

THESIS  
FOR THE DEGREE OF Ph.D.

Examination of atrial and ventricular arrhythmogeneity with surface  
electrocardiography during haemodialysis and in patients with dyslipidaemia

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## 1. Introduction

Atrial fibrillation is one of the most common arrhythmias managed in everyday clinical practice. Its incidence increases with age and the presence of structural heart disease. Increased risk of thromboembolic and stroke complications raise the clinical importance of this arrhythmia. Although the causes are diverse, hypertensive, ischemic and valvular heart disease, pericarditis and dilated cardiomyopathy, ionic disturbances and autonomic dysfunction are common. Most of the patients suffering from kidney disease have these abnormalities. Atrial fibrillation is characterized by multiple circulating reentrant wavelets due to disorganized atrial depolarization. Increased atrial dimension, decreased conduction velocity and shortened atrial refractory time are considered to be important causes for this mechanism. Recently, non invasive ECG methods have been introduced to assess the atrial arrhythmia risk of patients. Atrial arrhythmias frequently occur during haemodialysis, but uniform prevention methods are still not available.

Ventricular arrhythmias and as a consequence sudden cardiac death lead to the worsening of cardiovascular morbidity and mortality. Regarding 70 per cent of the arrhythmia cases the underlying cause is coronary artery disease. According to epidemiologic studies in the progression of atherosclerosis age, gender, underlying genetic features, hypertension, oral anticoncipients and last, but not at least lipid abnormalities play an important role. Numerous working groups have dealt with the effects of myocardial ischaemia on ECG morphology, however, the possible direct effect of lipoproteins on ventricular arrhythmogeneity in patients without ischemic heart disease have not been clearly defined yet. The inhomogeneity in repolarisation of the ventricular myocardium increases the danger of ventricular, life threatening arrhythmias. Recently, widespread non-invasive investigations have been introduced to evaluate the risk of ventricular arrhythmias (ECG, Holter ECG, stress test, signal averaged ECG, heart rate variability, baroreceptor sensitivity, echocardiography). It was realized, that repolarization changes in the ventricular myocardium may lead to the modification of certain parameters of the 12 lead surface electrocardiogram. Regarding heart diseases associated with high risk of arrhythmias, the danger of an arrhythmia event might be evaluated with the help of electrocardiographic markers. On the other hand, the direct effects of lipoproteins on ventricular arrhythmogeneity in patients without ischemic heart disease have not been clearly elucidated yet.

Clinical observations, collecting data, processing statistical results are the basic conditions of effective curative work. Relationship between arrhythmia research and everyday clinical

practice is signed by the fact, that the results of scientific studies become the essential part of clinical work in a short period of time.

## 2. Background

### 2.1. Epidemiology and causes of arrhythmias in end stage renal failure

The danger of various arrhythmias is increased in patients with end stage renal failure. Cardiovascular mortality proves to decrease in the average population, however, there is no similar tendency regarding patients receiving haemodialysis. Despite the continuous improvement of dialysis technology the cardiovascular mortality of patients with renal failure higher, than 50 % of all cause mortality, and its incidence is 17-times higher compared to the healthy population. Sudden cardiac death appears 1,4-25 % of haemodialized patients. Increased arrhythmia risk is partly caused by rapid changes in electrolyte levels and intracellular disturbances of potassium and calcium. Haemodialysis performed twice or three times weekly causes intermittent volume and pressure overload on the heart, which may influence atrial and ventricular wall stretch and exerts an unfavorable influence on myocardial vulnerability. Increased arrhythmia risk may be associated with myocardial hypertrophy (prevalence in patients with renal failure is approximately 56 %), which is often caused by hypertension, anaemia and accumulation of aluminium in the myocardial tissue. In patients with left ventricular mass index  $> 125$  g/m<sup>2</sup> the prognosis is worsened. Atherosclerosis is accelerated in patients with chronic renal failure due to decreased antioxidant activity and the so called atherogenic dyslipidaemia resulting in the decrease of coronary reserve capacity leading to myocardial ischaemia. The level of parathormone, angiotensin II, endothelin-1 may increase in uraemia leading to fibroblast proliferation in the myocardium. Consequently, myocardial fibrosis may occur which might be the anatomical substrate for various arrhythmias. In uraemia secondary hyperparathyroidism is often associated with the calcification of the myocardium resulting in heart failure, furthermore aortic and mitral valve calcification might be present. Owing to uraemic toxins pericarditis or myocarditis may appear, which contribute to the genesis of arrhythmias. Moreover, the dysfunction of the autonomic nerve system and an increased sensitivity to catecholamines may also play a role in the appearance of rhythm disturbances. Amyloidosis connected with haemodialysis - resulting in pulse generating and conducting disturbances, sudden cardiac death - may appear in the first years of treatment, though in 15 years all patients might be involved.

