Chapter 2

The Role of Electrocardiographic Markers in the Prevention of Atrial and Ventricular Arrhythmias

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Additional information is available at the end of the chapter

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Abstract

In our chapter, we overview the main clinical conditions that increase arrhythmogenicity, and we present the surface electrocardiogram (ECG) markers that could be suitable for the prediction of atrial and ventricular arrhythmias. We highlight the clinical value of the prolongation of the P-wave duration and P dispersion (Pd) in the prediction of atrial fibrillation, and we also expound the utility of QT interval, T-wave peak-to-end interval (Tpe), and Tpe/QT ratio (known as arrhythmogenic index (AIX)) in the prediction of ventricular arrhythmias. Furthermore, we present the results of our clinical investigations with regard to surface ECG markers among patients with increased arrhythmia vulnerability. Moreover, we mention other, novel, effectively used ECG markers.

Keywords: atrial fibrillation, P dispersion, P-wave interval, QT interval, T-wave peak-to-end interval, ECG markers, ventricular arrhythmias

1. Introduction

There are several diseases which may affect the pulse generation and the conduction in the heart. Patients suffering from these clinical conditions have increased probability for the occurrence of atrial and ventricular arrhythmias [1–4]. Numerous studies have been dealing with certain surface electrocardiogram (ECG) markers which could be suitable for the prevention of various cardiac rhythm disturbances [5–7]. Previously, it has been shown that the prolongation of the P-wave duration and P dispersion (Pd) can predict atrial arrhythmias [5, 8, 9]. Moreover, it has also been demonstrated that the prolongation of QT interval, T-wave peak-to-end interval (Tpe) and Tpe/QT ratio (known as arrhythmogenic index—AIX) could

predict ventricular arrhythmias [6, 7]. In our chapter we would like to present the electrophysiological substrates and pathogenetic factors taking part in arrhythmogenesis and to demonstrate ECG-based diagnostic opportunities that can help in the prediction and prevention of arrhythmias. Furthermore, we present the results of our studies to demonstrate the clinical use of these ECG markers.

2. Non-invasive electrocardiographic markers in the prediction of atrial fibrillation

2.1. Epidemiology and electrophysiological background of atrial fibrillation

The most common form of rhythm disturbances is atrial fibrillation (AF). Its prevalence is 0.12–0.16% among people younger than 49 years, 3.7–4.2% with regard to people aged 60–70 years and 10–17% among people aged 80 years or older [10]. Age, gender, hypertension, diabetes mellitus, heart failure and valvular heart disease are independent risk factors that may play a role in arrhythmogenesis. Moreover, AF may be caused by hyperthyroidism and excessive alcohol consumption [11, 12] (**Table 1**).

Cardiovascular causes of atrial fibrillation (%)	
Ischemic heart disease	17
Hypertensive cardiomyopathy	21
Valvulopathies	15
Dilated cardiomyopathy	9
Hypertrophic cardiomyopathy	5
Other structural heart diseases	9
Non-structural heart diseases	29

Table 1. Cardiovascular causes of atrial fibrillation.

In patients with end-stage renal failure, its prevalence is approximately 13%. Interestingly, 10% of subjects suffering from 'lone' AF have no comorbidity, detectable underlying structural or functional heart disease. Previous studies have also demonstrated that nearly 30% of patients with atrial fibrillation may have a positive family history. The predisposition for arrhythmia events was shown to be inherited in an autosomal dominant pattern. In a small proportion of familial AF, specific mutant genes were identified, and mutations were detected mainly in KCNE2, KCNJ2, and KCNQ1. While encoding the protein products of certain potassium channels, these are suggested to play a role in the maintenance of sinus rhythm [13–16].

Atrial anisotropy is thought to be one of the key points of increased atrial arrhythmia vulnerability, where the inhomogeneous spreading of atrial impulses can be secondary to an altered histological structure of the atrial myocardium (hypertrophy, fibrosis, and fatty degeneration)

[17–19]. Consequently, the dilation of both atria may appear representing an increased susceptibility for atrial arrhythmias [20]. Furthermore, increase in cardiac preload and afterload and electrolyte imbalances may also have an additive role in the increase of atrial arrhythmogenicity and reentry mechanism, where the latter is the electrophysiological substrate for atrial fibrillation.

2.2. Clinical consequences of atrial fibrillation

Irregular and high ventricular response due to AF, atrioventricular dissociation and the lack of atrial systole may contribute to low cardiac output syndrome. Patients usually complain about palpitation, fatigue, dyspnea, vertigo/dizziness, and chest pain. However, 11% of these patients are asymptomatic. Decrease in atrial blood flow velocity gives the chance for atrial thrombus formation. Mortality caused by atrial fibrillation is primarily connected with an increased risk for thromboembolic events and stroke (**Figure 1**) [10, 11, 21].

