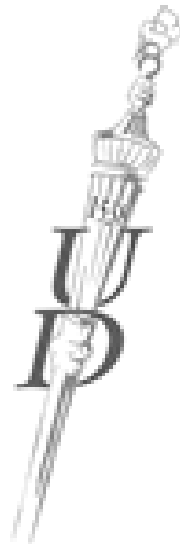


SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

**ELECTROCARDIOGRAPHIC CHARACTERIZATION OF VENTRICULAR
REPOLARIZATION AND EXAMINATION OF ECHOCARDIOGRAPHIC
PARAMETERS DURING HEMODIALYSIS AND HEMODIAFILTRATION**

by Árpád Czifra MD

Supervisor: Zoltán Szabó MD, PhD



UNIVERSITY OF DEBRECEN
Doctoral School of Health Sciences
Debrecen, 2016

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Supervisor: Zoltán Szabó MD, PhD

Head of the Examination Committee: Róza Ádány MD, PhD, DSc

Members of the Examination Committee: Marcell Clemens MD, PhD

László Márk MD, PhD

The Examination takes place at the discussion room of School of Public Health, Faculty of Public Health, University of Debrecen, on May 19, 2016, at 11 AM

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, on May 19, 2016, at 1 PM

Introduction

Occurrence of arrhythmias

The incidence of ventricular arrhythmias positively correlates with age. Their incidence grows higher above the age of 35. The average age of the population is known to be getting higher everywhere in the world. Moreover, the incidence of ventricular arrhythmias and sudden cardiac death also show an increase. The number of patients dying from sudden cardiac death reaches 450.000/year, whereas in our country more than 25000 cases are reported.

The background of ventricular arrhythmias

Various factors can play role in the genesis of ventricular arrhythmias. On one hand genetic factors and male gender, on the other hand acquired pathological factors can provoke cardiac rhythm disturbances. Coronary artery disease, ischemic cardiomyopathy, hypertension, hypertensive heart disease and lipid abnormalities are the most important provoking factors. Physical inactivity, smoking, alcohol abuse and inadequate alimentation are significant factors that may contribute to these pathological changes.

Kidney disease is a significant underlying substrate for the genesis of arrhythmias. The incidence of sudden cardiac death in patients suffering from kidney diseases was shown to be between 1.4-25%, where the most important arrhythmia was found to be ventricular tachycardia. The most common causes of ventricular arrhythmias in patients with chronic kidney disease are autonomic imbalance, altered baroreceptor activity, intermittent volume overload, hypertrophic cardiomyopathy, mitral valve prolapse, and ischemic heart disease. During hemodialysis the incidence of ventricular ectopic activity was reported to be between 18-76%, where hyperkalaemia and the alteration in calcium and magnesium serum concentrations, the decrease in blood volume and the rapid correction of metabolic acidosis, secondary hyperparathyroidism and the elevation in free fatty acid concentrations were the most notable underlying factors.

Ventricular repolarization and cardiac arrhythmias

Secondary to these factors the electrophysiological properties of the myocardial cells can change, thus, the shape of the monophasic action potential featuring the myocardial cell's electrical properties may also alter. As a result, inhomogeneous ventricular repolarization and anisotropy may appear, which seem to be the electrophysiological substrates for the

occurrence of various arrhythmias. Previously it has been shown that during hemodialysis the QT dispersion, measured on the surface ECG may be prolonged reflecting the inhomogeneous cardiac repolarization.

The electrocardiographic features of ventricular repolarization

In order to identify electrocardiographic parameters that can predict the onset of ventricular rhythm disturbances numerous investigations have been completed so far. Most of these studies aimed to achieve the electrocardiographic characterization of ventricular repolarizational abnormalities.

QT interval

The QT interval, as measured on a surface electrocardiogram (ECG), characterizes ventricular repolarization and predicts malignant ventricular arrhythmias and sudden cardiac death. Its length may change between the leads of the surface electrocardiogram. The prolongation of QT interval may be present in Romano-Ward or Jervell-Lange-Nielsen syndromes or after acute myocardial infarction. Furthermore, it may be related to congestive heart failure, dyslipidemia, hepatic cirrhosis, diabetes mellitus, sudden sympathetic activation (triggered activity) and renal failure.