## 2.2. Causes of atrial fibrillation and associated P wave changes

Atrial fibrillation appears in 3-5 % of patients older, than 65 years. Cardiac pump function may be decreased due to the lack of atrial contraction and the irregular ventricular movement. Fast ventricular response to atrial tachyarrhythmias may lead to angina pectoris, hypotension and serious haemodynamic deterioration, also further malignant ventricular arrhythmias may occur and the risk of thromboembolic events is increased. The chance of a stroke is 17-times higher in atrial fibrillation patients suffering from valvulopathy. Recently, electrophysiological studies have demonstrated that patients suffering from atrial fibrillation have longer intraatrial and interatrial conduction time of sinus impulses. Inhomogenous propagation of sinus impulses can be caused by altered microarchitecture and nonuniform anisotropic properties of the atrium, increased heart chamber size, wall thickness and pressure or volume overload conditions. Intra-, or intercellular factors may lead to site specific conduction differences. Due to atrial structural and electrophysiological heterogeneity, unidirectional blockage may occur, which plays an important role in the genesis of atrial premature complexes and reentry that may lead to fibrillation. P wave duration lengthening on 12 lead surface ECG and abnormal signal averaged atrial electrocardiogram have also been demonstrated.

The increase of P wave duration is thought to be an accepted indicator of atrial conduction prolongation, thus it might be useful in atrial arrhythmia risk stratification. P dispersion is a important parameter to prevent paroxysmal atrial fibrillation in patients with hypertensive heart disease, mitral and aortic valvulopathy, ischaemic heart disease, dilated and hypertrophic cardiomyopathy. After cardioversion the prolongation of P wave interval and dispersion may drive the attention to a recurrent arrhythmia. Regarding patients with dilated atria the chance of atrial fibrillation is higher than in patients without structural heart disease. Clinical data of patients suffering from paroxysmal and persistent or permanent atrial fibrillation was examined. According to the results, patients with atrial fibrillation longer than 48 hours had increased P wave interval and P dispersion. Moreover, it was showed that in case of symphatetic overdrive and physical activity P dispersion may increase. P dispersion may be prolonged after coronary artery bypass surgery and suitable for postoperative arrhythmia prevention. Furthermore, P dispersion may increase after acute myocardial infarction and shows an increased risk for postinfarction atrial fibrillation. The ECG data of patients with acute myocardial infarction treated either with primary transluminal coronary angioplasty or fibrinolysis were studied. P wave interval and P dispersion proved to be significantly shorter in patients treated with angioplasty. With reference to patients with atrial septal defect, Fontan

and subjects who underwent an operation due to Fallot tetralogia, the risk of atrial arrhythmias is increased and P interval and P dispersion may be prolonged. Prior to atrial fibrillation associated to hyperthyroidism, P interval and P dispersion may grow. Patients suffering from preexcitation syndrome were examined and prolonged P dispersion was found. Apart from the accessory pathway, the inhomogenous propagation of sinus impulse was also responsible for the increased risk of atrial arrhythmias. In case of sinus node disease due to the structural and electrical changes in the atrial myocardium, inhomogenous pulse conduction may result in the prolongation of P wave interval. In patients with interatrial conduction delay and recurrent atrial fibrillation the electrical pacing of the atrial septum results in decreased P interval. Paclitaxel, used for treatment of pulmonary and ovarian tumors, and 5-fluorouracil mainly used against gastrointestinal and breast cancer may increase P interval and dispersion. 523 healthy volunteers' electrocardiograms were examined. According to the results, P wave duration and P dispersion is longer in winter, than in summer. A population older than 65 years and another group of patients younger than 45 years were examined. P dispersion proved to be much longer in the older population.