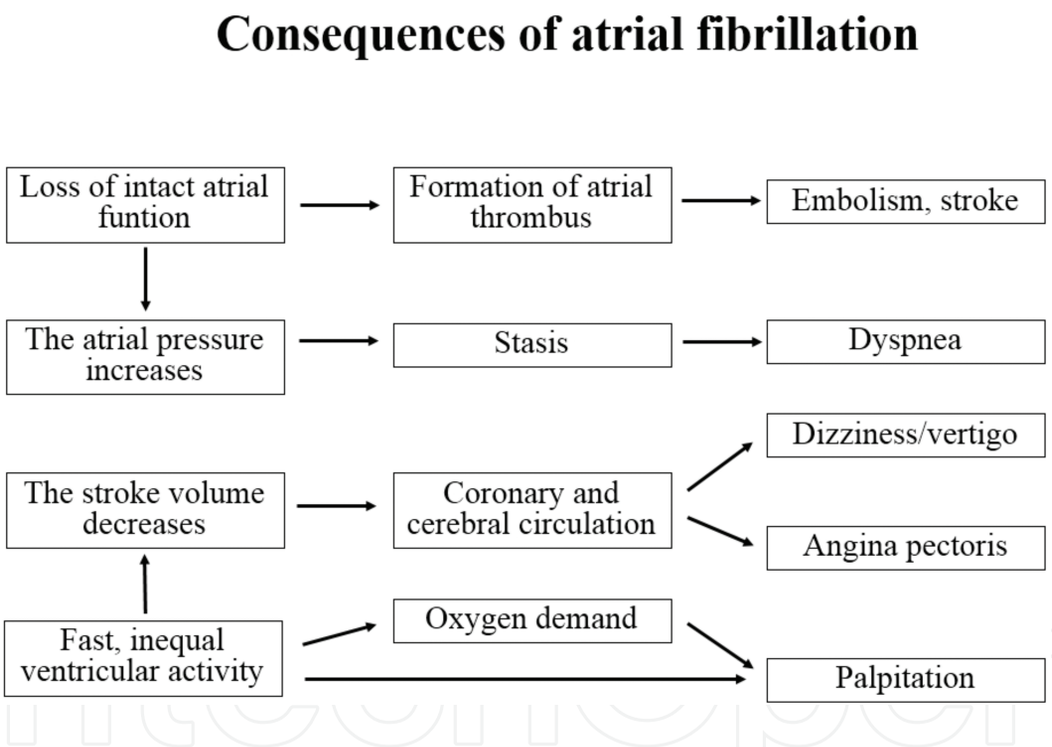

Figure 1. Pathomechanism and consequences of atrial fibrillation.

2.3. Electrocardiographic prediction of AF

2.3.1. P-wave duration and P dispersion

Due to the structural and electrophysiological heterogeneity of the left atrium, unidirectional block can occur, which plays a role in the genesis of atrial microreentry and premature beats. In patients with paroxysmal atrial fibrillation during sinus rhythm, the intra- and interatrial conduction time of the sinus impulse were shown to lengthen, and the duration of the P wave

measured on a surface electrocardiogram (ECG) is increased, where the prolongation of atrial conduction time is proportional with the duration of P-wave interval. Previously, it has also been shown that the prolongation of P-wave duration and P dispersion (Pd) can predict atrial arrhythmias. P-wave duration of the surface electrocardiogram is specified as the section from the first electrical activity following the T wave (or the U wave) to the intersection of the P wave's descending branch and the isoelectric line. The investigator should analyze three consecutive P waves each lead and calculate their average duration, where the result is the P wave duration in the given lead (**Figure 2**). P dispersion (Pd) is determined as the difference between the longest and shortest P interval. P interval and Pd can be corrected to the heart rate (Pmaxc, Pdc) according to Bazett's formula (Pmaxc = Pmax/√RR (ms), Pdc = Pd/√RR (ms)) (**Figure 2**) [5, 8, 9].

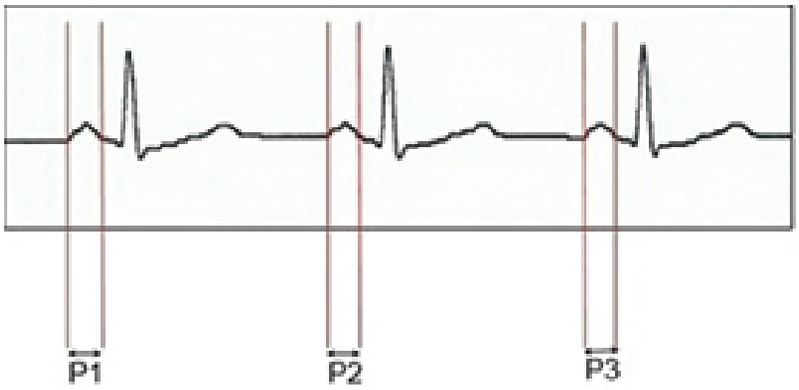

Figure 2. Measurement of P-wave duration on the surface ECG.