M cells and repolarizational inhomogeneity

The QT interval may be prolonged due to the side effect of certain drugs, showing the increased danger of proarrhythmia. Forty percent of the human left ventricle is built up by M cells (mid-myocardial ventricular cells) that do play an important role in the prolongation of repolarizational dispersion. This population of cells has an originally lengthened repolarizational time, thus as a consequence of certain drug therapies (e.g. amiodarone, sotalol) exaggerated increase in action potential duration may be explored, resulting in a transmural inhomogeneity of ventricular repolarization.

QT dispersion

QT dispersion is defined as the difference between the longest and shortest QT intervals measured on a surface electrocardiogram. QT dispersion has been proved to correlate with the duration of the monophasic action potential of the epicardial myocardial cells. Moreover, QT dispersion represents the regional alterations of the ventricular myocardial repolarization, also

characterizes the predisposition for arrhythmias based on reentry mechanism. The longer the QT dispersion the higher the danger of malignant ventricular arrhythmias and sudden cardiac death. QT dispersion is better correlating with the inhomogeneity of ventricular repolarization than QT interval. Furthermore, the measurement of QT dispersion can significantly help in the monitoring of antiarrhythmic therapy especially with the widely used antiarrhythmic drugs, amiodarone and sotalolol. Previously, the prolongation of the QT dispersion was 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 shown.

Methods and pitfalls of the electrocardiographic evaluation

Sometimes the measurement of QT interval is not easy, as it may be affected by the T and U waves' morphology. Sometimes T waves' shape may also be changed by the P wave. Moreover, there might be a difference between the manual and automatic methods of measurement of certain electrocardiographic parameters. Importantly, in the cases of manual electrocardiographic measurements inter-observer variability may appear. Although during the automatic evaluation of these parameters this type of error is known not to be present, but in most of the cases the necessary technical background is not available. QT interval highly depends on heart rate, therefore it has to be corrected to ventricular frequency (corrected QT interval - QTc). To achieve the corrected QT interval Bazett formula is widely used ($QTc = QT / \sqrt{RR}$). In the case of $QTc > 450$ msec the susceptibility for ventricular arrhythmias is significantly increased.

Heart failure and kidney disease

Heart failure can worsen the outcome of patients suffering from chronic kidney disease. Ventricular dysfunction appears in approximately 36% of the hemodialyzed. The frequency of heart failure is increased by 7% each year in subjects participating hemodialysis treatment. According to a recent study the median survival rate of 62 months among hemodialyzed patients decreased to 36 months when heart failure was present. The most common causes of heart failure in patients with chronic kidney disease are advanced age, female sex, hypertension, diabetes mellitus and atherosclerosis, ischemic and structural heart disease. Renoparenchymal hypertension is also an important factor, the frequency of which, in patients receiving renal replacement therapy, is estimated to be 89%. The adaptive mechanisms

induced by the nephrons' hyperfiltration, and the harmful effects of persistent high blood pressure caused by hypervolemia, have a major effect in the development of left ventricular hypertrophy, which can also lead to ventricular filling disorder. In 30-50% of patients suffering from heart failure isolated diastolic dysfunction develops without the worsening of systolic left ventricular function. Echocardiography is an important diagnostic tool in the early recognition of diastolic dysfunction which is an independent risk factor of cardiovascular mortality. Moreover, in the case of diastolic dysfunction relatively low volume overload may result in a significant end diastolic and pulmonary pressure increase that may contribute to the clinical symptoms of heart failure. The volume regulation has a unique role in the genesis of symptomatic heart failure where the incidence of both atrial and ventricular arrhythmias is increased, based upon volume overload, increased wall stress and the secondary occurrence of altered myocardial vulnerability.

Hemodialysis and hemodiafiltration

Previously a novel extracorporeal treatment method (hemodiafiltration) has been introduced in order to improve the efficacy of management of patients suffering from kidney diseases. The mortality rate of patients participating in hemodiafiltration programs has been reported to be 35%, lower than those receiving conventional hemodialysis.

Convective transport

Whereas conventional treatment eliminates uremic toxins, depending on their molecular weights, by diffusion, hemodiafiltration also eliminates the medium molecular weight toxic polypeptides (characterized by β -2 microglobulin) by convective transport. During hemodiafiltration high-flux filters are used resulting in high quantity of ultrafiltrate. In the everyday clinical practice post-dilution method is used where the substitution fluid is administered through the venous system after the filter. Approximately 18-24 litres of dialysate fluid has to be supplemented during a four hour treatment. The safety and effectivity of hemodiafiltration have been investigated by numerous studies. It has been shown that during hemodiafiltration the incidence of hypertension is decreased and the extracorporeal treatment is well tolerated.