### 2. 3 Atrial arrhythmias and end-stage renal failure

According to recent studies, the estimated prevalence of atrial fibrillation of patients with end stage renal failure is approximately 13 %. In patients on chronic haemodialysis, various arrhythmias may occur, moreover electrocardiographic changes might appear due to dialysis itself. Arrhythmias may develop especially at the beginning or 5 hours after termination of the treatment. There are few data about the importance of atrial arrhythmias, and atrial fibrillation in patients with end stage renal failure during haemodialysis. After a publication survey on this topic, a report was found on P wave duration changes during dialysis. Among the 21 patients, 18 showed an increase while 3 showed a decrease.

### 2. 4 Causes and clinical significance of changes in QT interval and QT dispersion

Syndrome associated with increased ventricular repolarization (long QT syndrome) may result in life threatening ventricular arrhythmias (torsades de pointes ventricular tachycardia) and sudden cardiac death. The repolarization phase of the cardiac action potential -represented by the QT interval on the surface ECG- is regulated mainly by potassium channels, such as delayed rectifier currents  $I_{Kr}$  and  $I_{Ks}$ . To our knowledge in congenital diseases associated with prolonged QT interval - Jervell-Lange-Neilson, Romano-Ward syndromes -, the abnormal ionic channel function leads to the change of repolarization. QT

prolongation may occur after myocardial infarction and in case of sudden sympathetic overdrive condition. Sympathetic activation may result in adrenergic-dependent afterdepolarization and triggered activity which may play a role in the genesis of torsades de pointes ventricular tachycardia. Regarding autonomic neuropathy associated with diabetes mellitus, uraemic neuropathy, and structural heart disease QT interval may increase. Furthermore, numerous drugs and chemicals may lead to QT prolongation. In patients with subarachnoid haemorrhage, arrhythmias frequently appear and they are followed by decreased serum potassium and magnesium, and increased QT interval. Recently published papers show that in case of standard settings QT interval is longer in women than in men. The difference between gender is not completely understood. The shortening of QT interval in men may be caused by testosterone's favorable effect on ventricular repolarization. According to a different point of view, women have less delayed rectifier potassium ionic channel. QT dispersion – i.e. the difference between the longest and shortest QT interval on the 12 lead surface ECG - reflects regional variations in myocardial repolarization, and also an ease of inducibility of reentrant arrhythmias. Higher values of QT dispersion have been found to be associated with an increased incidence of malignant ventricular arrhythmias and sudden cardiac death. QT dispersion may be longer in congenital long QT syndrome, but may increase in long QT syndrome caused by Vaughan-Williams I/A antiarrhythmic drugs. Prolonged QT dispersion may appear in uraemia and in patients with end stage renal failure on haemodialysis. In addition, QT prolongation may occur in autonomic neuropathy, acute myocardial ischaemia, congestive heart failure, hypertrophic cardiomyopathy, hypertensive heart disease and myocardial amyloidosis. QT dispersion is suitable for the risk stratification of patients waiting for heart transplantation. Also, the mid-myocardial M-cells – 40 % of the left ventricular wall - may play a role in the increase of the transmural dispersion of repolarization. This cell population is featured by long repolarization time, so drugs which increase repolarization may induce a stronger action potential prolongation than in the epicardial and endocardial cells. According to this theory the physiologic inhomogeneity of ventricular transmural repolarization depends mainly on the proportion of the ventricular cell layers.