2.3.2. Alterations of P-wave duration and P dispersion among patients participating renal replacement therapy

The incidence of atrial fibrillation is increased during hemodialysis (HD), and the prolongation of P-wave duration has been shown to be a valuable indicator of atrial conduction disturbances. Based on the aforementioned, we analyzed the length of P-wave interval and P dispersion on the surface ECG of 28 patients with end-stage renal failure on extracorporeal renal replacement therapies. According to our results, P-wave duration and P dispersion increased significantly at the end of the hemodialysis sessions compared to those measured at the beginning, and they remained lengthened 2 hours after the treatment [22]. Previously, a novel convective-transport-based renal replacement method, the hemodiafiltration (HDF), has been introduced. Lately, convective treatment has been proven to reduce mortality of these particular patients with end-stage kidney disease. This favorable effect of HDF may be partly caused by the decreased occurrence of atrial and ventricular arrhythmias. We intended to examine whether these suggested differences between hemodialysis and hemodiafiltration with regard to arrhythmia vulnerability could be shown as alterations of P interval and P dispersion on the surface ECG. We obtained clinical data from 30 patients receiving HDF over a period of 3 months; and the same group of patients was then evaluated during treatment with conventional HD for at least

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another 3 months. The duration of the P wave and Pd increased significantly during HD, but no such significant prolongations were observed in the case of HDF (**Figure 3**) [23].

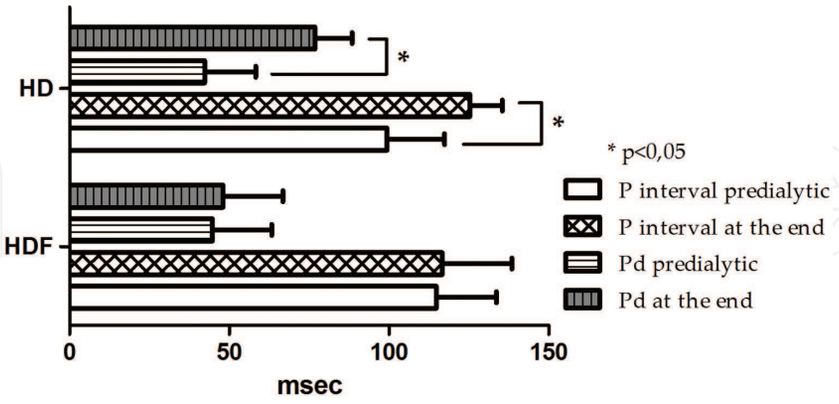

Figure 3. Changes in corrected P-wave duration (P interval) and corrected P dispersion (Pd) during hemodialysis and hemodiafiltration.

2.3.3. Biphasic P wave

Slow and inhomogeneous atrial conduction, thus atrial anisotropy, can appear as biphasic P wave in the inferior electrocardiographic leads (leads II, III, and aVF). In nearly 75% of patients with paroxysmal, AF has an increased duration of the initial portion of P wave in lead III [24]. Various investigations have reported the clinical value of P-wave measurements in the prediction of AF (**Table 2**) [22, 23, 25–30].

Underlying clinical condition	References
Hyperthyroidism	[25, 26]
Postcardiac surgery	[27, 28]
Renal failure and renal replacement therapy	[22, 23]
Pulmonary diseases	[29, 30]

Table 2. Studies which investigated alterations of the atrial phase of surface ECG.

2.3.4. Investigation of Ta wave

Inhomogeneous atrial repolarization may also play an additive role in the genesis of atrial arrhythmias and paroxysmal atrial fibrillation. Therefore, ECG analysis of atrial repolarization may provide further data on atrial arrhythmia vulnerability. Recently, a novel electrocardiographic marker the atrial T wave, also known Ta wave, has been shown to characterize atrial repolarization in patients with sinus rhythm. Due to its small amplitude within the PQ segment, signal averaging is necessary to soften the measurements. Moreover, in patients with physiologic atrioventricular conduction, it is generally localized in the subsequent QRS complex (name for the combination of three of the graphical deflections seen on a surface ECG

which corresponds to the ventricular depolarization) holding the measurements to be impossible. Nevertheless, characteristics of the detectable atrial repolarization phase of the ECG have been compared between individuals with sinus rhythm and paroxysmal AF. However, no significant differences with regard to the morphology, amplitude and length of Ta wave have been clearly elucidated yet [31].

3. Ventricular arrhythmias and sudden cardiac death

3.1. The role of electrocardiographic markers in the prevention of ventricular rhythm disturbances and sudden cardiac death

Despite the improvement in statistical data, cardiovascular diseases are responsible for approximately 17 million deaths every year in the world, where approximately 25% is related to sudden cardiac death [32]. Malignant ventricular arrhythmias (e.g. ventricular tachycardia and ventricular fibrillation) are the most important underlying rhythm disturbances responsible for these unfavorable statistics. The incidence of these ventricular arrhythmias correlates with age primarily due to the higher prevalence of coronary artery disease [33]. Sudden cardiac death has an estimated incidence of 1100–9000 in Europe and 800–6200 in the United States every year [32].

