$, $p = 0.12$).

In the STEMI-group with $\geq50\%$ ST-segment resolution at 60 minutes (indicating early tissue level reperfusion), the individual patients’ difference between hour medians of TWRabs for hour 2 – hour 1 was $-8 \text{ 000 uV}^4$, compared to $+700 \text{ uV}^4$ in the STEMI-group with $<50\%$ ST-segment resolution ($p = 0.001$).
The location of the changepoint by CUSUM showed no significant correlation to the time of 50% ST-resolution, neither in the entire STEMI-material (Spearman $\rho = 0.09, p = 0.27$), nor in the subgroup with $\geq 50\%$ ST-segment resolution at 60 minutes (Spearman $\rho = 0.039, p = 0.71$).
TWRrel increased during the initial hours of STEMI and remained at a higher level throughout the observation. The median of TWRrel in individual STEMI-patients showed a significantly greater increase from hour 1 to hour 2 than in the comparison group, +0.018% vs. +0.007% (p=0.009). No difference in the hour medians of TWRrel could be detected between STEMI with ≥50% and <50% ST-segment resolution. No relevant changes in TWRabs or TWRrel were detected in the late time window.

Figure 11. Medians of TWRrel for each recorded hour vs. time. From paper IV.
Discussion

**QT-dispersion**

Mean QTd during initial observation could be used for identification of patients at low risk during follow-up (paper I). The parameter was not successful in identifying the high-risk patients. The 548 patients described in paper I had a mixed etiology of the chest pain, with unstable coronary artery disease being the cause in 54% of the cases. In the latter 296 patients, the median QTdMean was 49 ms (31-67); it was 49 ms (30-63) in the 40 patients with other cardiovascular diagnoses and 30 ms (22-45) in the 212 patients with other diagnoses (this result is presented here only). Based on this comparison it may be suspected that the increase in QTd is not a direct result of the ischemia.

This observation is supported by the findings in the population with unstable coronary artery disease (paper II). If QTd would be caused by local repolarization differences between various regions of the myocardium, then a similar parameter that could be localized to a specific region should have a relation to regional coronary pathology. This hypothesis obviously presupposes a model, where the 12-lead ECG to a quantitatively significant degree directly is influenced by local potential differences, proximity potentials (see page 16), as opposed to the dipolar model where local potential differences only affect the ECG indirectly, by changing the global dipole (see pages 15 and 21). The possibility of proximity potentials is not in itself unreasonable, given the relatively large size of the heart. Early measurement in an isolated heart model under optimal conditions did report proximity potentials in unipolar leads with the electrode placed at the distance from the heart surface twice the diameter of the heart (Schaefer and Haas 1962, page 335) (24). It has been stated (originally by Taccardi), that only at a distance greater than five times the radius of the heart is the actual potential distribution similar to that explained by a single dipole (206). We were however unable to correlate QTd to the indices expressing the severity and localization of the coronary pathology (the CASS-score and the HW-score, see above).

The scores we used for the quantification of the coronary artery disease were computed from prospective evaluation by the angiographer but the vessels were assigned predefined weights from a model anatomy. This semi-static approach did not take into account the obvious individual variation in the
real anatomy and in individual cases the measures were certainly distorted. In a groupwise reasoning the approach can however be justified.

In our analysis of QTd (paper II), the leads V₁ and V₂ were the most prevalent leads with the shortest and longest QT-intervals, respectively. This finding is in agreement with other published materials (126, 152, 207). It may be caused by the large spatial angle between the lead lines (see page 15) of V₁ and V₂ vectors (152). Furthermore, V₁ often exhibits the lowest T-wave amplitude and a low amplitude is major source of error in the QT-measurement (207).