### 3.5 Lipid abnormalities and ionic channel function

In case of type IIb hyperlipidemia, elevated cholesterol, triglyceride and the qualitative changes of LDL-cholesterol may cause the genesis of small dense LDL, which leads to rapid atherogenesis. Besides, in type IIb dyslipidaemia decreased HDL-cholesterol is an important atherogenic factor. According to recent data, low density lipoprotein may increase the

cholesterol / phospholipid ratio in the cell membrane. Thus, an altered membrane fluidity may then lead to a different functioning of the transmembrane ionic channels. Cardiovascular mortality and morbidity are increased in patients with ischaemic heart disease associated with prolonged QT interval and QT dispersion. At the beginning of our investigations there was no exact data on the direct effect of lipid parameters on ventricular repolarization in patients without ischaemic heart disease.

#### 4. Subjects and Methods

##### 4.1. P wave and haemodialysis

Twenty-eight non diabetic patients ( 14 males and 14 females, mean age:  $58 \pm 16$  years, range: 24 years to 85 years ) with end stage renal failure were selected. The studied population had no significant impulse generation or conduction defect, autonomic or metabolic abnormality and previous episode of atrial fibrillation. Exclusion criteria were: current atrial fibrillation, no P wave on ECG or no clear point of return to isoelectric line. The underlying causes of chronic renal failure were chronic glomerulonephritis (  $n = 16$  ), hypertensive and vascular nephropathy (  $n = 5$  ), chronic tubulointerstitial nephropathy (  $n = 5$  ), and polycystic kidney disease (  $n = 2$  ). Prior to hemodialysis, M-mode, 2D images, pulsed and continuous wave Doppler transthoracic echocardiography were performed in all cases with Acuson Sequoia C 256 imaging system using 3.5 MHz transducer. Left atrial dimension, left ventricular systolic and diastolic function and left ventricular ejection fraction were determined. Eighty two percent of patients had arterial hypertension ( arterial blood pressure  $> 140/90$  mmHg or needing antihypertensive drug therapy ), 46 % had hypercholesterolemia (serum cholesterol higher than 5.2 mmol/L). Sixty-four percent of the subjects suffered from ischemic heart disease proved by stress test, one had recent myocardial infarction (3.6 %), eight patients suffered from mitral valve insufficiency (28.5 %), and five subjects had mitral valve stenosis (17.9 %). One underwent an operation for an aortic stenosis. Two of our patients were administered digitalis (7 %), eight subjects took nitrates (28 %), three were given beta blocking agent (39 %), 16 took ACE inhibitor (57 %) and calcium antagonists were used in 17 cases (60 %). Haemodialysis sessions were carried out in standard settings ( Fresenius 2008-E devices; Fresenius Medical Care, Bad Homburg, Germany ) with F6 and F8 polysulfone dialyzers (Fresenius ) for 3.5 to 4.0 hours 3 times per week. Bicarbonate dialysate fluids contained 140 mmol/L of sodium, 2.0 mmol/L of potassium, 1.5 mmol/L of calcium and 1.0 mmol/L of magnesium. During the sessions no drugs were administered, except isotonic NaCl and sodium heparin. Maintenance therapy consisting of digitalis glucosides,

nitrates, beta blocking and antihypertensive agents remained unchanged. Sodium, potassium, calcium, phosphate, and magnesium levels were measured four times during each session, and two hours after termination of hemodialysis. Serum urea nitrogen, creatinine, cholesterol, triglyceride and intact parathyroid hormone were also determined. Arterial blood pressure was monitored noninvasively during each session. All subjects underwent a conventional 12-lead ECG examination five times during the sessions: at the beginning, 15, 30 minutes after starting the dialysis, at the end and two hours after termination of the treatment. Simultaneous 12 lead ECGs were recorded by means of a 12-channel ECG equipment ( Hewlet Packard Page Writer 200i ), at a paper speed of 25 mm/sec. On every occasion, the ECG was obtained in a comfortable supine position. Throughout ECG recordings, all patients breathed freely and did not speak. ECG electrodes were not changed or renewed during and after hemodialysis. For measurement of P wave duration, the 12-lead ECG printouts were enlarged on the same photocopier by a factor of three. P wave duration was measured with calipers in all 12 leads by one observer in order to exclude interobserver variability. P wave duration was measured from the first electrical activity to the offset at the junction between the end of P wave deflection and the isoelectric line. P wave dispersion was defined as the difference between the maximum and minimum value of P wave duration. Three consecutive cardiac cycles were measured and averaged.