3.2. Pathomechanism of ventricular arrhythmias and sudden cardiac death

Various factors have been shown to play a role in the genesis of ventricular arrhythmias. Both congenital factors and acquired pathophysiological mechanisms can provoke these cardiac rhythm disturbances [33]. Previously, it has been demonstrated that *genetic predisposition* can contribute to the genesis of sudden cardiac death. Fifty percent increase has been confirmed in the likelihood of the occurrence of malignant ventricular arrhythmias in the presence of a family history of sudden cardiac death [34]. Furthermore, it has been shown that familial sudden death appears more frequently in patients resuscitated from primary ventricular fibrillation [35]. Previously, single nucleotide polymorphisms located in the 21q21 and 2q24.2 loci have been also shown to increase the risk of sudden cardiac death [36, 37]. However, certain concerns were raised with regard to these results, and further investigations are needed. The risk of sudden cardiac death is higher in males [38, 39]. On the other hand, coronary artery disease, ischemic cardiomyopathy and heart failure, hypertensive heart disease, and lipid abnormalities are the most important *acquired* provoking factors with regard to ventricular arrhythmogenesis and sudden cardiac death [3, 38]. Interestingly, kidney disease and hemodialysis itself have been demonstrated to be significant underlying substrates for the genesis of ventricular arrhythmias. The incidence of sudden cardiac death in patients suffering from kidney diseases was shown to be approximately 1.4–25% [4]. Furthermore, physical inactivity, smoking, alcohol abuse, and inadequate alimentation are significant pathophysiologic factors that may contribute to ventricular arrhythmogenesis [39] (**Table 3**). Most importantly 50% of sudden death appears in patients without a previously known heart disease, but most of these individuals suffer from ischemic heart disease. Therefore, 40% of the reduction in sudden

arrhythmia death is due to the effective management and prevention of coronary artery disease [38, 39]. Left ventricular systolic dysfunction has also been proven to be an important underlying factor for ventricular arrhythmogenesis. Left ventricular ejection fraction, an echocardiographic parameter, has been shown in association with increased probability for sudden cardiac death mainly in patients with myocardial infarction. Related to heart failure, certain biochemical indicators such as the B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide have also been shown to be useful in the risk stratification of sudden cardiac death [40, 41].

Congenital or acquired causes	Temporary factors
• Coronary artery disease	• Electrolyte imbalance
	◦ Hypokalemia, hypomagnesemia
• Hypertensive heart disease	• Endocrinological disorders
	◦ Thyroid
	◦ Suprarenal gland
• Cardiomyopathies	• Myocarditis
◦ Hypertrophic	• Pericarditis
◦ Dilated	
◦ Right ventricular dysplasia	
• Valvular diseases	• Toxic effects
	◦ Alcohol
	◦ Certain antibiotics
	◦ Antifungal agents
	◦ Antidepressants
• Primary electrophysiologic causes (channelopathies)	• PH abnormalities
◦ Brugada syndrome	• Smoking
◦ Long QT syndrome	
◦ Short QT syndrome	
• Congenital heart diseases	• Postoperative period
• Comorbid factors	• Malnutrition
◦ Pulmonary diseases	• Abdominal distension
◦ Kidney disease	

Table 3. Common causes of ventricular arrhythmias are shown. Congenital and acquired diseases may play a role in ventricular arrhythmogenesis; furthermore, temporary factors can additionally increase the susceptibility for rhythm disturbances.