**What remains of QTd when the dust has settled?**

QTd was originally assumed to stem from local repolarization differences (92). The current view holds that QTd mainly is a geometrical effect due to projection of the global T-wave vector on the scalar ECG (208), with a contribution from a measurement error that will be larger in T-waves of low amplitude. The result is rather sparse, in view of the impressive data and proven statistical associations collected in a multitude of studies. It should however be noted, that even if the underlying theory is flawed, the data are still valid. The case of QTd can be seen as a simple illustration to the thoughts of David Hume in the 18th century: We can observe a covariance of phenomena but we cannot directly perceive a causal relation behind any data. Instead, our conclusions have to be tested against their consequences. QTd is obviously increased in situations with increased repolarization inhomogeneity. It is tempting to explain the varying durations of QT in the different ECG-leads as a result of differences in the repolarization duration in different parts of the heart. If the differences in QT duration however were due to local repolarization differences, then the differences should vanish in a transformation to a form that is non-local (a global vector). This is not the case (154, 207).

Due to the common availability of implantable defibrillators (ICD), the research related to repolarization inhomogeneity today has a practical (and economical) potential that it has lacked earlier. The field has been revived by the discussion about QTd during the last 10 years. In the case of QTd, the old concepts from vector-ECG have proven to be right, while the limits of their applicability also have been drawn to light.

**Dipolar components of the T-wave**

S₂/S₁Median describes the form ("fatness") of the vectorial T-loop and is thus a measure of the T-wave morphology. In our work (paper III), the parameter was increased (i.e. the T-loop was rounder) in patients with conduction disturbance. We found no prognostic information in the parameter within the group. The highest value of the parameter was seen in the comparison group with ST-T pathology. This finding is in accordance with early
published results that showed a wide T-loop in ischemic heart disease (see page 37).

**The relation of \( S_2/S_1 \) ratio to QTd**

We found a modest correlation between \( S_2/S_1 \)Median and QTdMean (Spearman \( \rho = 0.56 \)). This is in agreement with findings by other groups. Badilini et al describe a weak correlation between QTd and the (normalized) individual dipolar principal components (189). In the study of Yi et al (183), \( S_2/S_1 \) ratio correlates only weakly to QTd and to the dispersion of QTpeak (see page 29), with Pearson \( r = 0.24 \) and 0.35, respectively. The group of Okin describes in two materials a similarly modest correlation between QTd and \( S_2/S_1 \) ratio, with a correlation coefficient of 0.25-0.30 (117, 184).

A lack of strong correlation between \( S_2/S_1 \) and QTd may seem surprising, since \( S_2/S_1 \) is an expression of the form of the T-wave loop and projections of the latter on the scalar ECG-leads are regarded as a main cause of QTd (153, 154). The relation between the parameters describing the T-loop and QTd is, however, nonlinear, as has been pointed out by Kors et al (153). An obvious source of nonlinearity stems from the fact that \( S_2/S_1 \) only relates to the geometrical form of the T-loop, with no reference to any time measure. The form of the loop is not directly affected by the speed with which the T-vector depicts the loop. QTd, on the other hand, corresponds to the time difference between two points on the T-loop, namely the two instances when the first and the last scalar projection of the T-loop reaches zero amplitude.

![Figure 12. The relation of QTd to the T-loop. The hypothetical QTd in this case would be (200-170)=30 ms.](image)

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In a sense, QTd can be seen as a rough measure of the T-wave complexity: With a narrow T-loop, exhibiting a low \( S_2/S_1 \) ratio, the \( T_{end} \) would occur almost simultaneously in all the scalar projections and result in a low QTd. A somewhat higher correlation was observed by Nowinski et al (113) between QTd and the parameter Teigenv (the inverse of \( S_2/S_1 \) ratio, see page 37), with Spearman \( \rho = -0.76 \). (In the material from paper III, Spearman \( \rho \) between the inverse of \( S_2/S_1 \) Median and QTdMean is –0.56.) The observation of Nowinski et al was by others interpreted as QTd being caused by a local effect that is detected in the vectorial T-loop (209). It is however doubtful, whether such an effect should be called local (210). By such approach, local processes will only be detectable if they change the direction and magnitude of the global vector. This global vector however will still be placed centrally in a dipolar model. Any information about localization of a process will only be indirect. Furthermore, a local process that does not affect the global vector will not be detectable by this approach. See page 21.

