# Electrocardiographic assessment of repolarization heterogeneity

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# Chapter 1

# Introduction
# Electrocardiographic assessment of repolarization heterogeneity

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## History of the electrocardiogram and the T wave

The development of electrocardiography has largely taken place in Leiden. Willem Einthoven was one of the founding fathers of electrocardiography, for which he received the Nobel prize in 1924[1]. Einthoven was head of the Leiden University Physiology Laboratory nearby the Academic Hospital[2]. Initially he improved Lippmann's electrometer, which Waller had used to record the first human ECG in 1887[3]. In 1895 Einthoven developed a mathematical formula to construct the actual ECG from the signal of the slow responsive electrometer. To discern his calculated ECG from its predecessor, he renamed the ABCD deflections into PQRST (Figure 1a) [4]. These names were universally adopted and are still in use today. He described the T wave more or less as "ein stumpf und aufwärts gerichte Spitze ". In the following years Einthoven developed the world famous string galvanometer[5], which allowed recording of high quality, stable electrocardiograms. In 1902 the first so recorded ECGs were published and the actual shape of the T wave was revealed (Figure 1b)[6].

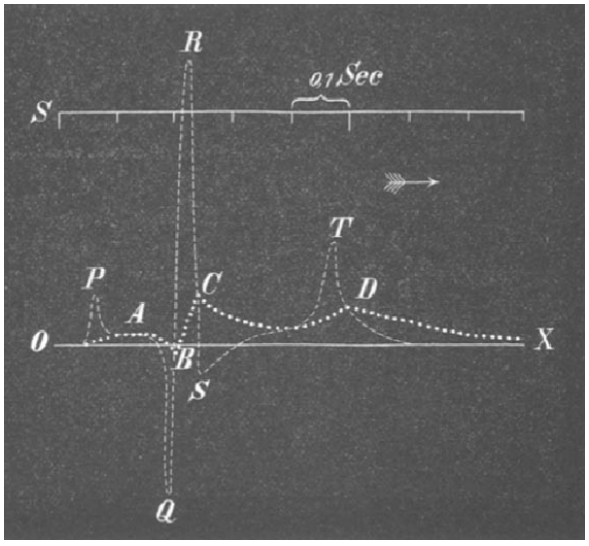



***Figure 1a.*** *Einthoven calculated the electrocardiogram from the signal of the slowly responsive electrometer and called the derived deflections PQRST, names that are still in use today. Einthoven. Pflügers Arch ges Physiol 1895.*

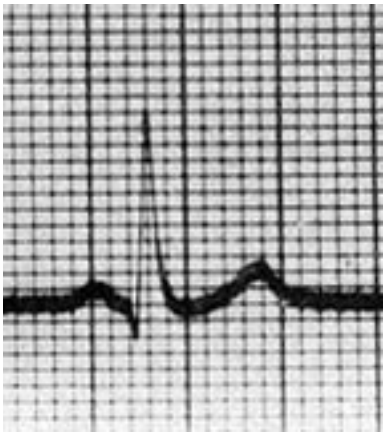


***Figure 2a.*** *In 1902 electrocardiograms recorded with the string galvanometer were first published. Einthoven. In: Herinneringsbundel Prof. Rosenstein 1902.*

# The T wave and action potentials

The T wave depends on differences in timing of the repolarization of myocardial cells. Schematically, when two action potentials are subtracted, a T-wave emerges[7] (Figure 2). The repolarization time of a given myocardial cell consists of the summation of the activation time and action potential duration (APD).

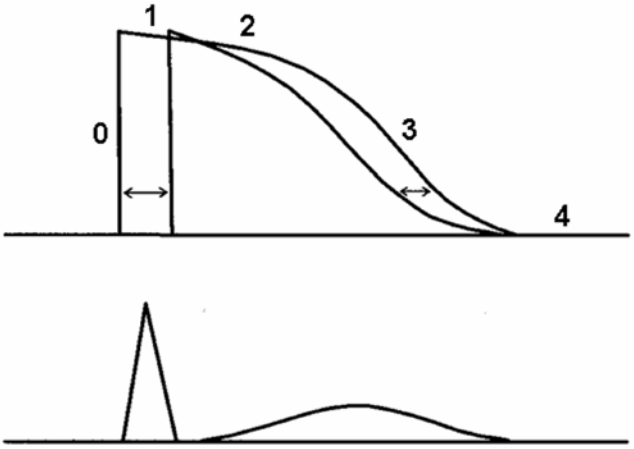



***Figure 2.*** *Schematically, when two action potentials are subtracted, a T-wave emerges. 0 = fast depolarizing upstroke, 1 = initial rapid recovery phase, 2 = plateauphase, 3 = repolarization, 4 = resting potential. Adapted from Franz et al. Prog Cardiovasc Dis 1991.*

The primary function of the cardiac electrical system is the coordination of myocardial contraction. After the upstroke of the action potential, myocardial contraction starts, thereafter the plateau phase of the action potential is responsible for the continuation of myocardial contraction. In combination with the specific organization of the myocardial fibers, the contraction of myocardial cells results in a wringing motion[8] of the heart that efficiently propels the blood[9]. Furthermore, action potential durations have the tendency to correct for differences in activation time. In general, the earliest activated regions have the longest action potential duration and the latest activated regions have the shortest action potential duration. These repolarizing properties result in a more homogeneous repolarization[10;11] and relaxation[12].

## Heterogeneity of the repolarization and arrhythmias

Besides a direct relation with mechanical function, the shape of the action potential (AP) also has protective electrophysiological properties.
The relatively long plateau phase of the cardiac action potential prohibits tetanus in the myocardium, which occurs relatively frequently in skeletal muscle [13].
Furthermore, the tendency of APDs to compensate for different activation times diminishes repolarization heterogeneity[10;11], which reduces the risk of arrhythmias. Heterogeneous repolarization facilitates the formation of functional barriers surrounded by excitable tissue[14;15]. Re-entrant arrhythmias may be initiated by an adversely timed stimulus that reaches such a barrier and circles around it[16]. As a consequence, abrupt, local differences in refractoriness facilitate re-entrant arrhythmias. Repolarization differences between nearby areas are therefore potentially more arrhythmogenic than repolarization differences between areas more distant from each other (Figure 3).