Benefits of hemodiafiltration

The effect of hemodiafiltration has not been clearly elucidated yet. The effective clearance of vasodilator materials and the consequently appearing modulation in peripheral vasomotor activity are thought to be the important advantages of this treatment modality. The high sodium content of the substitution fluid can explain the lower incidence of hypotensive episodes. Hemodiafiltration was shown to have a higher clearance of uremic toxins, depending on their molecular weights. It also eliminates the medium molecular weight toxic polypeptides (characterized by β -2 microglobulin) by convective transport. Using high flux membranes biocompatibility increases, thus, the concentration of acute phase proteins and inflammatory mediators (e.g. C reactive protein, interleukin-1, interleukin-6, rheumatoid factor) do not increase during and after the sessions. By lowering the concentration of beta-2 microglobulin the incidence of amyloidosis can also be decreased by at least 50%. By using high flux membranes and ultrastereile dialyzing solution both oxidative stress and lipid profile can improve. In 80-100% of patients participating hemodialysis programs anemia occurs, indicating the administration of erythropoietin. Interestingly, hemodiafiltration is suitable to lower the need of erythropoietin use. This phenomenon is not clearly understood and needs further investigations (the altered inflammatory activity may be one of the reasons). Rarely, in the case of conventional hemodialysis peripheral neuropathy may appear, nevertheless during convective treatment these consequences can soften. Taking all these favorable findings into consideration nowadays hemodiafiltration is considered one of the most effective and modern renal replacement techniques. However, the effects of hemodiafiltration on ventricular arrhythmia tendency have not yet been clearly elucidated yet. Also, it is not clear to what extent the changes in ventricular arrhythmia susceptibility affect the mortality rate, compared to conventional hemodialysis. Therefore, our question is whether electrocardiographic markers, reflecting ventricular repolarization, differ with renal replacement modalities.

Questions

As a PhD student of the Clinical Centre University of Debrecen it was my privilege to investigate the pathomechanism, diagnosis, management and non-invasive risk stratification of arrhythmias in the Institute of Internal Medicine. During my clinical practice I regularly meet patients with the previous history of cardiac rhythm disturbances. In order to improve the quality of life and mortality statistics of this population I decided to deal with this borderline area of nephrology and cardiology. I realized that the exact effect of convective transport on

the genesis and occurrence of ventricular arrhythmias has not been clearly understood and investigated yet. Furthermore it has not been determined whether hemodiafiltration and hemodialysis have an altered effect on cardiac function and intracardiac pressure conditions (left ventricular systolic and diastolic ability).

Objective

During my scientific research I tried to give an answer to the following questions.

Investigation of ventricular repolarizational electrographic markers during hemodialysis and hemodiafiltration

- a) Do QT interval and QT dispersion change during hemodialysis and hemodiafiltration?
- b) Is there any difference between the two treatment modalities with regard to the quantitative and qualitative arrhythmia occurrence obtained from Holter electrocardiography recordings?
- c) Is there a significant correlation between certain laboratory markers (especially electrolytes) and electrocardiographic parameters?
- d) Is there a difference with regard to the change of nitrogen-monoxide (NO) and asymmetric-dimethyl arginine (ADMA) between the different renal replacement therapies?

Investigation of echocardiographic markers during hemodialysis and hemodiafiltration

- a) Evaluation of functional and structural heart disease of the studied patients.
 - ⇒ measurement of left atrial cross diameter before and after the treatments
 - ⇒ evaluation of left ventricular systolic function (ejection fraction) using the Simpson's formula
 - ⇒ exploration of left ventricular diastolic function by means of Doppler echocardiography
 - Determination of mitral flow velocity in early diastole (E) and pre-systole (A) using Doppler technique.
 - Featuring mitral annular longitudinal velocity (Ea) by means of tissue Doppler imaging.
 - Evaluation of left atrial pressure load by calculating the E/Ea ratio.

- Measurement of the interventricular septum and the left ventricular posterior wall and the determination of left ventricular mass index.
- b) Observation of the change in echocardiographic parameters during the different renal replacement therapies.
 - c) Is there a correlation between the echocardiographic parameters and electrographic markers?
 - d) Can any correlation be determined between echocardiographic variables and NO, ADMA?