### 3.2. QT interval, QT dispersion and dyslipidaemia

Ninety-six primary type IIb hyperlipidemic patients (44 men and 52 women, mean age:  $53 \pm 13$  years) and 101 healthy controls (58 women and 43 men, mean age:  $46 \pm 16$  years) were examined. The study population consisted of apparently healthy individuals not taking any medication and who attended routine health checks at our outpatient clinic. The studied subjects did not have any impulse generation or conduction defects, and endocrine, kidney and liver diseases were excluded. Further exclusion criteria were: atrial fibrillation, unmeasurable T wave on surface ECG, taking of any drugs that might affect QT interval duration, or taking antihyperlipidaemic drugs. None of our subjects received drugs which might lengthen or shorten QT interval when the diagnosis of hyperlipidemia was confirmed. There were no subjects suffering from ischemic heart disease in the studied population. Myocardial ischemia was excluded with the data obtained from all the studied subjects' detailed history, physical examination, rest ECG and stress test. Furthermore, all patients and controls underwent a 2 D, M-mode echocardiography. Regarding the whole study population, 50 subjects (25.3%) proved to be regular smoker, 22 patients (22.9%) in the hyperlipidemic



group, and 28 (27.7 %) among controls. Forty subjects of the whole study population (20,3 %) drank alcohol occasionally (ethanol intake 1-150 g/week), 40 in the patient group (41,6 %) and none among controls. No subject suffered from diabetes mellitus and/or hypertension in the studied population. All individuals underwent a conventional 12-lead ECG examination. On every occasion, ECG was obtained in a comfortable supine position. During ECG recordings, all patients breathed freely and were not allowed to speak. For measurement of QT interval, 12-lead ECG printouts were enlarged on the same photocopier by a factor of three. QT interval was measured with calipers in all 12 leads and was measured from the first electrical activity to the offset at the junction between the end of T wave deflection and the isoelectric line. QT measurements were performed in a blinded fashion. QT dispersion was defined as the difference between the maximum and minimum values of the QT interval of the 12-lead surface electrocardiogram. Three consecutive cardiac cycles were measured and averaged in each lead. Correlation between heart rate and the studied ECG and laboratory markers was examined, and the corrected maximum QT value and corrected QT dispersion were calculated using Bazett's formula. Furthermore, we studied the possible effects of body weight (Body Mass Index-BMI) on ECG markers. M-mode, 2D images, pulsed and continuous wave Doppler transthoracic echocardiography were performed in all cases with Acuson Sequoia C 256 imaging system using 3.5 MHz transducer.

#### 4. Statistical analysis

Statistical analyses were performed using SAS 6.12 for Windows. Parameters were characterized with descriptive statistics (case number, mean, standard deviation, median and quartiles). Temporal change of both ECG markers and the corrected values was determined by Friedman's ANOVA. Relations between variables were assessed using Kruskal-Wallis nonparametric ANOVA. Correlations between ionic parameters and ECG markers were assessed using Spearman rank correlation. Ionic changes in time were established using repeated measures ANOVA. Relations between the BMI, lipid parameters and ECG markers were determined by using Pearson's correlation test, and Spearman rank order correlation test. The possible effect of ethanol and smoking were assessed using median and Mann-Whitney U test. In addition, a multivariate regression analysis was performed to evaluate correlations between variables.

A value of  $p < 0.05$  was considered to be significant.