**Nondipolar components of the T-wave**

The nondipolar components are a quantification of the difference between actual recordings with a specific method (12-lead ECG, BSM, MCG) and the simple dipolar source model. The correlation between the nondipolar components and QTd is weak (see page 40). Local repolarization inhomogeneity (in a stricter sense of an abnormal inhomogeneity of the myocardial source) is one imaginable cause of the nondipolar components. Other possibilities may include

- effects due to the complexity and changes in the thoracic medium, such as variations in water content
- movement artifact, due to heartbeat and respiration
- a discrepancy between the actual source and the dipolar model, appearing even in normal case
- noise

Following arguments speak in favor of the abnormal repolarization inhomogeneity as the cause of the nondipolarity:

- In early animal experiments, where an artificial dipolar source was introduced in the thoracic cavity, no nondipolar components could be detected on the surface (2).
- The nondipolar content of the T-wave is increased in pathological conditions and carries a prognostic impact (see page 40).
- When repolarization abnormalities are induced in an experimental setting with a simple conducting medium, the nondipolar content increases (67).

The link is supported by our observations that the nondipolar content is increased in conditions with increased arrhythmogeneity and assumed increase of repolarization inhomogeneity (papers III, IV). An interpretation of in-
creased absolute TWR in conduction disturbances (paper III) as a sign of increased repolarization inhomogeneity is in agreement with the described very low value of TCRT (indicating a large ventricular gradient, see page 36) in 9 patients with LBBB (211).

In a separate analysis of material III (see page 68), we found no signs of higher noise level in patients with higher nondipolar content of the T-wave.

**Absolute or relative T-wave residue?**

An unresolved issue is, whether the nondipolar content of the T-wave should be expressed by the absolute value of the nondipolar residue (absolute TWR) or its ratio to the total power of the T-wave (relative TWR, see page 39). In some instances (15, 178, 179), the relative TWR has been preferred, being a dimensionless ratio that is normalized with respect to the total power of the T-wave. It is however not self-evident that this is advantageous. The ratio will be affected by changes in the total power of the T-wave, even if the absolute level of the nondipolar components is unchanged. This has been observed experimentally in a Langendorff preparation of rabbit heart by Biagetti et al (67). The experiments confirmed that the TWR represents a small fraction of the total T-wave power. Repolarization abnormalities induced by premature stimuli and exposition to d-sotalol both resulted in increases in absolute TWR, as well as in the total power of the T-wave. The ratio of these two (relative TWR) was however either unchanged (after d-sotalol) or decreased (after premature stimuli).

A similar effect was seen in our work on patients with conduction disturbance (paper III). The patients with LBBB had a low TWRrelMedian, in spite of a high TWRabsMedian. The total power of the T-wave (the variance of the amplitude between T onset and T end) in this group was presumably high (reflected in a large T-wave area and corresponding to a clinical observation of high T-wave amplitudes in LBBB). The increase in the total power due to the conduction disturbance was greater than the increase of the nondipolar components and the latter was not reflected in the relative TWR. The absolute and relative TWR exhibited different patterns during the initial course of STEMI. The relative TWR did not separate between the groups with and without rapid reperfusion and its fluctuations were presumably affected by a changing total power of the T-wave.

A normal range during stationary conditions can probably be more easily defined for TWRrel than for TWRabs. The latter may on the other hand be more appropriate for studies of a time course when the variations are more important than the absolute level.
Do we need the dipolar model?