Patients and methods

Patients

During the examination clinical data of thirty non-diabetic patients, with end stage renal failure were studied (18 males, 12 females, mean age 60 ± 13.6 years). Firstly, we collected and analyzed data of patients while they received hemodiafiltration, then the same subjects during treatment with conventional hemodialysis for at least three months were evaluated. This was followed, at the time of the following regular hemodialysis, by further data collection and investigation. Our patients did not have impulse generation and/or conduction disorders, autonomic nervous system diseases, diabetes mellitus; Parkinson's disease, amyloidosis or sarcoidosis. Moreover, patients on medication which may affect atrial and ventricular depolarization and repolarization (e.g. haloperidol, methadone, amiodarone, sotalol, selective serotonin reuptake inhibitors, macrolide antibiotics, antifungal agents) were excluded from the investigations. Likewise, thyroid dysfunction and altered calcium metabolism may affect atrial pulse conduction, hence patients suffering from such endocrine disorders were also excluded from the study. None of our patients had any history of atrial fibrillation. Our study population suffered from end stage kidney disease (Stage 5). All patients participated in regular hemodialysis program in our center, and were willing to give their informed consent to take part in the study. The chronic kidney disease of the studied population was caused by the following: chronic glomerulonephritis (n = 5), hypertensive and vascular nephropathy (n = 12), chronic pyelonephritis (n = 1), polycystic kidney disease (n = 2), analgesic nephropathy (n = 3), renal agenesis (n = 1), systemic lupus erythematosus (n = 2), and vasculitis (n = 4). Ninety percent of the patients suffered from hypertension (arterial blood pressure requiring antihypertensive

therapy > 140/90 mmHg), 16.7% had hypercholesterolemia (serum cholesterol >5.2 mmol/L) and 10% had ischemic heart disease as proven by stress test. The patients – after receiving detailed information about the trial – confirmed, in writing, their will to participate in the study, and the Ethics Committee of the University of Debrecen approved the study protocol.

Hemodialysis and hemodiafiltration

Hemodialysis and hemodiafiltration were performed three times a week in 4-hour long sessions with Fresenius 4008 S and H machines (Fresenius Medical Care, Bad Homburg, Germany), and with Fx60 and Fx80 high-flux polysulfone dialyzers (Fresenius). During hemodiafiltration post-dilution method was used. The replacement solution was manufactured on-line from ultrapure water and consisted of 138 mmol/L sodium, 2 or 3 mmol/L potassium (in 13 cases 2 mmol/l in 17 cases 3 mmol/l), 1.5 mmol/L calcium, 0.5 mmol/L magnesium, and 1 g/L glucose. During the sessions no drugs other than sodium heparin solution was administered. The previous drug therapy (digitalis, nitrates, beta-blockers and calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers) remained unchanged. The arterial blood pressure was monitored non-invasively. The blood flow was 338 ± 11.6 ml/min and did not differ significantly during the respective procedures ($p < 0.05$).

12-lead surface electrocardiogram

Electrocardiograms were recorded at 25 mm/sec recording speed (Hewlett Packard Page Writer 200i) while the patients were in the supine position. Copies of the recordings were made with a magnifying factor of 3; in every lead three QT intervals were measured. In order to eliminate the inter-observer variability the values were calculated with calipers by one examiner in a blinded fashion. The end of the T-wave was determined as the beginning of the TP interval; in the case of the U-waves, the deepest point between the T- and U-waves marked the end of the interval. Three consecutive sections were defined, then their average was calculated and the resulting value used as the QT value in the given lead. In the statistical analysis, the longest QT value of the 12 leads was used as the QT interval (QTmax), and the QT dispersion (QTd) was determined as the difference between the longest and shortest QT interval. The QT interval and QTd were corrected to heart rate (QTmax c, QTd c) according to Bazett's formula: $QT_{max\ c} = QT/\sqrt{RR}$ (msec), $QT_{d\ c} = QTd/\sqrt{RR}$ (msec).

Echocardiography

Before and after the renal replacement therapy transthoracic echocardiography (M-mode, 2 D) was performed with pulsed, continuous wave and tissue Doppler techniques (Philips ATL HDI 5000 imaging system with a 3.5 MHz transducer). During the examinations the left atrium's cross diameter was measured from the parasternal long-axis view, then, based on an apical four-chamber view, the Simpson's method was used to determine the left ventricular ejection fraction. Using the Devereux-Reichek formula the left ventricular mass index was calculated ($\{1.04 \times [(\text{end-diastolic diameter of the left ventricle} + \text{interventricular septum thickness} + \text{the posterior wall thickness of the left ventricle})^3 - \text{end-diastolic diameter of the left ventricle}^3] - 14\} / \text{height}$). The early diastolic transmitral peak flow velocity (E) was determined from the apical four-chamber view by means of a pulsed-wave Doppler, and the peak flow velocity in the late diastolic period during the atrial contraction (A) was also determined. The time between the beginning and the end of the E-wave deceleration slope was defined as deceleration time (DT). Using Tissue Doppler Imaging (TDI) we evaluated the early diastolic velocity of the septal mitral annulus (Ea) from the apical approach. In order to estimate the left ventricular filling pressure we calculated the ratio of the E and Ea (E/Ea). With regard to diastolic dysfunction, patients were divided into three groups. The diameter of the inferior vena cava was also measured from the subcostal view.