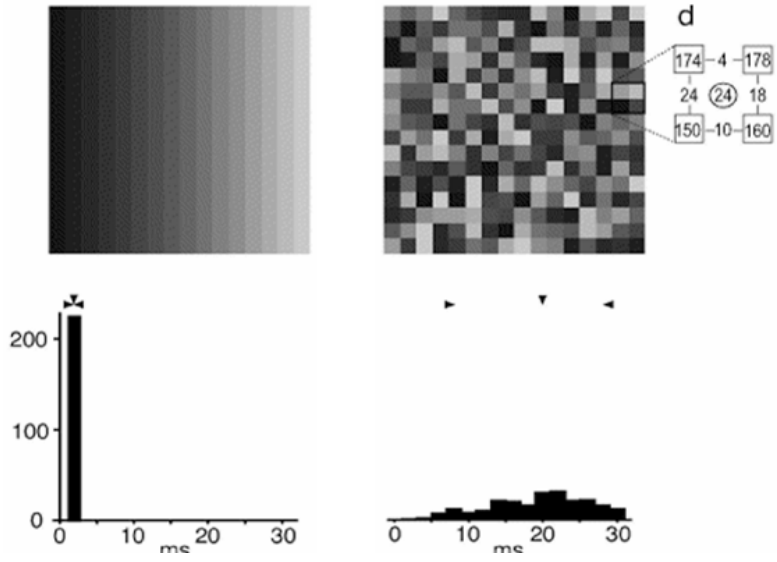



***Figure 3.*** *Dispersion in repolarization or refractoriness depicted by varying grey scale in two simulated fields of 256 (16×16) electrode sites. Lower panels show histograms of these local inhomogeneity values, corresponding to the two fields. Arrowheads above histograms indicate the values of percentiles P5 ( ► ), P50 ( ▼ )(median) and P95 ( ◄ ).*

*Although the median dispersion of refractory period is the same in both conditions, the left figure shows global dispersion, with smoothly changing differences in refractoriness. Only in the right figure local dispersion exists with possible higher susceptibility to functional barreres and re-entry arrhythmias. Local inhomogeneity values are calculated on the extreme right as the maximum (24 ms, circled) of absolute differences (4, 10, 18 and 24 ms) within a neighbourhood of four electrode sites. Adapted from Burton and Cobbe. Cardiovasc Res 2001.*

As can be inferred from the above, repolarization heterogeneity is thus linked to arrhythmogenesis due to the relationship with refractoriness. When the AP of a myocardial cell is still in its plateau phase (phase 2) the cell is absolute refractory, to the contrary, when the cell is fully repolarized (phase 4) the cell is fully excitable. Any phase in between, on the down slope of the APD (phase 3), will result in a partially excitable cell, also named the relatively refractory period, during which a strong stimulus is still able to depolarize the cell[17]. An exception to these principles is, for example, post-repolarization refractoriness, which can be present in ischemic myocardium[18]. An ischemic cell may be refractory despite having reached phase 4.

Action potentials can be recorded using microelectrodes or monophasic action potential catheters[19]. The action potential duration is defined as the $APD_{90}$, which is the time interval from upstroke of the action potential to the moment when action potential amplitude has decreased by 90 % of its maximum amplitude. In vivo, repolarization studies in animals are mostly performed using needle electrodes allowing the measurement of activation recovery intervals (ARIs). The ARI is measured from the negative deflection of the activation complex to the positive deflection of the repolarization wave on the unipolar electrogram. ARIs are a surrogate measure of APD, but with a good correlation[20;21] between recorded monophasic action potentials and ARIs [20].
As stated before, repolarization heterogeneity may form the substrate for an arrhythmia, but a trigger is also necessary to initiate an arrhythmia. Early after depolarizations may occur in the setting of a disturbed repolarization and may serve as this trigger. The premature stimulus itself also modifies the repolarization heterogeneity[22;23]. Even in patients without overt structural heart disease, closely coupled, multiple extrastimuli are able to induce ventricular fibrillation. Arrhythmias can also be maintained by continuously firing foci[24-26].

## Physiological heterogeneity of the repolarization

Repolarization heterogeneity is mostly classified in transmural and apico-basal heterogeneity. Repolarization heterogeneity between the left and right ventricle also exists, but data are scarce.

# Transmural repolarization heterogeneity

The nature of the transmural repolarization differences is not entirely clear; some studies dispute the existence and direction of the transmural repolarization gradient[27;28]. The presence or absence and direction of the transmural gradient is essential for the understanding of the formation of the normal T wave and will be discussed in detail the following paragraphs.

As early as in 1931 Wilson proposed the existence of a ventricular gradient, caused by non-homogeneous action potential durations throughout the heart[29]. Despite opposite polarities of de- and repolarization currents, human QRS complexes and T waves attain the same polarity in most ECG leads. This concordance between QRS complexes and T waves can be explained by an inverse transmural repolarization order (from epi-to-endocardium) compared to the excitation order (from endo-to-epicardium)[29;30].

**Animal studies**

In canines the polarity of T waves can be varied by changing transmural APD differences by local warming or cooling[30]. Warming is known to shorten APD and cooling is known to lengthen APD[31]. Epicardial warming as well as endocardial cooling cause upright, concordant T waves. Endocardial warming and epicardial cooling cause inverse, discordant T waves[30].

Van Dam and Durrer measured refractory periods in dogs and found the shortest refractory periods in the midwall. Intermediate APDs were recorded from the endocardium and the longest APDs from the epicardium. They reported negative T waves in unipolar leads from the epicardial surface[32]. On the other hand, Burgess et al. measured longer endocardial than epicardial refractory periods[33].

Abildskov studied refractoriness and repolarization times (defined as activation time plus refractory period) in 15 anesthetized dogs[34]. In 5 dogs, transmural excitation and repolarization studies were performed immediately after thoracotomy. Despite an earlier excitation, the endocardium repolarized later than the epicardium, as reflected by longer refractory periods and later repolarization times (figure 4).