The division into dipolar and nondipolar components is based on the dipolar model of the myocardial source. When regarding ECG-signal morphology at the gross scale of classical clinical electrocardiography, the dipolar model is a reasonable, practically useful approximation. Below this level, nondipolar information is found. The nondipolar components of the T-wave are assumed to reflect repolarization inhomogeneity. Formally, they however just quantify the discrepancy between the real electric field measured on the surface and the dipolar model (see page 15).

The reasons for use of the dipolar model are the pedagogical and computational simplicity. In PCA, the computations are, however, independent of the model. It may here be conceptually more appropriate to avoid the dichotomy into dipolar and nondipolar components. This approach has been used in studies using Karhunen-Loève transformation (see page 73) of the ST-T segment during PCI-induced ischemia (222, 223).

Methods used with respect to the data quality

The signals consist of a large number of ECG-recordings, automatically collected in clinical populations with severe symptoms of chest-pain. The data thus contained with necessity a number of artifacts. A number of protective mechanisms was employed to shield the results from the effects of the artifacts.

Each ECG-recording was derived by a median approach using several cardiac cycles (see above, Subjects and methods, ECG-recordings). Robust statistical techniques with rank based measures and nonparametric tests were mainly used in the description and comparison of the parameters. Median and interquartile range exhibit statistical breakdown points of 0.5 and 0.25, i.e. half and a quarter of the sampled values can approach infinity without substantially affecting the descriptors (212). Arithmetic mean was only used in describing QTd in each patient, obtained from ECG-recordings with \( \geq 10 \) valid leads. This demand on number of valid leads was stricter than in many other materials (see pages 29 and 49) and aimed at decreasing the number of erroneous values included in the computation of this parameter. (The correlation between the mean and the median values was also very high: In the population of 800 patients described in paper III, the QTdMean showed a correlation to the median of QTd in the same recordings for each patient with Spearman \( \rho = 0.97 \); this result is presented here only.)

In the computation of the PCA-based parameters (papers III, IV), all available ECG-recordings were used and the material thus contained a higher proportion of recordings with artifacts. PCA is however not dependent on any critical points during the measurement interval and thus less sensitive to noise than for example QTd or Tpeak-Tend interval. Furthermore, the robust statistical measures that were used in the description for each patient will
only to a slight degree be affected by outlier values computed from an artifact. In comparison, the description of changes will be more sensitive to outliers. Therefore, the changes in the PCA-derived parameters were computed from filtered and median averaged dataseries (see above, Subjects and methods, Statistics).

In the material with chest pain and nondiagnostic ECG (paper III), the noise level was directly evaluated in a random sample of 2886 ECG-recordings: From the entire available data of 800 patients, 56 patients were randomly selected. From each of these, 1/20 of all ECG-recordings was drawn at random. The ECG-recordings were classified into three levels with respect to the noise severity: Recordings of good quality and recordings with moderate and high levels of noise. The classification was done by an automatic algorithm, detecting four types of noise: AC-noise, baseline wandering, muscle noise and electrode noise of mechanical origin. In the random sample, 80% of the recordings were classified as being of good quality; 15.1% contained moderate level of noise and 4.9% contained high level of noise. The 665 patients without conduction disturbance from the same material were dichotomized at the median of TWRabsMedian and the two halves compared with respect to relative prevalence of extreme outliers, CQV and median relative error (see above, Subjects and methods, Statistics). The group with higher TWRabsMedian actually had a smaller percentage of extreme outliers (3.1 vs. 4.3%, p<0.0005). No difference was detected in the CQV (36 vs. 34%, p=0.09) and the median relative error of TWRabs (0.32 vs. 0.33, p=0.14). The variability and repeatability of TWRabs was thus not affected by its level. (These results are presented here only.)

**STEMI as a model**

The setting of thrombolized STEMI in a large number of patients (paper IV) is very different from the common clinical model of repolarization-related arrhythmogeneity, the long QT syndrome (LQTS, see page 26). In comparison, the STEMI-situation offers a (groupwise) distinct event, known to trigger a sequence of arrhythmogenic mechanisms. On the other hand, the state presents a "dirty" mix of conduction disturbances and other arrhythmogenic mechanisms apart from the repolarization inhomogeneity. It is however difficult to imagine that a parameter, supposed to mirror repolarization inhomogeneity, should not react during the first hours of a STEMI.