Holter-electrocardiography

Holter-ECGs (GE Medical SEER Light) were performed, where monitoring was started before the therapies and ended 24 hours afterwards. The number of supraventricular premature beats was compared to the total number of beats and the resulting modulus was used to eliminate the variations arising from the short differences between the duration of the examinations.

Laboratory examinations

The serum electrolyte levels were measured four times during the sessions and 2 hours afterwards. Serum sodium, potassium, total calcium, ionized calcium, phosphate and magnesium levels were measured. Before and two hours after the sessions NO concentration of the serum was determined by the modified method of Navarro-Gonzalez and ADMA

concentrations in the plasma were determined using enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

The statistical analysis was carried out with the help of the SAS 8.2 for Windows software. The variations of the investigated parameters over time and the difference between the two modalities were investigated by using repeated measures ANOVA. The correlation between the parameters was analyzed by using the Pearson's test when the distribution was normal and by Spearman's rank test in the case of not normal distribution. Throughout the analysis the $p < 0.05$ probability level was considered statistically significant.

Results

Changes of electrocardiographic parameters during different treatment methods

Both QTmax and QTd showed an increase during hemodialysis, but no significant changes were observed during hemodiafiltration. Although these parameters were significantly different even at the beginning of the sessions, these electrocardiographic markers were found to be within the physiologic range. Neither QTmax and QTd nor QTmaxc and QTdc showed significant changes during the first 30 minutes of the hemodialysis, however, in subsequent measurements prolongation was observed in all parameters. QTmax was 388.66 ± 31.81 msec at the beginning of hemodialysis, and increased to 400.66 ± 39.12 msec at the 30th minute, and reached its maximum by the 240th minute (418.67 ± 46.06 msec, $p < 0.0001$), then remained prolonged compared to the baseline value at two hours post treatment (391.33 ± 43.21 msec). QTd was 31.33 ± 10.08 msec before the start of hemodialysis with the largest prolongation being observed at the 240th minute (51.33 ± 14.56 msec, $p < 0.0001$). Compared to the baseline value, this was still found to be prolonged at 34.66 ± 12.79 msec at two hours following the treatment ($p = 0.11$). QTmaxc lengthened from the base value of 435.4 ± 28.42 msec to 454.93 ± 32.76 msec at thirty minutes ($p = 0.006$), and this value steadily increased. Even after it started decreasing, we still found that the prolongation was significant 2 hours after the treatment (453.26 ± 28.00 msec, $p = 0.0002$). QTdc rose from 34.96 ± 10.95 to 43.46 ± 13.28 msec in the first half hour of the hemodialysis ($p = 0.63$) and reached its maximum at the 240th minute (58.27 ± 15.54 msec, $p < 0.0001$). In contrast, QT parameters did not change significantly during hemodiafiltration. No malignant ventricular arrhythmias appeared, however the occurrence of ventricular premature beats was shown to be significantly higher during hemodialysis (HDF: $183,1 \pm 476$ vs. HD: $256,2 \pm 657$,

p=0,018). The ratio of ventricular premature beats to the total number of heart beats also differed significantly (p<0,05). There were no significant correlations between ventricular premature beats and QT parameters, although the left ventricular ejection fraction correlated negatively with the number of ventricular premature beats in both treatment modalities (HDF r=-0.55, p=0.0015, HD r=-0.36, p=0.046).

Renal replacements modalities and laboratory parameters

The total calcium and ionized calcium showed an increase (p<0.05), while the potassium, magnesium and phosphate levels significantly decreased in both modalities (data not elaborated). During hemodiafiltration sodium levels did not change significantly, however, in the case of hemodialysis a decrease was observed in the 15th and 30th minutes (p<0.05) compared to the baseline levels. Urea and creatinine showed significant decrease during both therapies. During hemodiafiltration, a negative correlation was observed between both the total calcium (r=-0.54, p<0.05) and ionized calcium (r=-0.51, p<0.05) levels, and the corrected QTmax interval; in the case of hemodialysis the sodium and the QTmax c showed a positive correlation (r=0.46, p<0.05).