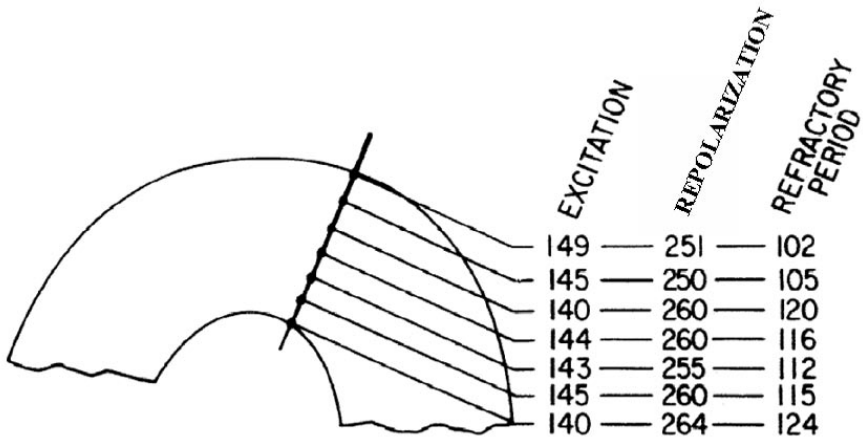



***Figure 4.*** *Despite an earlier excitation, the endocardium repolarized later than the epicardium, as reflected by longer refractory periods and later repolarization times. Recovery times are used as a surrogate for repolarization time (excitation time + refractory period = repolarization time) Adapted from Abildskov. Circulation 1975.*

Spach and Barr used intramural and epicardial electrodes to measure potential distributions during excitation and repolarization[35]. Beforehand they recorded ECGs to ensure positive (concordant) T waves, and excluded several dogs with negative T waves. Depolarization spread in accordance with the findings of Durrer and coworkers[36] from endo- to epicardium, starting at the left midseptum and ending at the base. In general, positive potentials were recorded from the epicardium compared to more negative potentials recorded from the endocardium, implying an earlier epicardial repolarization.

El-Sherif et al. performed 3-D mapping of arrhythmias emerging under long QT conditions in an in-vivo canine model[37]. They found that subendocardial focal activity can maintain arrhythmias but may result in reentrant arrhythmias when the repolarization heterogeneity was large enough. Steep transmural differences in ARI across the wall contributed to this repolarization heterogeneity.

Recently, Janse et al. published a study performed in dogs[28] that was in line with the findings of Janse's thesis published in 1971[38]. The epicardial repolarization time was not earlier compared to the endocardial repolarization time. However, the published canine ECG showed discordant QRS complexes and T waves[28] as opposed to the T and QRS concordance found in humans.

Different species, and more specifically different mammals of different size may show

either concordance or discordance on their ECG[39]. In dogs concordance may be either present or absent[35]. In chimpanzees, a species genetically close to humans, concordance is present in most leads[40]. The ECGs of the giraffe as well as the humpback whale[41] show discordant T waves. Several studies disputing the presence of an epi- to endocardial transmural repolarization gradient, depicted surface ECGs with discordant ECGs. Results obtained from these species can therefore not be extrapolated to the human repolarization. Before selecting animals for an invasive repolarization study, electrocardiograms should be recorded to assure concordant T waves.

**Human studies**

Franz et al. recorded left ventricular endocardial monophasic action potentials in 7 patients undergoing catheterization (for suspected coronary disease in 5 patients and aortic disease in 2 patients)[10]. Additionally, they measured epicardial monophasic action potentials during surgery for coronary artery bypass grafting in 3 other patients. To compare endo- and epicardial recovery times in these different patients, and during different interventions, they normalized the repolarization times (RT = activation time + APD) of endo-and epicardium on the individual QT intervals on the surface ECGs. Expressed as percentage of the QT interval, epicardial RTs (71-84 %) were shorter than endocardial RTs (80-98%).

Taggart et al. measured left ventricular ARIs in 21 patients during CABG[42]. Measurements were performed during right ventricular stimulation at different cycle lengths and during spontaneous atrial beats. No statistical differences were found between any of the recording sites. However, when closely observing the transmural ARI graphs, a trend towards a 5 ms shorter subepicardial ARI than subendocardial ARI can be detected. Electrograms provided as example show that the epicardial ARI is 14 ms shorter than the subendocardial ARI. These differences are small but consistent. Possibly, the interindividual variation in ARI is larger than the intraindividual variation in transmural ARI, rendering them undetectable by the used statistical methods. Understandably, Taggart et al. used short needles, the edge of the deepest electrode reaching only 7.15 mm. The authors state that the first 0.5 to 1.0 mm is epicardial fat, this would mean that the center of the deepest electrode reaches only to a depth of 6.5 mm from the epicardial myocardial surface. Therefore the endocardium is virtually left out of these experiments.

In conclusion, in animal studies the direction of a transmural gradient determines the

polarity of the T wave. An epi- to endocardial gradient is responsible for concordant T waves. The results of these animal studies combined with the interpretation of the above mentioned human studies suggest that a small transmural epi- (early repolarization) to endocardium (later repolarization) repolarization gradient is likely to be present under physiological conditions in humans.

**M-cells**

M-cells may play a pivotal role in transmural repolarization heterogeneity[43]. Part of the debate on transmural dispersion is the discussion whether M-cells have a significant physiological effect on the repolarization.

Yan and Antzelevitch demonstrated the presence of M-cells in a preparation of the left ventricular free wall[43]. This preparation was made by dissecting a wedge shaped part of the left ventricular wall with its supplying large epicardial artery (which was perfused subsequently). Monophasic action potentials were recorded from epi- and endocardial cells and from the mid-myocardial cells, which were named: M-cells. The M-cells in this preparation had the longest APD and the epicardial cells the shortest APD. The difference in action potential duration and amplitude between these cell layers mainly determined the morphology of the T wave in a pseudo-ECG recorded across the wedge preparation. The shorter epicardial APD and earlier repolarization time resulted in a positive T wave directed towards the epicardium.

Drouin et al. confirmed the presence of M-cells in wedge preparations of 4 apparently healthy human hearts[44]. M-cells were found 1 mm up to 4-5 mm from the epicardial surface, constituting of approximately 30 % of the myocardial mass. M-cells demonstrated an increased rate-dependence of their already longer APD duration during electrical stimulation with 1 to 0.1 Hz. The lower the stimulation frequency, the longer the APD, thereby increasing transmural repolarization heterogeneity.

Anyukhovsky et al. performed a comparative study of wedge preparations and in vivo canine hearts[45]. They measured APDs in transmural wedge preparations and ARIs in in vivo hearts. In the wedge preparations they found M-cells; midmyocardial cells with relatively long APDs that were more sensitive to abrupt changes in cycle length than endo- and epicardial cells. Noteworthy is that the epicardial APD were longer than endocardial APD. However, they did not find any transmural difference in (averaged) ARIs in vivo, supposedly caused by electrotonic interaction between myocar-

dial cells. However, in their example an endocardial (shorter repolarization time) to epicardial (longer repolarization time) gradient was present and accompanied by an ECG with a discordant T wave.

Conrath and Opthof used (strand-) simulation models to study the effects of electrical coupling on transmural repolarization differences[46]. Their conclusion is plausible: in physiological conditions, M-cells do not introduce large transmural repolarization differences; due to intact electrotonic coupling the repolarization differences become smaller.