The arrhythmogeneity in acute coronary occlusion is associated with development of electrical heterogeneities in the myocardium, due to several possible causes (213). A conduction delay, fragmentation and diastolic activity appear instantaneously in the electrogram (214). A partial gap junctional uncoupling diminishes the normal electrotonical interaction and unmasks differences between the cells (46). At the same time, a residual coupling between a large mass of dying cells with decreased membrane potential and normal surrounding cells will have a proarrhythmic effect by electrotonically
depressing the latter. The effects of ischemia are thus indirect. In line with these mechanisms is our observation (paper IV) that the decrease of the nondipolar content of the T-wave during the course of thrombolized STEMI is related to, but not tightly chronologically coupled to the resolution of the ST-elevation.

**Properties of the repolarization measurements**

Repeated observations have shown that QTd contains prognostic information but its properties make it unsuitable as a reliable marker and the clinical value of QTd is restricted. Furthermore, QTd contains no information regarding the local differences in the underlying myocardium and lacks the deeper causal association with repolarization inhomogeneity that was hoped for. The limitations of QTd are thus of a fundamental nature and will not be overcome by improved methodology.

The concept of repolarization inhomogeneity is ambiguous. It is determined by the differences in activation time and by the differences in the duration of action potentials (83). Locally it can be expressed as the difference in repolarization time, measured by MAP in two sites (56) (see page 22). This measure thus also includes the propagation factor. (Other authors have however also used the difference in action potential duration in MAP (57), a measure that will exclude the propagation factor).

The nondipolar components of the T-wave are assumed to reflect a localized heterogeneity of action potential duration (179). It can be concluded that this "voltage-based" measure also is directly affected by the propagation properties. A separation of the propagation property from the local repolarization property can be achieved by the concepts of primary and secondary T-wave and QRST-area (see pages 35 and 24). This approach can differentiate between the "disparate repolarization" and the "activation sequence" (34). The recently proposed parameter TCRT (see page 36) has similar attributes and reflects the global distribution of action potential duration (179). The properties of propagation, as well as of local repolarization, are however at play in both normal and arrhythmogenic conditions. One arrhythmogenic factor consists of differences between parts of the myocardium at a single instant, i.e. a "voltage domain dispersion" (68). This factor is determined by both the activation (propagation) properties and the local repolarization properties. The combination of the two properties in a marker could therefore be a useful characteristic and a separation might remove the traces of the arrhythmogenic effect.

We were nevertheless not able to link the nondipolar content to any powerful prognostic information. The number of deaths in the population with conduction disturbances may possibly have been too small for the risk factor to manifest itself (paper III population A, 34 deaths within 24 months among the 135 patients with a conduction disturbance), considering that the proportion of deaths attributable to arrhythmias late after a myocardial infarction
may be somewhere in the range 20-25% of the total mortality (this, although, in a population unselected with respect to conduction disturbances) (6). All the ECG-recordings in the present materials were collected during the initial hours of observation after an acute episode. This approach is adequate for studies of the relation between the measured parameters and repolarization. When considering a long-term prognostic impact, recordings obtained later in the course and presumably reflecting a chronic risk might be more appropriate.

Clinical implications

A multitude of noninvasive prognostic markers for long term outcome have to date been considered: Markers related to repolarization (QTd, the PCA-derived parameters, other T-wave descriptors mentioned in the background section), depolarization (QRS-duration, presence of a conduction disturbance, signal averaged ECG), autonomic function (heart rate variability, baroreceptor sensitivity, heart rate turbulence), unspecific arrhythmogeneity (prevalence of asymptomatic arrhythmias in Holter recordings), as well as more general markers of heart disease (heart rate in Holter recordings, heart rate during exercise and recovery, left ventricular function, natriuretic peptides) (6, 215).