*Significant correlations were observed between certain electrocardiographic parameters and serum electrolyte levels. (r values). QTmax: QT interval, QTmaxc: corrigated QT interval, QTd: QT dispersion, QTdc: corrigated QT dispersion, tCa: total calcium, iCa²⁺: ionized calcium (*p<0.05)*

| HDF | QTmax | QTmaxc | QTd | QTdc |
|-------------------|--------------|---------------|------------|-------------|
| tCa | -0,27192 | -0,54647* | -0,03585 | -0,04488 |
| iCa ²⁺ | -0,30389 | -0,50775* | -0,09232 | -0,09422 |
| HD | QTmax | QTmaxc | QTd | QTdc |
| Na ⁺ | 0,36653 | 0,46199* | 0,13464 | 0,0578 |

Serum glucose levels showed an increase at the end of both modalities (HD: 5.69±1.16 mmol/L vs. 6.81±1.53 mmol/L (p<0.05), HDF: 5.25±0.72 mmol/L, vs. 7.07±1.58 mmol/L, (p<0.05) and it persisted a two hours after treatments. During hemodiafiltration and conventional hemodialysis both NO and ADMA concentrations were observed to decrease significantly two hours after completion of the treatments (HD: NO 30.3±0.76 µmol/L vs.

12.23±5.7 µmol/L, p<0.05, HDF: NO 29.4±18.25 µmol/L vs. 11.55±5.54 µmol/L, p<0.05, HD: ADMA 0.69±0.2 µmol/L vs. 0.55±0.16 µmol/L, p<0.05, HDF: ADMA 0.64±0.18 µmol/L vs. 0.59±0.15 µmol/L, p<0.05). However, during hemodiafiltration NO concentration showed a positive correlation with the late diastolic transmitral flow velocity (A) (r= 0.42, p=0.02) and the ratio between the early and the late diastolic flow velocities (E/A) (r=0.45, p=0.011). Furthermore, ADMA level changes did not correlate significantly with the studied echocardiographic parameters.

Volume removal during hemodialysis and hemodiafiltration

Body weight and the body mass index (BMI) decreased significantly in both modalities (BMI HD: 24.39±4.19 kg/m² to 23.59±4.2 kg/m²; BMI HDF 24.37±4.12 kg/m² to 23.6±4.14 kg/m²). The change in body weight was determined separately by gender, and it can be concluded that in both cases a significant reduction occurred (p < 0.05). Importantly, the difference between the volume removals did not prove to be significant (p= 0.34). It can be stated that effective volume removal did not differ significantly during the two treatment modalities.

Changes of heart rate and blood pressure during the different treatment methods

Changes in ventricular rate were characterized by the RR cycle length. During hemodiafiltration the RR length was increased (852±104.3 msec, p<0.05) at the 30th minute, indicating the provisional decrease of the heart frequency, and then it decreased. In the case of hemodialysis, the RR cycle length was observed to decrease (800.6±96.2 vs. 746.6±125.5 msec, p<0.05) 2 hours after treatment. Regarding blood pressure in both treatment modalities a rapid decrease occurred after the start of the sessions, which compared to baseline values, reached a significant level by the 15th minute. The systolic blood pressure did not change significantly after this, however, the diastolic values showed an increase after the treatment. During hemodiafiltration the systolic and diastolic values were higher even at the initial stages of the sessions (HDF: systolic 152±24 Hgmm, diastolic 83±19 Hgmm, HD: systolic 144±22 Hgmm, diastolic 79±14 Hgmm), but it did not proved to be significant.