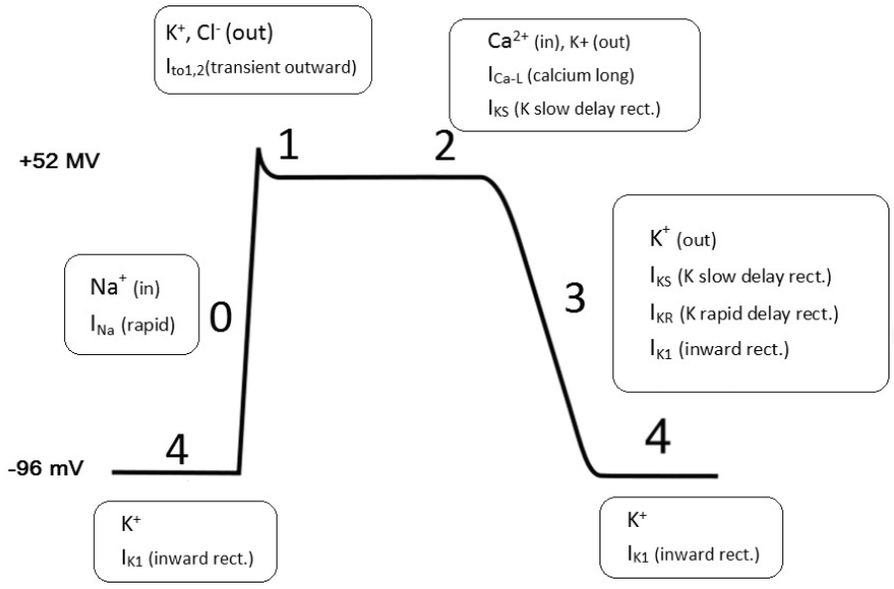

Figure 4. The monophasic action potential of a ventricular myocardial cell is shown. The plateau phase largely depends on the potassium and the calcium ion channel activity. The longer the plateau phase, the more increased the myocardial cell's repolarization. M cells show a prominent prolongation in action potential diameter and develop early after depolarizations in response to rapidly activating delayed rectifier potassium current (IKr) blockers.

3.3. Ventricular repolarization and cardiac arrhythmias

Secondary to the pathophysiologic factors, the electrophysiological properties of the myocardial cells can change, resulting in the modification of the duration and amplitude of the monophasic action potential featuring the myocardial cell's electrical properties (**Figure 4**) [42]. As a result, inhomogeneous ventricular repolarization and anisotropy may appear, which seem to be one of the electrophysiological key points in the genesis of ventricular arrhythmias. Previously, it has been shown that a mid-myocardial population of cardiac myocytes (e.g. M cells) can play an important role in the prolongation of repolarizational dispersion [43, 44]. From an electrophysiologic point of view, these special cells have been shown to be between Purkinje and ventricular myocytes, while they show a significant prolongation in action potential diameter and develop early after depolarizations in response to rapidly activating delayed rectifier potassium current (IKr) blockers [45]. In the meantime epicardial and endocardial myocytes are less likely to do so. Accordingly, due to certain drug therapies (e.g. amiodarone and sotalol) or other provoking factors, an exaggerated dispersion in transmural action potential duration may come alive, resulting in an increased danger of transmural inhomogeneity of ventricular repolarization and an increased susceptibility for ventricular arrhythmias (**Figure 4**) [42, 46].

3.4. QT interval and dispersion

QT interval represents the electrical repolarization of the ventricular myocardium. Patients with increased susceptibility for the development of malignant ventricular dysrhythmias can be identified with the determination of QT interval [47]. Duration of the QT interval is changing

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in the different leads of the surface electrocardiogram. QT dispersion (QTd) is derived from the interlead alterations of QT intervals. This is a useful parameter to describe the differences in ventricular recovery times representing the prolongation of myocardial repolarization [48]. QT dispersion has also been proven to correlate with the duration of the monophasic action potential of the epicardial myocardial cells. Since these electrocardiographic markers have been introduced to predict ventricular arrhythmias and sudden cardiac death, they are considered to be among one of the non-invasive parameters [49]. The prolongation of QT interval can be congenital (e.g. Romano-Ward or Jervell and Lange-Nielsen syndromes) or acquired. Congenital syndromes are caused by mutations in at least five different ion channel genes resulting in the defects in the sodium channel (SCN5A, LQT3), the rapidly activating delayed rectifier channel (IKr) (HERG, LQT2 or KCNE2, LQT6), and the slowly activating delayed rectifier channel (IKs) (KvLQT1, LQT1 or KCNE1, LQT5), respectively [50]. QT prolongation can be acquired and may occur after acute myocardial infarction, congestive heath failure, dyslipidemia, diabetes mellitus, sudden sympathetic autonomic activation (triggered activity) and renal failure [6, 51–55]. In individuals with liver cirrhosis, the lengthening of QT interval has not been shown to be related to the etiology of the liver disease and seems to appear both in alcoholic and nonalcoholic patients [46]. In addition, QT prolongation may be associated to certain drug interactions (e.g. haloperidol, methadone, amiodarone, sotalol, selective serotonin reuptake inhibitors, macrolide antibiotics, and antifungal agents) [56]. QT dispersion may also be affected by various diseases (amyloidosis, sarcoidosis, carcinoid, hemochromatosis, diabetes mellitus, thyroid dysfunction, or Parkinson's disease) [57–63].

3.5. QT measurements and their clinical use

Since these repolarizational variables are modified by numerous causes, the thorough investigation of patient's history is one of the leading points during the determination of arrhythmia risk. Considering the required standards for precision, the measurement of QT interval still remains subjective as the terminal point of the T wave usually cannot be clearly defined. QT interval can be measured manually or automatically [49, 64]. During manual investigations, improvement in consistency of the results and the minimization of interobserver variability may be achieved by the measurements performed by one examiner. During the threshold method, the point where the T wave reaches the isoelectric line is determined as its end. According to the tangent method, the end of T wave is defined as the point where a given tangent line overtakes the isoelectric line, where the tangent line is the last part of the T wave at its maximum downslope. To get more accurate data, the average of three sequential periods in a given lead is calculated and defined as QT interval [47, 48] (**Figure 5**). QT measurements may also be performed by means of computers with the superimposed median beat method, where an electrocardiographic complex is constructed for each of the 12 leads. These medians are superimposed on each other. Afterwards, QT interval is determined from the earliest onset of the Q wave to the latest offset of the T wave. Moreover, QT interval can be measured from the point of maximum convergence for the Q-wave onset to the T-wave offset [48].