## 5. Results

### 5.1. P wave changes during haemodialysis

P wave duration (P maximum) and P wave dispersion did not show any significant change for the first 30 minutes of hemodialysis. The average of P maximum values was  $58 \pm 16$  ms at the beginning which increased to  $98 \pm 8.9$  ms by the end of dialysis ( $p < 0.0001$ ). P maximum determined two hours after completion of sessions still remained lengthened ( $93 \pm 14$  ms). The average of pre-dialysis P dispersions was found to be  $23 \pm 10$  ms, which increased to  $41 \pm 16$  ms by the end of the sessions ( $p < 0.0001$ ). P dispersion measured two hours after the end decreased to  $35 \pm 16$  ms, which did not prove to be a significant change compared to its value at termination. P dispersion showed a significant lengthening ( $p < 0.05$ ) at the end of dialysis in patients with dilated left atrium, i.e., diameter  $> 45$  millimeters. P maximum did not prove to change significantly in the two subgroups of patients. During the sessions serum sodium did not show a significant change. Compared to the beginning ( $5.4 \pm 1.02$  mmol/L), serum potassium showed a significant decrease from the 30<sup>th</sup> minute ( $4.8 \pm 0.7$  mmol/L) till the end ( $3.9 \pm 0.47$  mmol/L) ( $p < 0.0001$ ). Two hours after the completion of the sessions, potassium increased significantly compared to the value at the end ( $4.7 \pm 0.6$  mmol/L) ( $p < 0.0001$ ). Phosphate levels decreased by the end (from  $2.0 \pm 0.5$  mmol/L to  $1.2 \pm 0.34$  mmol/L) ( $p < 0.001$ ), followed by a non-significant increase measured two hours after completion of the sessions. Calcium concentrations at the end showed significantly higher values compared to the beginning (from  $2.2 \pm 0.2$  mmol/L to  $2.71 \pm 0.23$  mmol/L) ( $p < 0.0001$ ), but decreased two hours after the completion of the sessions ( $2.6 \pm 0.1$  mmol/L) ( $p < 0.0001$ ). Regarding serum magnesium, no significant change occurred. Using Spearman rank correlation a significant negative relationship was found between P maximum and serum potassium ( $p < 0.0001$ ) ( $r = -0.4$ ), also P dispersion and serum potassium proved to correlate significantly negatively ( $p < 0.01$ ) ( $r = -0.2$ ). A positive correlation was found between serum calcium and P maximum ( $p < 0.0001$ ) ( $r = 0.5$ ), and serum calcium and P dispersion ( $p < 0.009$ ) ( $r = 0.21$ ). We did not find significant relationship between phosphate level and the studied ECG markers. RR interval at the beginning was found to be  $863 \pm 203$  msec, which decreased to  $783 \pm 94$  msec by the termination and it remained shortened at the value of  $784 \pm 95$  msec measured two hours after finishing the treatment. No atrial fibrillation occurred during the sessions.