In conclusion, from the wedge preparation studies we know M-cells exist. However, the electrophysiological significance of M-cells in the normal heart is probably small. Large, abrupt repolarization differences due to different repolarization properties of different cells are smoothened by electrotonic interaction with surrounding cells. However, arrhythmias mostly emerge under unphysiological conditions. For example, in heart failure patients connexins are down regulated, which produces uncoupling between transmural muscle layers leading to marked repolarization heterogeneity between epicardial and deeper myocardial layers. Therefore, decreased connexin expression patterns can potentially contribute to an arrhythmic substrate in failing myocardium[47]. Another argument against the functional significance of M-cells is that APD lengthening appears only at unphysiological slow rates. However, Torsade de pointes arrhythmias are known to be initiated after a short-long(-short) sequences[48]. Thus, arrhythmias mostly emerge under pathological conditions, with less electrical coupling, greater cycle length changes and adversely timed extrastimuli. These conditions may increase the electrophysiological expression of M-cells resulting in an increase of transmural repolarization heterogeneity to a critical level and an increased susceptibility to arrhythmias.

## Apico-basal repolarization heterogeneity

Besides a (small) transmural gradient, an apico-basal gradient is probably also present under normal conditions. However, data on apico-basal repolarization heterogeneity is contradicting. The apico-basal gradient is also crucial for the inscription of the normal T wave. The normal T wave forms the basis for further studies on irregular T waves and electrocardiographic indices of repolarization heterogeneity throughout this thesis. An essential aspect of the discussion on the apico-basal gradient is the issue whether action potentials overcompensate or undercompensate for differences in activation times. This would imply difference or similarity between activation and repolarization patterns.
In the following studies on the apico-basal gradient, repolarization and activation times were measured parallel to the ventricular walls, on either the epicardium or the endocardium, or both. Subsequently, we will present an analysis based on the characteristics of QRS and T vector loops recorded in healthy subjects.

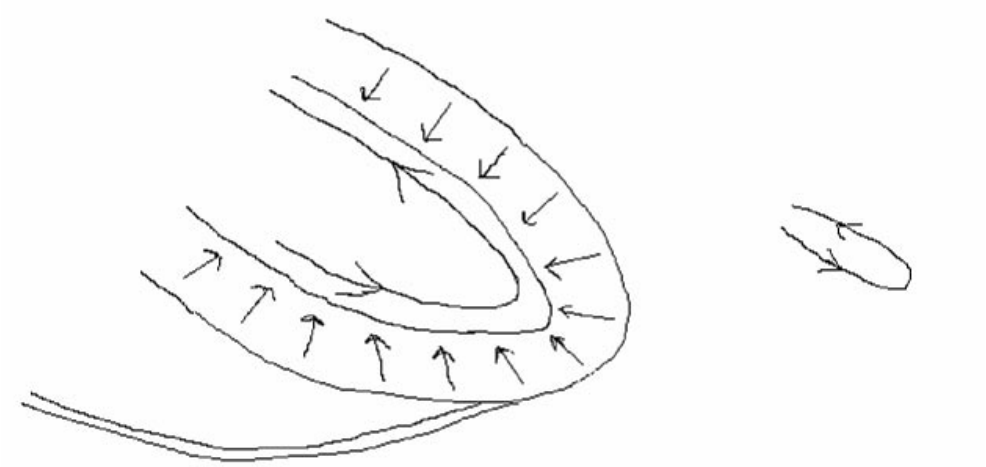
Burgess et al. reported shorter refractory periods at the base than at the apex in dogs[33].
Restivo et al. however found shorter apical than basal APDs in guinea pigs measured with voltage sensitive dye. Long QT syndrome type 3 was mimicked with anthopleurin-A. Anthopleurin-A exacerbated the normal epicardial uniform apex-base APD gradient, resulting in heterogeneous repolarization gradients, functional blockades, re-entry and ventricular tachycardias[49].
Gepstein et al. measured endocardial ARI in 13 swine during atrial activation and ventricular pacing[50]. He found that even after a short period of pacing, ARIs adapted to and compensated for depolarization times. In most pigs ARIs did not overcompensate for the depolarization time, causing repolarization patterns to follow the depolarization patterns. Refractoriness was measured in 3 swine and appeared to be inversely related to the depolarization time, thus overcompensating the depolarization times. The quickness of this ARI adaptation to depolarization times suggests that electrotonic coupling played an important role in the shortening of ARI.
Franz et al. showed that differences in activation time were compensated by action potential duration differences so that repolarization was nearly homogeneous measured on the endocardium in some patients as well as measured on the epicardium

in other patients[10]. Only a trend towards a longer repolarization time of the first activated regions (diaphragmatic and apico-septal) compared to the later activated regions was present. When all activation times (AT) and action potential durations of individual patients were plotted, an inverse relation was found with an average slope greater than negative unity (-1.34), which shows that action potential duration overcompensate for activation time, thereby contributing to concordant T waves.
Yuan et al. measured endocardial monophasic APD in eight patients referred for arrhythmia treatment to the electrophysiological laboratory and in 10 swine[51]. They showed that in most patients and swine, repolarization followed depolarization, despite shorter MAP at later activated sites. In patients the slope between AT and APD was -0.45, showing an incomplete compensation of differences in activation times.
Yue et al. measured in 13 patients, mostly referred for idiopathic monomorphic ventricular tachycardia, ARI with a non-contact mapping system[11]. They showed that on the endocardial surface ARI compensated for AT, but not over-compensated, as the overall regression slope between activation times and ARIs was -0.76. During sinus rhythm, RTs were better compensated (slope - 0.81) than during premature stimulation (slope -0.61).

Summarizing, data on human repolarization is limited and contradicting. The discussed older study shows an overcompensation of depolarization time by the action potential durations. The repolarization pattern measured on either the endo- or epicardium (parallel to the ventricular walls) is suggested to be the reverse of the depolarization pattern. However, the more recent studies discussed here found that repolarization followed the depolarization order at the endocardium.
The patients in the above studies were not completely healthy, therefore analysis of the QRS and T vector loops of healthy subjects may provide some additional information regarding the normal sequence of repolarization. Typically, the same global orientation and direction of inscription of the QRS and T loops was found in healthy humans[52-54]. These properties are in agreement with a similar de- and repolarization order measured parallel to the ventricular walls, from midseptum to apex ending at the lateral base, and a reversed transmural repolarization sequence from epi- to endocardium[53].
Furthermore, the normal T vector loop points to the apex and is smaller and more elongated than the QRS vector loop. These properties implicate a smaller heteroge-

neity of repolarization times than of activation times, with a larger apico-basal than transmural repolarization gradient (Figure 5).