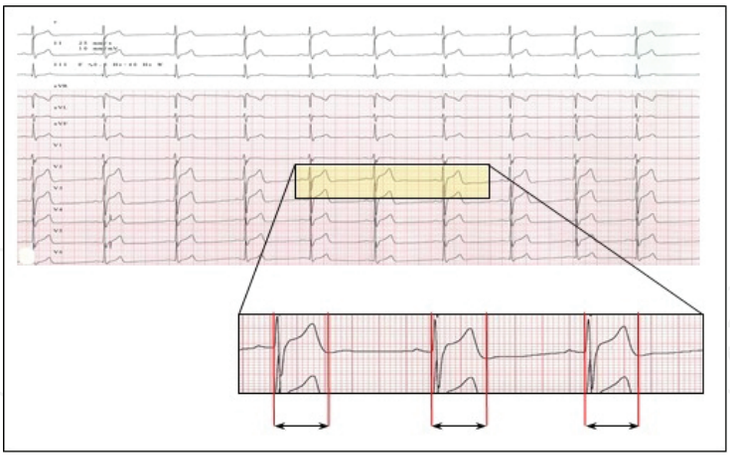

Figure 5. The manual measurement of the QT interval of the 12-lead surface electrocardiogram. The calculation and averaging of three consecutive sections may provide a more accurate result in the given lead.

Ventricular rate has a significant influence on QT interval's duration. When heart rate accelerates, QT interval shortens. Therefore, QT interval has to be corrected to heart rate (QTc) using the Bazett's formula ($QTc = QT/\sqrt{RR}$) (borderline QTc, male 431–450 ms and female 451–470 ms; abnormal QTc, male ≥ 451 ms and female ≥471 ms). Normal values of QT dispersion vary in a very wide range from 10 to 71 ms. The QTc >450 ms value has been reported to have an increased risk for ventricular arrhythmias [49]. With regard to patients suffering from liver cirrhosis, a special relationship between QT interval duration and heart rate exists; thus, a specific 'cirrhosis formula'—similar to the Fridericia's—should be used. Measurement of QT interval and dispersion can help in the monitoring of antiarrhythmic therapy especially with the widely used antiarrhythmic drugs, amiodarone and sotalol [46, 56]. Previously, the prolongation of the QT dispersion has been shown to represent recurrent ischemia after percutaneous transluminal coronary angioplasty. Lately, the eligibility of QT dispersion in the evaluation of long-term outcome of patients waiting for cardiac transplantation has also been discussed. Life-threatening ventricular rhythm disturbances of patients with long QT syndromes often caused by a sudden increase in sympathetic activity, and beta-blockers have been shown to significantly reduce these arrhythmic episodes. In patients who remain symptomatic despite treatment with beta-blockers (mostly patients with LQT2 and LQT3), left cardiac sympathetic denervation may be a therapeutic solution. In the case of cardiac arrest, ICD should be implanted; however, there are controversial data regarding the ICD therapy in subjects with no such previous history [47, 49, 50].

3.5.1. Changes in QT interval and QT dispersion in hyperlipidemia and kidney disease

The susceptibility to malignant ventricular arrhythmias increases proportionally with the lengthening of QT interval. Progressive atherosclerosis is an independent risk factor of the occurrence of sudden cardiac death. In our study clinical data of 96 patients with hyperlipidemia were compared to 103 controls. Serum LDL-C (low density lipoprotein – cholesterol) and Tg levels were positively correlated with corrected QT interval and QT dispersion, so lipid parameters may affect these ECG markers [65]. Furthermore, we investigated the ECG

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parameters representing ventricular repolarization in the case of 30 patients receiving hemodiafiltration (HDF) over a period of 3 months, and we obtained data from the same patients after treatment with conventional hemodialysis (HD) for at least another 3 months. The duration of the QT interval and QT dispersion was only increased significantly in the case of HD, but no similar significant prolongations in the case of HDF could be observed (**Figure 6**) [66].