## 5.2. Effect of lipids on QT interval and QT dispersion

Regarding lipid parameters, a significant difference was found between hyperlipidaemic and control group: serum cholesterol ( $p < 0.0001$ ), LDL-cholesterol ( $p < 0.0001$ ), triglyceride ( $p < 0.0001$ ), apo-B ( $p < 0.0001$ ). There was no significant difference between the two groups of subjects regarding HDL-cholesterol, apoA1 and lipoprotein-(a). QTmax was found to be  $430 \pm 34$  msec in patients, while  $370 \pm 27$  msec was observed in controls ( $p < 0.0001$ ). Regarding corrected QTmax we recognized a difference between patients and controls ( $470 \pm 41$  msec vs.  $402 \pm 36$  msec) ( $p < 0.0001$ ). QTd proved to be  $59 \pm 18$  msec in patients and  $34 \pm 14$  msec in controls ( $p < 0.0001$ ). Also, corrected QTd differed significantly ( $65 \pm 20$  msec in patients, and  $37 \pm 15$  msec in controls) ( $p < 0.0001$ ). Regarding the whole study population's data obtained from Pearson's correlation test a positive significant correlation was found between cholesterol, triglyceride, LDL-cholesterol and all the studied ECG parameters, and also between HDL-cholesterol and QTmax, apo-B and QTd. There was no significant relationship found between lipoprotein(a), apoA1 and the studied ECG markers. Body mass index (BMI) proved to be  $27 \pm 4$  kg/m<sup>2</sup> in patients, while it was  $22.8 \pm 4.5$  kg/m<sup>2</sup> in controls ( $p < 0.0001$ ). Regarding all subjects, body mass index showed a positive correlation with QTmax ( $p < 0.0001$ ,  $r = 0.32$ ), corrected QTmax ( $p < 0.0001$ ,  $r = 0.31$ ), QTd ( $p < 0.0001$ ,  $r = 0.27$ ), corrected QTd ( $p < 0.0001$ ,  $r = 0.28$ ), and also with cholesterol ( $p < 0.0001$ ,  $r = 0.3$ ), triglyceride ( $p < 0.0001$ ,  $r = 0.35$ ), LDL-cholesterol ( $p < 0.0001$ ,  $r = 0.3$ ) and apoB ( $p = 0.02$ ,  $r = 0.15$ ). A multivariate analysis completed with the backward elimination model was performed to identify the predictors that may have a strong influence on the studied ECG parameters. Regarding the whole study population, the average resting RR interval proved to be  $0.84 \pm 0.09$  sec,  $0.83 \pm 0.04$  sec recorded in patients, and  $0.85 \pm 0.12$  sec in controls. The difference between the two groups of subjects did not prove to be significant in this regard. To evaluate the relationship between gender and ECG we performed a Mann-Whitney U test. Regarding the whole study population we did not find a significant correlation between these variables. To investigate the exact role of body weight and dyslipidemia in the changes of certain ECG markers, we performed a multivariate test including all the examined ECG parameters, lipid markers and BMI. Cholesterol proved to be in the strongest relationship with the studied variables. To get further data on the possible effects of BMI and lipids on the ECG markers, we performed a Spearman rank order correlation test. To determine BMI's independence from lipid parameters we divided lipid data by BMI. All quotients were in a significant strong correlation with the ECG parameters. A Mann-Whitney U test was performed to evaluate the possible relationship between alcohol

utilization, smoking and ECG parameters. Surprisingly, results showed that QTmax and corrected QTmax were significantly increased in non-smokers and teetotallers ( $p < 0.05$ ).

## 6. Discussion

Complexity of cardiovascular abnormalities and the presence of risk factors increase the arrhythmia risk in patients with end stage renal failure. Atrial arrhythmias occurring during haemodialysis due to their frequency and complications, have significant clinical importance. Our 28 patients with end stage renal failure ( with no history of atrial fibrillation ) were studied during hemodialysis sessions. At the end of the sessions, P wave duration and P dispersion were found to be significantly increased compared to those at the beginning, and they still remained lengthened two hours after the termination of the treatment. Regarding left atrial dimension measured by echocardiography, an increased P dispersion occurred at the end of dialysis in patients with atrial diameter larger than 45 millimeters. These data suggest that an enlarged left atrium may result in increased atrial arrhythmogeneity. On the basis of our data obtained from correlation test, we conclude that changes in calcium, potassium levels may have an unfavourable effect on atrial arrhythmogeneity.

According to recent data low density lipoprotein may increase the cholesterol / phospholipid ratio in the cell membrane. Consequently, an altered membrane fluidity may then lead to a different functioning of the transmembrane ionic channels. In a recent study published in 2005 the effect of intracellular free fatty acids on myocardium was examined. In the hyperlipidaemic transgenic mice population during the 3-month period of time atrial dilatation, diastolic left ventricular dysfunction and the prolonging of the corrected QT interval were observed. The possible cause of the electrocardiographic change was supposed to be the altered functioning of the voltage dependent potassium channels. In the present study we examined type IIb hyperlipidemic patients without ischemic heart disease, in order to estimate the direct effect of lipid parameters on certain markers of the 12-lead surface electrocardiogram. QTmax, QTd, corrected QTmax and corrected QTd were found to be significantly increased in patients with type IIb hyperlipidemia compared to healthy controls. On the basis of our data, obtained from the correlation test, we conclude that an increase mainly in serum total cholesterol, triglyceride, LDL-cholesterol and ApoB may have an unfavorable effect on cardiac arrhythmogeneity. Controversial data exist on the effect of obesity and weight reduction on electrocardiographic markers. According to a recent study weight reduction in obese children and adolescents is associated with the reduction of heart rate and the shortening of the QT interval. In this paper blood chemistry analyses revealed no