***Figure 5.*** *Proposed normal human repolarization order in accordance with vectorloop morphology*



*Transventricular repolarization follows activation sequence from sepum to apex to base. Transmural repolarization gradient is small, but inversely directed from epi- to endocardium.*

## ECG indices of repolarization heterogeneity

Repolarization heterogeneity predisposes to arrhythmias[14;15;37]. Therefore, a non-invasive index of this repolarization heterogeneity potentially would have great clinical value. More than hundred years after its discovery, the ECG is still an easily available, cheap and valuable diagnostic test. At present, the standard 12-lead configuration is most used in the routine clinical setting. Therefore, we used the 12-lead configuration throughout this thesis.

### QT interval

The traditional electrocardiographic repolarization index is the QT interval, defined as the interval from the start of the earliest QRS complex to the latest end of the T-wave in any lead. The QT interval represents the interval from the earliest depolarization to the end of the repolarization anywhere in the heart.

The risk of arrhythmias in long QT patients increases with the duration of the QT(c) interval[55]. A large proportion of drugs with arrhythmogenic side-effects decrease the

rapid delayed rectifier, a repolarizing potassium current, thereby lengthening the QT interval[56]. Therefore, the American Federal Drug Administration requires QT interval testing for every new drug before market release is authorized. Despite its widespread use, the QT interval has some important limitations as estimator of repolarization heterogeneity. By definition, the QT interval is dependent on the longest action potential durations. However, the duration of the longest action potentials is not related to repolarization heterogeneity per se. For example, amiodarone lengthens the action potential durations homogeneously throughout the ventricular wall and has an anti-arrhythmic effect rather than a pro-arrhythmic effect[57].

The QT interval varies with heart rate. To estimate the QT interval during varying heart rates, correction factors are needed. The most commonly used formula is Bazett's[58], probably due to its simplicity.

$$QTc = QT / \sqrt{RR}$$

However, the Bazett formula has a tendency to overcorrect the QT interval at fast heart rates and to undercorrect the QT interval at slow heart rates, see Figure 6[59].

Measurement of the end of the T-wave is often difficult due to slowly decreasing slopes at the end of the T-wave, low amplitude T waves and overlap with the P-wave at fast heart rates[60]. Furthermore, the practical and theoretical disputes to discern the end of the T wave from the U wave have not been settled[61;62]. A practical solution is often chosen to set the end of T at the crossing of the baseline with the steepest tangent to the descending part of the T wave[63] or at the T-U nadir[60].
In summary, the QT interval represents the end of the repolarization anywhere in the heart and may be useful in conditions which are characterized by a lengthened repolarization. However, the QT interval does not directly assess repolarization heterogeneity.

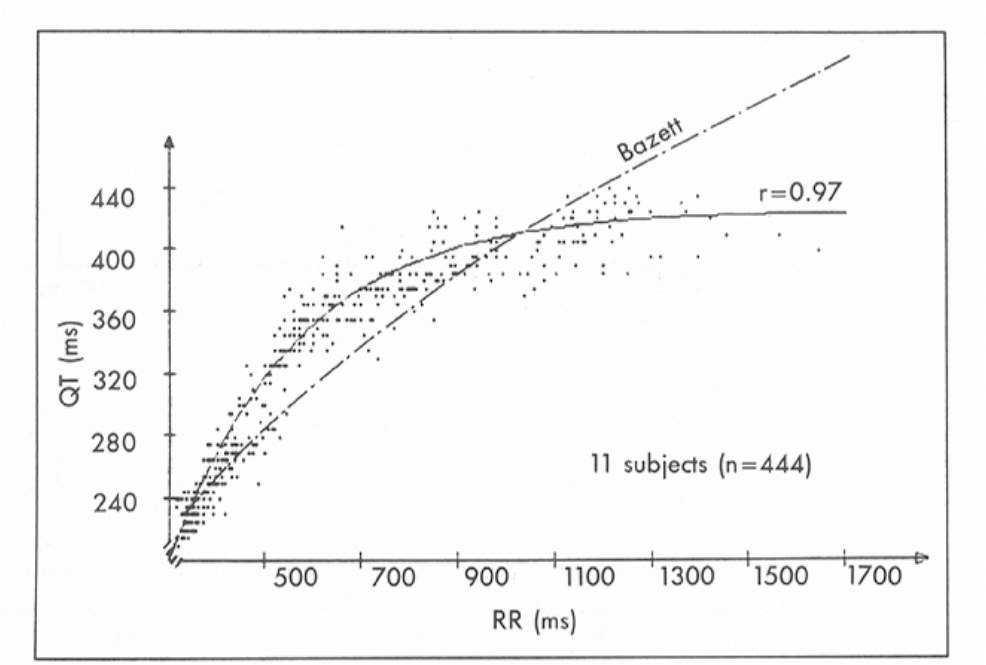



***Figure 6.*** *The Bazett formula has a tendency to overcorrect the QT interval at fast heart rates and to undercorrect the QT interval at slow heart rates. Lecocq et al. Am J Cardiol. 1989.*

**Tapex-end interval**

More recently, Yan and Antzelvitch proposed the Tapex-end interval, the interval from the apex of the T-wave to the end of the T-wave, to assess transmural repolarization heterogeneity[43]. Their proposal is based on sophisticated experiments in a wedge preparation of the left ventricular free wall of canine hearts[64]. As stated before, their findings appoint the midmyocardial M-cells as the cells with the longest APD. The APD of these cells were reflected in the end of the T wave in the pseudo-ECG they recorded across the preparation (Figure 7). The epicardial cells appeared to have the shortest APDs and the end of the repolarization in these cells coincided with the moment of the apex of the T-wave. They concluded that the Tapex-end interval is therefore a measure of the difference between the epicardial and mid-myocardial repolarization times, *i.e.*, transmural repolarization heterogeneity.