Echocardiography and renal replacement therapy

In the case of both modalities E and E/A values positively correlated with changes in body weight (p<0.05), however regarding E/Ea and body weight a significant correlation was

observed only in the case of hemodiafiltration ($r=0.38$, $p=0.04$). Similar trends were found between E/Ea and the left atrial diameter. During hemodiafiltration the decreasing atrial diameter was significantly correlated with the decrease in E/Ea, while such correlation was not observed during hemodialysis ($p=0.15$). Moreover, the starting diameter of the inferior vena cava showed a significant correlation with the E/Ea decrease, but only in the case of hemodiafiltration ($r=0.46$, $p=0.001$). The pre- and post-treatment left ventricular ejection fraction (HD: 56.57 ± 9.2 vs. 56 ± 7.7 , HDF: 56.47 ± 8.7 vs. 54.57 ± 6.8), left ventricular mass index (HD: 211 ± 69 g/m² vs. 193 ± 64 g/m², HDF: 188 ± 62 g/m² vs. 185 ± 65 g/m²), left ventricular end-systolic and end-diastolic diameters did not change significantly, and none of these parameters showed a statistically significant correlation. Left ventricular ejection fraction showed a significant negative correlation with ventricular premature beats ($p<0.05$). During both treatment modalities a positive correlation was found between left ventricular mass index and QTmax, QTmaxc and QT dispersion ($p<0.05$).

The changes of different echocardiographic parameters are summarized in the following table.

HD: hemodialysis, HDF: hemodiafiltration, E: early diastolic transmitral peak flow velocity, A: late diastolic transmitral peak flow velocity, Ea: early diastolic myocardial relaxation velocity of the mitral annulus, LA: left atrium, VCI: vena cava inferior ($p<0,05$)*

| | HD | | HDF | |
|-----------------|------------------|-----------------|------------------|-----------------|
| | Before treatment | After treatment | Before treatment | After treatment |
| E (cm/s) | 103,4±26,5 | 77,9±22,6* | 106±26,5 | 72±22* |
| E/A | 1,37±1,27 | 0,97±0,63 | 1,2±0,46 | 0,83±0,34* |
| E/Ea | 12,6±3,55 | 9,88±4,6* | 11,65±4,5 | 8,43±4,46* |
| LA (mm) | 45,4±6,5 | 43,4±6 | 45,1±5,25 | 40,8±5,8* |
| VCI (mm) | 18,7±2,8 | 16,2±2,6* | 19,7±3 | 15,1±2,8* |

Discussion

QT dispersion reflects the regional alterations in ventricular repolarization. Its prolongation predicts the increased risk of reentry arrhythmias, malignant ventricular rhythm disturbances and sudden cardiac death. The lengthening of QT interval may appear in congenital diseases (e.g. Romano-Ward and Jervell-Lange-Nielsen syndromes). Moreover, it may be prolonged due to the effect of certain drugs and in the case of acute myocardial infarction, heart failure and dyslipidemia. Duration of the QT interval may be affected by various physiological factors (e.g. ventricular rate and catecholamine release). Previously, it has been shown that mortality rates of patients on hemodiafiltration is 35% less compared to subjects treated with hemodialysis. This advantageous result may be caused by numerous factors. Hemodiafiltration has significantly higher clearance with regard to small and medium weight substances (e.g. blood urea nitrogen, creatinine, phosphate, beta-2 microglobulin, complement, leptin, cytokines, homocysteine, and uremic toxins). The use of high flux membranes increase biocompatibility thus, the concentrations of acute phase proteins and inflammatory mediators (e.g. interleukin 1, 6, CRP, and rheumatoid factor) are not elevated. Reducing the concentration of beta-2 microglobulin the incidence of amyloidosis can be lowered by at least 50%. Using high flux membranes and ultrastereile dialyzing solutions oxidative stress can be decreased and lipid profile may be improved. During hemodiafiltration the incidence of anemia needing the administration of erythropoietin can be decreased and need for erythropoietin may be lowered as well, that might be resulted from the alteration of inflammatory background. Taking all these to consideration we suggested that patients on hemodiafiltration programs may get further advantages from the slower progression of target organ damage. According to our present results it can be stated that during hemodiafiltration no significant alterations with regard to the studied ECG parameters could be observed compared to conventional hemodialysis. This favorable tendency may be explained by the more effective detoxication and the more balanced osmotic and volume conditions observed during the convective treatment. This statement can also be confirmed by our observation that during hemodiafiltration left atrial diameter decreased significantly showing the differences in intracardiac and intravascular pressure conditions. Furthermore, the more significant increase in ventricular rate may suggest the altered dynamicity of intracardiac volume conditions with regard to these treatment modalities. All these findings may be supported by the non-significant differences with regard to effective volume removal. The behavior of serum