A method to detect relevant markers of repolarization inhomogeneity and arrhythmia risk in conventional 12-lead ECG would have great clinical impact. Even though ECG is technically inferior to BSM and MCG for the quantification of repolarization inhomogeneity, it has the great advantage of practical simplicity and general availability. The necessary technology can relatively easily be incorporated in the routine equipment. The repolarization-related markers treated in the present work, in particular the nondipolar components of the T-wave, have an association with known arrhythmogenic mechanisms. They may therefore be more specific and better suited for selection of a subpopulation appropriate for intervention than the markers not associated with any particular mechanism. Neither of the markers of repolarization inhomogeneity investigated in the present work however currently meets the requirements for clinical usefulness.

Among the other markers mentioned above, decreased left ventricular function (in combination with other markers (216) and alone (217, 218)) has been used for decision regarding ICD-implantation in primary preventive trials with a statistically shown subsequent decrease in mortality. The opinion is however divided when it comes to the clinical meaning of the findings and consequences as to implant ICD on this ground. In other studies, ICD-implantation based on combinations of decreased left ventricular function and pathological signal averaged ECG (219) or heart rate variability (10) failed to reduce mortality or did reduce arrhythmic mortality
but not total mortality. Other promising markers have failed to prospectively identify the population with high risk (104, 172). The properties of a relevant marker are linked to the questions regarding the acceptable risk of the original condition, acceptable complication rate and acceptable cost-benefit relation of the intervention. In individual decisions regarding ICD implantation for primary prevention of arrhythmic death, the requirements on a predictor are very strict and it can be doubted that a single relevant marker ever can be found. More realistic future scenarios involve delimiting low-risk groups, as well as targeting separate subgroups at high risk, based on combinations of several markers (220). It seems logical to include an adequate marker of repolarization inhomogeneity in such a test battery.

Future directions

In our and others' approach, all the eight principal components derived from the PCA of the eight independent ECG-leads are processed. The eight principal components will contain the noise present in the original recordings. The nondipolar content of the T-wave in 12-lead ECG corresponds to <0.5% of the total power (paper III) and this quantitatively small part of the ECG-signal will be very sensitive to noise. The low signal-to-noise ratio in the principal components of higher order results in a high relative error and low repeatability of measurements in individual recordings. In a future approach, the signal-to-noise ratio of the nondipolar measures might be increased and the relative error decreased by omitting the components of highest order from the computation. The ECG-based measurements could be validated by a comparison to measurements obtained from MCG-recordings of the T-wave.

The sampling frequency of 240 samples/second, used in the current project yields about 70 samples from the T-wave, a slightly low number for a PCA of eight variables (221). An increased sampling frequency might thus diminish the error and in addition open a possibility of separate analysis during the early and the late repolarization phase, as has been done experimentally (67).
Conclusions

- QTd in patients with unselected chest pain, measured as the mean value of automatic measurements from multiple recordings was a powerful marker for cardiac events during follow-up. It could be used for selection of low-risk patients but was not effective in identifying high-risk patients. QTd, measured in a single ECG-recording was not associated with prognosis.
- No additional prognostic information was detected in the variations in QTd during observation time.
- QTd, measured as the mean value of multiple recordings, was increased in a population with unstable coronary artery disease. QTd could not be related to the severity of coronary disease. The derived, localized parameter QTdiff could not be linked to the localization of coronary pathology. QT dispersion in ischemia was increased by a mechanism unrelated to the localization and severity of the coronary disease.
- In patients with conduction disturbance, QT dispersion was weakly correlated to the nondipolar content of the T-wave and moderately correlated to $S_2/S_1$Median.
- The nondipolar content of the T-wave increased with increasing conduction disturbance. Increased conduction disturbance thus seems to be associated with increased repolarization inhomogeneity and reflected in the nondipolar content. The nondipolar components of the T-wave contained a moderate amount of prognostic information not present in a simple ECG-diagnosis of a conduction disturbance.
- The nondipolar content of the T-wave was increased and has an increased variability in patients with thromboloyzed STEMI. Early tissue level reperfusion, as indicated by 50% resolution of the ST-elevation within 60 minutes was associated with a greater decrease in absolute TWR. The increased absolute TWR reflects a property of the repolarization phase that is related to the evolution of the ST-elevation. The two measures do however not reflect identical ECG-properties of the STEMI-development and their changes do not occur at the same time.
Appendix A