Their experiments provide pathophysiological insight in various forms of long QT syndrome. A large number of drugs with arrhythmic side effects are known to inhibit the delayed rectifier current. In wedge experiments these properties were shown to

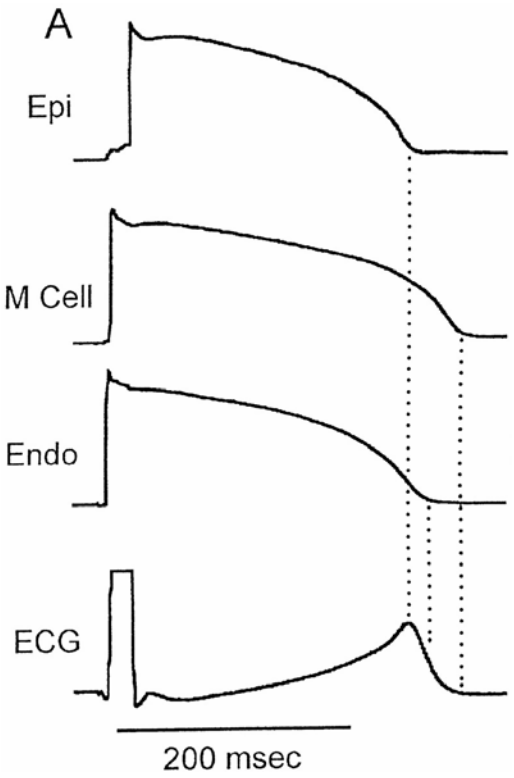



***Figure 7.*** *The apex and the end of the T-wave recorded in the pseudo-ECG were linked to the repolarization of different cell layers in the ventricular wall. The end of repolarization of the cells with the longest APDs, the midmyocardial M-cells, coincided with the end of the T wave. The end of repolarization of the cells with the shortest APDs, the epicardial cells, coincided with apex of the T wave.*
*Yan and Antzelevitch. Circulation 1998.*

preferentially lengthen the APD of cells with already the longest APD, the APD of the M cells. This increases the differences in repolarization time between M-cells and surrounding cells, thereby increasing repolarization heterogeneity and facilitating arrhythmias, which could be induced even in a small preparation as the wedge preparation[65]. Congenital long QT syndrome, types 1, 2 and 3 were mimicked in the wedge with respectively, $I_{Ks}$, $I_{Kr}$ and $I_{Na}$ inhibition[66;67]. These experiments showed that transmural repolarization heterogeneity was the culprit for torsade de pointes-like arrhythmias, and that transmural dispersion was adequately reflected in the Tapex-end interval in the pseudo-ECG of the wedge preparation.

Although their experiments were elegant and insightful, the finding that Tapex-end was a measure of transmural dispersion of the repolarization in the pseudo-ECG, recorded across the wedge preparation, led to the assumption that these findings could be extrapolated to the surface ECG[68-70]. This, however, is unlikely. First of all, one would need a transmural ECG. This is definitely not the case in ECG leads recorded with electrodes at some distance from the heart, *i.e.*, the limb leads and leads V5 and V6. Laws of physics prescribe that at every moment all leads register the electrical field generated by the heart and that the amplitude of a recorded potential is inversely dependent on the squared distance from the source. Even if in leads V2, V3 and V4, which are recorded from electrodes overlying the heart, would reflect some local information, this would be a composite of information obtained from the right ven-

tricle and information from the anterior wall of the left ventricle. Therefore also these precordial leads do not reflect pure transmural dispersion of the repolarization.
The apex of the T-wave is probably inscribed when, spreaded across the heart, most cells simultaneously repolarize. The end of the T wave is inscribed when the cells with the longest APD, wherever in the heart, are repolarized. So the Tapex-end interval has an indirect link with repolarization heterogeneity generated in the whole heart[71]. These theoretical deductions were recently evaluated by detailed mapping studies using more than 50 epi- and endocardial monophasic action potential recordings in pigs. In these experiments, the apex of the T wave coincided with the earliest repolarization of cells anywhere in the heart while the end of the T wave was recorded when the last cells repolarized, which were endocardial cells in nine out of ten pigs[72].

During electrical stimulation the origin of the Tapex-end interval is completely different. The Tapex-end interval is related to the progression of the repolarization wave front spreading from the pacing electrode through the heart[73]. The slow myocardial cell-to-cell activation has a significant influence on the de- and repolarizing time of the cells, so that not only the depolarization but also the repolarization spreads from the site of stimulation through the heart.
The opposite direction of the repolarizing current compared to the depolarizing current causes an opposite orientation of the T-wave compared to the QRS complex observed during pacing.
During abnormal, slow activation the Tapex-end interval is related to the interval from the moment the repolarization wave front approximately attains is maximal surface area (Tapex) to the moment when the last parts of heart repolarize (Tend). The areas of the heart that repolarize last are the areas that are geometrically and electrophysiologically farthest away from the pacing electrode. In chapter 5, the behavior of the Tapex-end interval during pacing is further clarified.

**QT dispersion**

In 1990, QT dispersion, calculated as the longest minus the shortest QT interval in any of the 12 standard ECG leads, was introduced as a marker of local repolarization heterogeneity[74]. Promising initial studies, in which QT dispersion was associated with arrhythmic risk[74;75], triggered a large number of studies on this new ECG index. More than 850 publications can be currently retrieved (April 2006). However, more recently, QT dispersion as a measure of local heterogeneity came under serious

criticism[76;77]. QT-interval differences in ECG leads depend on different projections of the (global) heart vector on the 12 lead vectors. The end of the QT interval in an ECG lead is partly determined by the angle of the terminal T vector with the lead vector[76]. A terminal T vector that is directed perpendicular to a lead vector, is not registered in that lead and shortens the QT interval. Therefore, the end of the T-wave in a certain lead can not be interpreted as the end of repolarization in the myocardial region closest to that lead. Thus, QT dispersion does not represent local repolarization differences. An additional problem of QT dispersion is the low reproducibility[78;79], for example due to the subjectivity involved in exclusion of low-amplitude T waves and the difficult measurement of the end of T waves in noisy ECGs. These insights strengthened the opposition against QT dispersion[80-82]. Nevertheless, QT dispersion may have a weak relation with repolarization disturbances and was associated with arrhythmias in some studies[83;84]. A large QT dispersion is for example found in patients with low amplitude T waves. Low amplitude T waves can be caused by triangulation of the APD[85], which is thought to be related to a decreased repolarization reserve in, for example, patients with the long QT syndrome, *i.e.*, the patient group in which the initial promising results were found[74].
Articles providing data on the risk-estimating capabilities of QT dispersion are still frequently published. Although QT dispersion is an indirect measure of repolarization heterogeneity, QT dispersion remains in use, probably due to habituation and its accessibility.