significant changes except the decrease of serum cholesterol, triglyceride and uric acid. Recently numerous papers have dealt with the possible relationship between BMI and lipid parameters, though the results are still controversial. According to our data, there is a positive correlation between BMI and the lipid parameters. During the multivariate test, cholesterol showed the strongest correlation with the variables, furthermore the correlation test showed, that lipid parameters had a strong influence on the ECG markers. These findings suggest, that in our study population dyslipidemia may directly lead to the lengthening of QT interval and QT dispersion.

## 7. Summary

The frequency and complications of atrial and ventricular heart rhythm disturbances give the reason for the prevention of arrhythmias. Individuals with a history of paroxysmal and persistent atrial fibrillation have significantly longer intra-, and interatrial conduction time of sinus impulses, thus P wave duration lengthening on 12 lead surface electrocardiogram (ECG) has been demonstrated. Atrial fibrillation often occurs in patients with end stage renal failure.

At first we examined twenty-eight patients (14 males and 14 females, mean age:  $58 \pm 16$  years) with end stage kidney disease and searched for relationship between ECG parameters (the longest P wave duration  $P_{max}$ , and P dispersion  $P_d$ ), atrial diameter and electrolyte changes. The average of  $P_{max}$  was  $58 \pm 16$  ms at the beginning of haemodialysis which increased to  $98 \pm 8.9$  ms by the end of the treatment ( $p < 0.0001$ ). The pre-dialysis  $P_d$  was found to be  $23 \pm 10$  ms, which increased to  $41 \pm 16$  ms by the end of the sessions ( $p < 0.0001$ ).  $P_d$  showed a significant lengthening ( $p < 0.05$ ) at the end of dialysis in patients with dilated left atrium, i.e., diameter  $> 45$  mm. Both ECG parameters were in a significant negative correlation with potassium, and in a positive correlation with calcium.

The effects of lipoproteins on ventricular arrhythmogeneity in patients without ischemic heart disease have not been clearly defined yet. We studied the effect of lipid parameters on the longest QT interval ( $QT_{max}$ ) and QT dispersion ( $QT_d$ ) of 12 lead surface ECG in 96 patients (44 men and 52 women, mean age:  $53 \pm 13$  years) with primary IIb hyperlipidaemia, without ischaemic heart disease and in 101 healthy control subjects (58 women and 43 men, mean age:  $46 \pm 16$  years). Cholesterol, LDL-cholesterol, triglyceride, apo-B, and both ECG parameters increased significantly in patients. A positive correlation occurred between cholesterol, triglyceride, LDL-cholesterol and the studied ECG markers,

and a significant relationship was found between HDL-cholesterol and QTmax, and between apo-B and QTd. Lipid parameters affected the ECG markers independently of body weight.

## 8. Main original observations

1. P wave interval and P wave dispersion increase during haemodialysis - at the end of haemodialysis and 2 hours after termination – which represents the increased risk of paroxysmal atrial fibrillation.
2. Decrease in serum potassium and increase in serum calcium play a basic role in the electrocardiographic changes during hemodialysis.
3. In patients with left atrial diameter > 45 mms P dispersion significantly increases during haemodialysis.
4. QT interval and QT dispersion longer in primary IIb hyperlipidaemic patients without myocardial ischaemia, than in healthy subjects.
5. Cholesterol, LDL-cholesterol, triglyceride and apo-B affect QT interval and QT dispersion independently from body weight in primary IIb hyperlipidaemic patients without ischaemic heart disease.
6. Cholesterol, LDL-cholesterol, triglyceride and apo-B have a direct effect on Qt interval and Qt dispersion.
7. QT interval and QT dispersion may help to recognize hyperlipidaemic patients with increased risk of ventricular arrhythmias.

## 9. Publication (The thesis is based on)

### 9.1. Original articles

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## 9.2. Other articles associated to the thesis

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### 9.4. Lectures

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