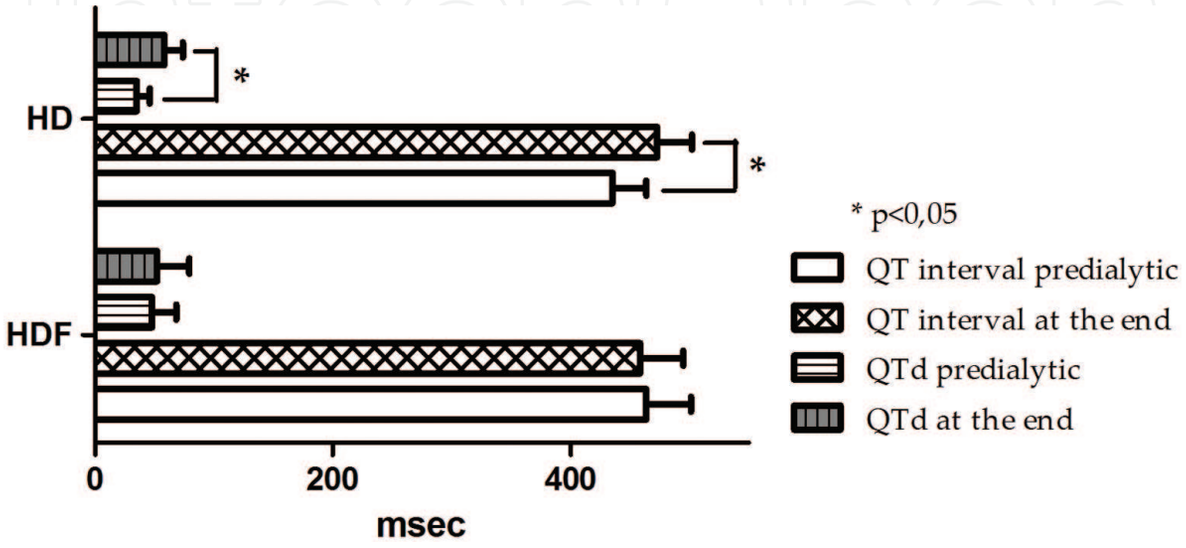

Figure 6. Prolongation of corrected QT interval and corrected QT dispersion (QTd) during different renal replacement therapies.

3.6. QT variability

Previously, numerous studies have been dealing with the beat-to-beat variability in QT interval of the surface electrocardiogram in order to quantify temporal dispersion of ventricular repolarization [67]. Its increase has been associated to long QT syndrome, heart failure, myocardial ischemia, hypertrophic cardiomyopathy, and panic disorder [68–72]. Increased QT variability has also been shown to predict appropriate implantable cardioverter-defibrillator shocks. Moreover, increased variability has been observed with regard to sudden cardiac death in patients with myocardial infarction without ICD therapy [73, 74]. QT variability may also increase in healthy people with postural change from the supine to standing position and after activities that increase beta-adrenergic tone [75]. QT variability is measured by a special computer algorithm that is able to analyze QT-interval signals that are derived from multiple channels [76].

3.7. Short QT syndrome

Short QT syndrome, an inherited disease, is characterized by QT interval <300 ms and an increased risk for paroxysmal atrial fibrillation and ventricular arrhythmias. Short QT syndrome is also related to an increased risk of sudden cardiac death, likely caused by

ventricular fibrillation [77]. More genetic mutations of sodium and calcium channels have been reported to be an underlying substrate for this clinical entity (KCNH2, KCNQ1 and KCNJ2). Increased activity of outward potassium currents in phase 2 and phase 3 leads to the decreased duration of cardiac action potential, resulting in the shortening of refractory periods. This mechanism is thought to be responsible for the genesis of reentry mechanism and increased dispersion of ventricular repolarization [77, 78]. Besides ICD, antiarrhythmic drug therapy also has to be taken into consideration. Only quinidine, a sodium channel blocker, has been shown to normalize the QT interval at resting heart rates, while it restored the heart rate dependence of QT interval towards an adaptation range of healthy individuals by prolonging the duration of cardiac action potential [79, 80]. However its further effects remain to be elucidated.

3.8. Early repolarization

Recently, a J-point elevation of ≥0.1 mV in two adjacent leads occurring on the surface electrocardiogram manifested as terminal QRS slurring (the transition from the QRS segment to the ST segment) or notching (a positive deflection inscribed on terminal QRS complex) associated with concave upward ST-segment elevation and prominent T waves has been introduced as an early-repolarization (ER) pattern [81, 82]. A transmural voltage gradient between the ventricular epicardium and endocardium may be responsible for this phenomenon [83, 84]. ER commonly occurs in the general population (approximately 10%) and often exists in athletes and youngsters and at slower heart rates in individuals without known cardiac diseases [85]. However, recently, studies have emphasized a possible link between ER and life-threatening ventricular dysrhythmias [86]. The electrocardiographic signs of ER may be associated with a shorter QT interval and can display high dynamicity affected by ventricular rate and pauses, mediators of autonomic nervous system, androgen hormones and certain drugs (sodium channel blockers, beta-blockers, quinidine and isoproterenol) [87–91]. Importantly, a distinction between ER, short QT and Brugada syndromes sometimes proves to be difficult on the basis of electrocardiography, where genetic tests may be valuable in identifying the underlying ion channel defect [89, 92, 93]. Subjects with ECG signs of classic ER have minimal risk for ventricular arrhythmias, and the recognition of high-risk patients is often a real challenge [93, 94]. The susceptibility for ventricular arrhythmias may increase when ER is associated with heart failure, hypokalemia or acute coronary syndrome [95, 96]. Furthermore, the family history of ERS or sudden death, the extension of electrocardiographic signs of ER into a Brugada syndrome pattern, the presence of horizontal ST segment following the J wave, ER signs localized in inferior or infero-lateral leads, the presence of coupled ventricular premature beats, increase in parasympathetic tone, also the association of ER with short QT intervals, young age and male gender draw the attention to a higher arrhythmia risk [94, 97–99]. In high-risk patients with ER syndrome and a family history of sudden death, quinidine and/or ICD implantation can be a therapeutic solution. Furthermore, cilostazol, a phosphodiesterase III inhibitor, has been shown to normalize the aforementioned ECG changes. In the case of ER syndrome-mediated electrical changes, a beta-adrenergic agent (e.g. isoproterenol) may be a useful therapeutic solution [100].