**T-wave amplitude**

T-wave amplitude, the maximal amplitude of the T-wave or the apex of the T-wave, reflects the maximal potential difference in the heart during the repolarization. The larger the differences in duration and amplitude of action potentials from different parts of the myocardium, the higher the T-wave amplitude becomes[86]. Syndromes or conditions associated with heterogeneity of the repolarization causing large-amplitude T waves are long QT syndrome type 1 and hyperkalemia. The high amplitude T waves of long QT-1 syndrome were realistically mimicked in wedge preparations of the canine left ventricular wall[66]. An $I_{Ks}$ blocker in combination with isoprenaline caused a relatively long APD in the M-cells, causing a high amplitude T wave in the pseudo-ECG recorded across the ventricular wall. These findings concur with the observed propensity for arrhythmias in long QT 1 patients associated with exercise[87;88]. Hyperkalemia is well known to cause high amplitude T waves and ar-

rhythmias, likely to be due to increased repolarization heterogeneity[89]. Furthermore, in the acute phase of myocardial infarction the AP of the infarcted cells changes; the upstroke velocity falls, maximum amplitude dips and APD shortens[90]. This causes potential differences between injured and normal cells and a systolic "injury" current directed from normal to ischemic cells. These injury currents cause ST elevation and increased T-wave amplitude.

Although T-wave amplitude is an indicator of repolarization heterogeneity in the above conditions, T-wave amplitude is insensitive or even misleading to certain other changes in AP morphology. Triangulation of APs in response to pro-arrhythmogenic drugs is associated with increased repolarization heterogeneity and decreases T-wave amplitude[91]. Also, long QT syndrome type 2 is typically associated with low amplitude T waves[92]. Furthermore, a high inter-individual variation in T-wave amplitude exists due to variations in body fat and internal ventricular diameter. Additionally, cancellation has a strong influence on the T-wave amplitude. Based upon animal and modeling studies Abildskov and Klein assessed the amount of cancellation during ventricular depolarization to be approximately two thirds of locally generated potential differences[93]. Based upon measurements of refactoriness by Durrer[32], Burgess and Abildskov assessed the amount of cancellation during repolarization even more than 90 %, due to opposed directions of repolarization vectors within the wall[94]. The lower T-wave amplitude observed during biventricular pacing compared to single sided pacing is probably caused by a larger cancellation of two repolarization wave fronts instead of one wave front[73;94].
In conclusion, the use of T-wave amplitude as a measure of repolarization heterogeneity has serious limitations, but T-wave amplitude may be an accurate reflection of repolarization heterogeneity in specific conditions.

**T-wave area**

T-wave area reflects magnitude and duration of repolarization differences throughout the heart. Several studies showed a relation between repolarization heterogeneity, assessed from a limited number of action potential recordings, and T-wave area. T-wave area correlated with increased repolarization heterogeneity in rabbit hearts measured by epicardial monophasic action potentials[95] In dogs, T-wave[96] and QRST[97] surface area was related to repolarization heterogeneity and a lowered threshold for ventricular fibrillation.[98] Drugs that lengthen APD of specific cell layers, for ex-

ample, $I_{Kr}$ blockers that foremost lengthen midmyocardial APD, cause an increased T-wave area in left ventricular wedge experiments[99]. Mathematical simulation studies confirmed these experimental findings. Human heart-in-thorax models showed that increased repolarization heterogeneity resulted in increased T-wave area[100;101], as presented in chapter 4 of this thesis[101].

T-wave area can be determined in individual leads or in the vector magnitude constructed by means of the inverse Dower matrix[102;103]. T-wave area can be objectively and automatically measured. Furthermore, this index is relatively insensitive to noise. Small, peaked oscillations will average out, having little influence on total T-wave area. Its disadvantage is, like T-wave amplitude, a high inter-individual variation which makes individual risk assessment difficult if only one ECG is available. Serial ECG analysis started before a potentially pro-arrhythmic event would therefore be more suited to evaluate repolarization heterogeneity by measurement of T-wave area.

**QRS-T angle**

An increased QRS-T angle is predictive for (sudden) death. Kardys et al. showed that a wide QRS-T angle predicted cardiac death in a general population of more than 6000 men and women older than 55 years [104]. After adjustment for cardiovascular risk factors, hazard ratios of abnormal QRS-T angles for sudden death were 4.6 (CI 2.5-8.5). Zabel et al. tested five ECG variables of T-wave morphology in patients after myocardial infarction [105]. Only the spatial angle between depolarization and repolarization was shown to contribute to the risk stratification of these patients, independent of classical risk factors. Other studies underscored the prognostic value of the spatial QRS-T angle and the orientation of the T axis [106-108]

The spatial angle between the QRS and T vectors is normally 78 ± 26° [109]. A small QRS-T angle is caused by a similar direction of de- and repolarization. Several pathologies may cause a wide QRS-T angle. An altered activation pattern may cause a similar de- and repolarization sequence as described in the paragraph on the Tapex-end interval. Due to the similar de- and repolarization order, but opposite direction of the currents, the QRS and T vectors then attain an opposite direction, and a large QRS-T angle. Furthermore, ischemia may alter the repolarization process and the direction of the T vector. Any other condition that disturbs the normal distribu-

tion of the action potential durations throughout the heart may increase the QRS-T angle.

The multitude of pathologies that may cause an increased QRS-T angle explains the excellent predictive value of this ECG index. Therefore, an increased QRS-T angle is a final common pathway and not very specific for increased repolarization heterogeneity. Nevertheless, this ECG index can be measured accurately (and automatically) and may therefore be useful as a general indicator of the electrophysiological status of the cardiac patient.

**T-wave complexity**

Methods used to describe the complexity of the T wave are essentially morphological descriptors of the T-waves in the ECG. We used singular value decomposition to calculate T-wave complexity in this thesis. Singular value decomposition was introduced in cardiology as an algebraic algorithm to distillate non-redundant signals from multiple leads (up to 200) obtained with body surface mapping. We used singular value decomposition to reconstruct the T waves of the eight independent ECG leads (I, II, V1-6) into 8 independent components that are by definition orthogonal to each other (Figure 8). If the T waves can be described by only the first few components, the T waves have a relatively simple shape and are similar to each other in the different leads. The more components are needed to accurately describe the T waves and thus contain a significant amount of information, the more complex the T waves. The energy contained in the eight components is quantified by the corresponding singular values. To calculate T-wave complexity, we divided the higher, more complex singular values 2 to 8 by the first, most simple singular value. Another variation we and others used was the ratio of the second to the first singular value[110]. Although one influential group used the absolute value of the singular values 4-8[111], according to our observations, these highest singular values have a low signal-to-noise ratio. Nevertheless, this method appears to have prognostic capabilities[112;113]. Furthermore, T-wave complexity has been shown to yield independent prognostic information in patients with cardiovascular disease[113]. In patients with arrhythmogenic right ventricular dysplasia, higher T-wave complexity is associated with arrhythmias [114]. Additionally, T-wave complexity is increased in patients with primary repolarization disturbances and can be used to discriminate these patients from healthy individuals [110]. Van Oosterom mathematically proved that a higher repolarization heterogeneity leads to increased T-wave complexity.[115]