The description and processing of the ECG-signal makes use of concepts originating from matrix algebra, statistics and signal theory. In the following, some of the basal notions are described. The present work considers in the first hand arrhythmogenic factors associated with repolarization, rather than algebraic tools for signal analysis. In this context therefore relative ease of understanding has been preferred to a formally stringent expression.

**Vector magnitude** (length) is the square root of the sum of the squared lengths of its orthogonal components (a generalization of Pythagoras' theorem):

\[ |x| = \left( \sum_{n=1}^{N} x_n^2 \right)^{1/2} = \sqrt{x_1^2 + x_2^2 + x_3^2 + \ldots} \]

**Energy** of a discrete signal is defined as the sum of squared magnitudes over time:

\[ E = \sum_{n} |x_n|^2 \]

**Power** of a signal is defined as energy per interval

\[ P = \frac{1}{N} \sum_{n=1}^{N} |x_n|^2 \]

**Variance** of a signal is equivalent to the power of the signal with its mean removed:

\[ \sigma^2 = \frac{1}{N} \sum_{n=0}^{N-1} (x_n - \bar{x})^2 \]

The ECG-signal is sampled from several ECG-leads. The lead signals that are collected from separate electrodes can be said to be **physically** mutually independent (as opposed to the signals that are reconstructed from combinations of other leads). The physically independent signals, however, to a degree contain the same information, i.e. the signals are not **algebraically** mutually independent. An algebraic independence can be obtained by transforming the information from the original variables (ECG-leads) into a set of derived virtual variables, represented by vectors that are mutually orthogonal (see below).
Covariance expresses association between two variables. It is computed from the values of each variable for each occasion and the mean of the variables in the entire series:

$$\text{cov}(x_1, x_2) = \frac{1}{N} \sum (x_1 - \bar{x}_2)^* (x_2 - \bar{x}_2)$$

In a situation with multiple variables (for example measurements from ECG-leads), a covariance matrix can be constructed from covariances between all pairs of variables. Covariance between a variable and itself (making the diagonal elements in the matrix) equals the conventional variance for the variable. The elements below the diagonal will mirror those above the diagonal, since $\text{cov}(a,b)=\text{cov}(b,a)$:

$$
\begin{bmatrix}
\sigma^2(x_1) & \text{cov}(x_1,x_2) & \text{cov}(x_1,x_3) \\
\text{cov}(x_2,x_1) & \sigma^2(x_2) & \text{cov}(x_2,x_3) \\
\text{cov}(x_3,x_1) & \text{cov}(x_3,x_2) & \sigma^2(x_3) \\
\vdots & \vdots & \vdots & \ddots
\end{bmatrix}
$$

The covariance between two mutually independent variables is zero. The strength of association can however not be directly estimated from the absolute value of covariance, since the latter also is dependent on the numerical values of the variables (scale dependence). Scale independence is achieved by computing the correlation coefficient. The latter varies between –1 and 1 and one way to derive it is from the covariance and the standard deviations of the two dataseries:

$$r_{1,2} = \frac{\text{cov}(x_1,x_2)}{\sigma_1 \sigma_2}$$

For a situation with multiple variables, a correlation matrix can be constructed:

$$
\begin{bmatrix}
1 & r_{1,2} & r_{1,3} & \ldots \\
 r_{2,1} & 1 & r_{2,3} & \ldots \\
 r_{3,1} & r_{3,2} & 1 & \ldots \\
\vdots & \vdots & \vdots & \ddots
\end{bmatrix}
$$