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3.9. T-wave alternans (TWA) and T-wave peak-to-end interval

T-wave alternans is defined as an alteration in the morphology of the T wave in an AB-AB or every-other-beat pattern (**Figure 7**). It has been introduced as a non-invasive ECG marker for evaluating spatiotemporal heterogeneity of ventricular repolarization [101]. By reflecting the intracellular changes in calcium handling and showing beat-to-beat alternations of action potential duration of the ventricular cells, this electrocardiographic parameter seems to be capable for the prediction of ventricular repolarizational heterogeneity and the predisposition for ventricular arrhythmias [102].

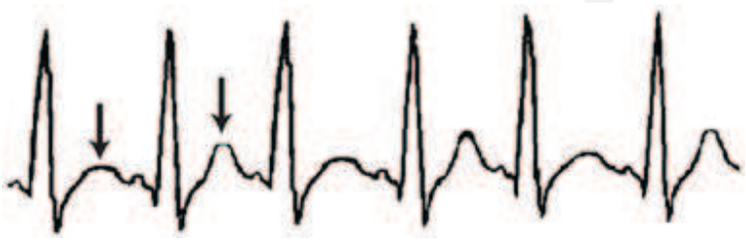

Figure 7. Alternation in the morphology of T waves on the surface electrocardiogram. Based on Narayan [101].

The electronic filtering of the T wave on a 'microvolt level' (i.e. microvolt T-wave alternans (MTWA)) creates even greater applicability of this non-invasive electrocardiographic method [103]. Therefore, MTWA has also been introduced as a valuable tool for the risk stratification of sudden cardiac death. Importantly, MTWA seems to have a particular role in the risk stratification between patients who need implantable cardiac defibrillators and those who do not [103–105]. TWA test is usually conducted during treadmill or bicycle exercise or with the administration of chronotropic agents in order to achieve an optimal ventricular rate, since TWA may occur in normal individuals at heart rates >120 beats/min. Occasionally, pacemaker stimulation required to maintain stable ventricular frequency. A target ventricular rate range of 105–110/min was determined for pathologic alternans in adults. If ectopic or premature beats constitute >10% of beats, the affected portion of the electrocardiogram is not recommended for TWA examination [106–108]. MTWA tests' results can be positive, negative or indeterminate. Patients with indeterminate results have to be investigated again [109]. In the case of a negative test, the probability of malignant ventricular arrhythmias and sudden cardiac death are low (with 98% accuracy for follow-up periods of 12–24 months in clinical studies) [110]. However, these patients have to undergo a repeated investigation every 12–24 months. Subjects with a negative MTWA test are not likely to require a defibrillator. Importantly, TWA testing may be equivalent to an electrophysiology study. Nevertheless, at present there is no definitive evidence available that can prove the real effectiveness of this method in guiding the antiarrhythmic treatment [107]. Previously a novel electrocardiographic marker, T-wave peak-to-end interval (Tpe) has been reported to represent the transmural dispersion of repolarization of the left ventricle and the vulnerability to ventricular arrhythmias [6, 111]. The prolongation of Tpe has been shown to be associated with increased mortality rates in long QT syndrome, acute myocardial infarction, sleep apnea and hypertrophic cardiomyopathy [6, 111, 112].

Reference value of T-wave peak-to-end interval is considered to be 94 ms in the case of male and 92 ms with regard to female subjects [113]. In addition, the Tpe/QT ratio is used as an arrhythmogenic index (AIX) of ventricular arrhythmogenesis [7, 114]. It has been demonstrated that in patients with acquired QT syndrome, the Tpe/QT ratio is superior to QT interval and QT dispersion in the prediction of torsades de pointes ventricular tachycardia [115]. Also, Tpe/QT ratio was shown to be a valuable predictor of sudden cardiac death [116–118].

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