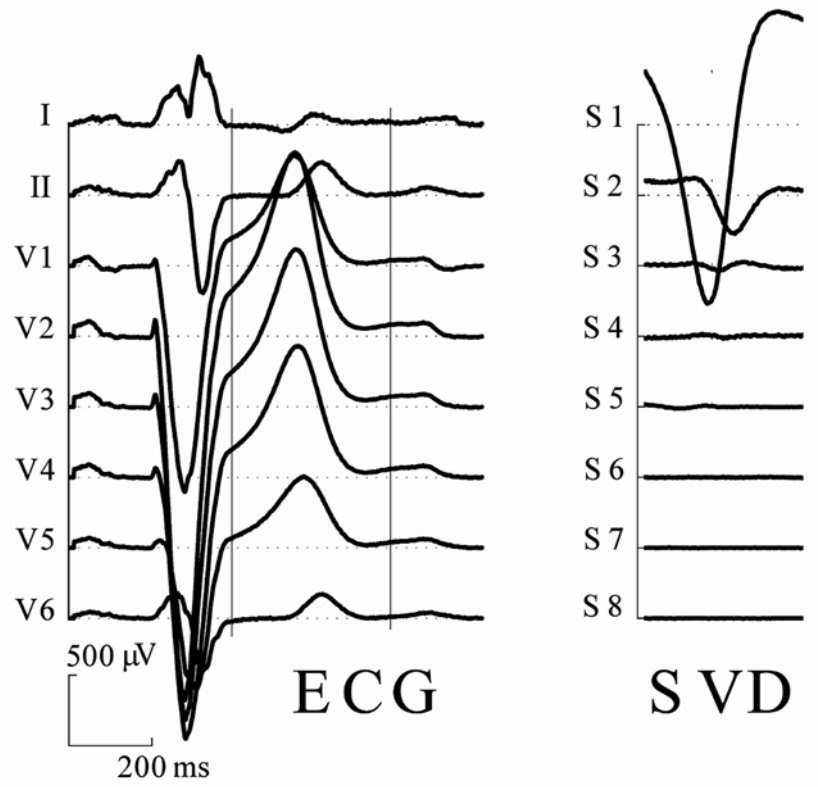



***Figure 8**. Singular value decomposition was used to reconstruct the T waves of the eight independent ECG leads (I, II, V1-6) into 8 independent components that are by definition orthogonal to each other.*

Our opening statement that T-wave complexity is essentially an index of the morphology of the T wave can now be further refined. T-wave complexity is related to the simplicity of the T-wave form; a smooth T-wave that is similar in different leads can be described by fewer singular values than an irregularly shaped T-wave. Although every clinician knows that irregular T-wave morphology deflects an abnormal repolarization, the advantage of singular value decomposition is the objective quantification of T-morphology aberrancy.

**Ventricular gradient**

The concept of the ventricular gradient was originally formulated by Wilson in 1931[29]. The ventricular gradient is calculated by summation of the integral of the spatial depolarization and repolarization vectorloops. This results in the gradients of

AP differences only, while excluding the influence of the depolarization order. When activating the heart from an ectopic focus (as a ventricular extra stimulus), the ventricular gradient was supposed to remain unaltered as the ventricular gradient reflected heterogeneity of action potential (duration and amplitude) and not the activation order. Despite the attractive theoretical background, APD appeared to be influenced by the depolarization order. Adaptation of the APD to activation order that persists after restoration of the original activation order is apparent even after a short time of ectopic activation, a phenomenon which is called T-wave memory[116]. Furthermore, the direction of the activation wavefront compared to the fiber direction has an effect on APD[117]. Moreover, the mechanism of arrhythmogenesis is dependent on repolarization differences, which is the resultant of activation and APD; or more specifically refractoriness, which has been shown to facilitate re-entry arrhythmias. Nevertheless, the ventricular gradient still reflects the APD heterogeneity, whether this APD pattern is modified by the activation pattern or not. The ventricular gradient remains an interesting concept in research-oriented ECG analysis. The ventricular gradient can be particularly useful to discern between primary and secondary repolarization changes.

**Aim and outline of the thesis**

Repolarization changes due to several interventions were evaluated by measurement of several ECG indices of repolarization heterogeneity in several groups of healthy subjects and patients. Detailed study of different ECG indices in different patient groups may provide insight in their behavior and may guide the appropriate use of these electrocardiographic indices of repolarization heterogeneity.

In chapter 2 healthy males are subjected to normotensive stress (modified tilt testing) and hypertensive stress (handgrip). Different tilt angles of the legs are applied to achieve the same heart rate during both stressors to be able to compare the effects of these stressors on electrocardiographic indices of repolarization heterogeneity without the errors introduced by heart rate correction.

An increase in sudden cardiac death has been observed during or immediately after exercise. In chapter 3 we measure electrocardiographic indices of repolarization heterogeneity during and after maximal exercise testing. The fitness level of the subjects varied from professional marathon ice skaters to untrained subjects. The response to vigorous exercise is compared in athletes with the largest hearts to the untrained subjects.

Electrocardiographic indices may differ in their reaction on increasing repolarization heterogeneity. In chapter 4 a mathematical ECG simulation model is used to observe whether various ECG indices adequately reflect increasing local repolarization heterogeneity.

In chapter 5 the electrocardiographic effects of pulmonary valve replacement in Fallot patients with dilated right ventricles are studied. In these patients QRS duration is known to be predictive of ventricular arrhythmias. We use an interactive ECG analysis program to accurately measure the QRS duration before and a half year after surgery. Changes in right ventricular end-diastolic volumes were previously studied with cardiac magnetic resonance imaging and are incorporated in the present study.

In chapter 6 we extend the analysis of the Fallot patients with electrocardiographic indices proposed to measure repolarization heterogeneity. We measure the changes in these indices due to pulmonary valve replacement and study the possible relation with arrhythmias.

Previous studies on cardiac resynchronization therapy have suggested a detrimental effect of epicardial pacing on the transmural repolarization heterogeneity, causing arrhythmias in vulnerable patients, who can be identified by electrocardiographic evaluation. In chapter 7 we study the effects of different pacing modes of cardiac resynchronization devices on electrocardiographic indices of repolarization heterogeneity. Subsequently we use a simulation model to interpret the electrocardiographic findings from our heart failure patients.

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