Principal component analysis (PCA) can use the covariance- or correlation matrix of a dataset for constructing a new set of mutually independent virtual variables, in descending order of magnitude, each expressing the maximal variance in one orthogonal direction of the dataset. The computation is achieved by standard matrix algebraic methods. In some instances, the procedure is known as Karhunen-Loève transformation.
The virtual parameters are expressed by **eigenvectors** to the covariance- or correlation matrix. These are by definition orthogonal, i.e. mutually independent. Each of the eigenvectors is directed along the maximal variance, which remains in the data after the calculation of the larger components. The procedure can be seen as a rotation of the coordinate system from the original data-independent orientation to an orientation that is optimally adjusted to the variance in the dataset (the eigenspace). The size of the independent virtual parameters is expressed by the principal components (**eigenvalues**).

![Figure 13. Reduction of data in 3 variables to 2 principal components.](image)

If exact reconstruction of the original data is attempted, then the number of components must be the same as the number of original variables. A data reduction is achieved if the components, which contribute with a small percentage of the original variance are discarded. The reconstruction from the reduced number of components will then exhibit a well-defined error with respect to the original data. (In practical situation the original data also contain noise, that will propagate into the principal components. The signal-to-noise ratio decreases in the principal components of higher order. Excluding the principal components of higher order can thus be advantageous by reducing the noise.)

A more stringent mathematical background of PCA is provided elsewhere (15, 130, 185, 224-226).
Eigenvectors and eigenvalues
For a square matrix $B$, $v$ is an eigenvector to $B$ and $k$ is an eigenvalue to $B$ if

$$B \cdot v = k \cdot v$$

A numerically simple example:

$$B = \begin{pmatrix} 3 & 1 \\ 0 & 3 \end{pmatrix}, \quad v = \begin{pmatrix} 1 \\ 0 \end{pmatrix}$$

$$B \cdot v = \begin{pmatrix} 3 & 1 \\ 0 & 3 \end{pmatrix} \cdot \begin{pmatrix} 1 \\ 0 \end{pmatrix} = \begin{pmatrix} (3 \cdot 1) + (1 \cdot 0) \\ (0 \cdot 1) + (3 \cdot 0) \end{pmatrix} = \begin{pmatrix} 3 \\ 0 \end{pmatrix} = 3 \cdot v$$

$$\begin{pmatrix} 1 \\ 0 \end{pmatrix}$$
is thus an eigenvector to the matrix $B$ and $3$ is an eigenvalue to the matrix $B$

CUSUM
The cumulative sums method is useful for detection of sustained changes in the mean of a data sequence. CUSUM-charts are used in quality control and statistical monitoring of ongoing processes (227). The method has been applied in neurophysiology (228-230), circulatory physiology (231) and research in family planning (232). In each consecutive point $n$, a cumulative sum is computed by adding the difference between the local value and a reference value (here the mean of the entire data series):

$$S_n = 0$$

$$S_n = \sum_{i=0}^{n} (x_i - \bar{X}) = 0 + (x_1 - \bar{X}) + (x_2 - \bar{X}) + \ldots + (x_n - \bar{X}) = S_{n-1} + (x_n - \bar{X})$$

A CUSUM function for the series is then constructed from the cumulative sums in all points. For a hypothetical data series with no changes, no data points will deviate from the mean and all the CUSUMs will be zero. For a data series containing a change, the series of CUSUMs initially successively increase or decrease from zero. At the data point where the change occurs (changepoint), the CUSUM function reverses its direction and starts to reapproach zero. The localization of the changepoint can be estimated by the position of this maximal (or minimal) cumulative sum (233) (the CUSUM-estimator).
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