potassium, magnesium, phosphate and calcium was found to be similar in both modalities thus, we conclude that the significant changes in ECG parameters are possibly not based on the alterations of these electrolyte markers. In the case of hemodiafiltration significant negative correlation was found between QTmaxc and total calcium, ionized calcium, while QTmaxc and serum sodium correlated positively during the conventional therapy. According to these result we conclude that certain ionic imbalances can play a role in the modification of ventricular repolarization depending on the type of extracorporeal treatment modality. It can be clarified that the careful control of these electrolyte parameters may reduce the risk of sudden ventricular arrhythmias. Left ventricular mass index was shown to play a role in arrhythmogenesis apart from the type of renal replacement method. The connection between systolic left ventricular dysfunction and the propensity for ventricular arrhythmias has been clearly elucidated by our results and it was found to be valid for both treatment modalities. With regard to the increased number of ventricular premature beats observed during the conventional therapy obtained from 24 hour Holter ECG monitoring it is concluded that hemodialysis can lead to an increased ventricular vulnerability compared to hemodiafiltration. With regard to left ventricular diastolic function and the parameters establishing intracardiac pressure conditions a significant difference have been observed during echocardiography. The correlation between E/Ea ratio and body weight was found to be significantly positive only during hemodiafiltration while the change in left atrial diameter was shown to correlate significantly with the decrease of E/Ea ratio. This can be explained by the differences in volume distributions between the different renal replacement therapies. Both NO and ADMA were found to be decreased significantly during the therapies which shows the similar metabolism of these materials. Nevertheless, with regard to the mitral flow parameters (A and E/A) and NO, a significant correlation was recognized only in the case of hemodiafiltration. This phenomenon draws the attention to the more effective lowering of intracardiac pressure and the improvement in diastolic function during hemodiafiltration.

Taking all these to account the favorable electrocardiographic and echocardiographic changes observed during hemodiafiltration may be caused by the effective lowering of intracardiac volume and pressure, and the significant detoxication capability of convective transport itself.

Summary

1. QT interval and QT dispersion did not show significant change during hemodiafiltration, but both electrocardiographic markers significantly increased in the case of hemodialysis.
2. The significant correlation observed between serum calcium and QT interval during hemodiafiltration and the correlation between serum sodium and QT interval during hemodialysis indicate the role of ionic imbalance in the genesis of an altered ventricular repolarization and suggest the importance of electrolyte profiling during extracorporeal renal replacement sessions.
3. Ventricular premature beats appeared significantly more often in the case of hemodialysis, showing an increased ventricular myocardial vulnerability during these sessions.
4. The decrease in E/A ratio, the positive correlation between E/Ea and body weight, the connection between left atrial diameter and E/Ea, and the significant correlation between the diameter of the inferior vena cava and E/Ea demonstrate the favorable effect of decreased intracardiac pressure on diastolic left ventricular function during hemodiafiltration.
5. NO and ADMA concentrations were observed to decrease during both renal replacement therapies indicating the similarity of their metabolism. However, with regard to A, E/A, and NO significant correlations could only be observed in the case of hemodiafiltration proving its particular favorable effect on left ventricular diastolic function.
6. The significant decrease in left atrial cross diameter observed during hemodiafiltration confirms the differences in intracardiac pressure and volume conditions between the different renal replacement methods.
7. The correlation between systolic dysfunction and the predisposition for ventricular arrhythmias were found to be valid in both renal replacement therapies.
8. Positive correlations were shown between left ventricular mass index and the studied electrocardiographic markers in both renal replacement methods indicating the sovereign pathogenic role of ventricular hypertrophy in the genesis of cardiac arrhythmias.

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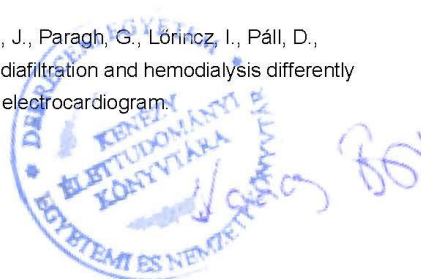
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List of publications related to the dissertation

1. Barta, K., **Czifra, Á.**, Kun, C., Páll, A., Kulcsár, J., Paragh, G., Lőrincz, I., Padra, J.T., Agarwal, A., Zarjou, A., Balla, J., Szabó, Z.: Hemodiafiltration beneficially affects QT interval duration and dispersion compared to hemodialysis.
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List of other publications

3. Páll, A., **Czifra, Á.**, Sebestyén, V., Becs, G., Kun, C., Balla, J., Paragh, G., Lőrincz, I., Páll, D., Padra, J.T., Agarwal, A., Zarjou, A., Szabó, Z.: Hemodiafiltration and hemodialysis differently affect P wave duration and dispersion on the surface electrocardiogram.
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