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Assessment of atrial electromechanical delay and left atrial mechanical functions in chronic kidney disease

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ABSTRACT

The risk of atrial fibrillation (AF) development was revealed to be increased in patients with end-stage renal disease (ESRD) Elongation of the time of atrial electromechanical delay (AEMD) is a famous typical of the atrium. AEMD is a risk factor for AF development and it could be associated with chronic kidney disease (CKD). The aim of our study is to examine mechanical functions of the left atrium (LA) and AEMD times in ESRD. A total of 86 participant, 46 with ESRD and 40 as the control group, were included in the study. The demographical and laboratory information were documented. Echocardiographic dimensions were achieved in all patients. Left atrial mechanical functions and AEMD durations were calculated. Demographic and laboratory characteristics of the groups were similar except the mean diastolic blood pressure, hemoglobin, creatinine, glucose, uric acid, calcium and potassium levels. The echocardiographic assessment exposed that the ventricular septal thickness (12.7±1.5 vs. 10.4±1.5, $p<0.001$), posterior wall thickness (12.6±1.6 vs. 10.1±1.9, $p<0.001$), LA dimension (40.9±5.3 vs.34.6±2.6, $p<0.001$) and diastolic parameters decreased in the ESRD group when compared to the control group; also, LA volumes, mechanical functions, inter atrial EMD (33.2±9.1 vs. 22.7±7.7, $p<0.001$), intra-right-EMD (18.5±7.7 vs. 13.2±6.4, $p=0.001$) and intra-left-EMD (18.5±7.7 vs. 13.7±5.7, $p=0.002$) were also different between groups. ($p<0.005$) The correlation analysis showed that serum ferritin levels were correlated with AEMD. We found deteriorated LA functions and elongation in the times of AEMD in the ESRD group compared with the control group. Additionally, we found positive correlation between ferritin levels and AEMD. This result show that AEMD might be used to predict the risk of development of AF in patients with ESRD.

1. Introduction

Atrial fibrillation (AF) is the most often faced arrhythmia in clinical practice and is a major cause of ischemic stroke (Go et al., 2001). In some studies, the risk of AF development was revealed to be increased in patients with end-stage renal disease (ESRD) who are in a haemodialysis program (Korantzopoulos and Goundevenos, 2009). Also AF was shown to increase cardiovascular mortality by complicating patients with chronic kidney disease (CKD). Increased

atrial electromechanical delay (AEMD) reproduces heterogeneity of inter and intra-atrial conductivity and is a risk factor for AF development. At this time, AEMD may be measured during echocardiography non-invasively, which produce similar results to invasive electrophysiological study (Deniz et al., 2012).

Inter-atrial and intra-atrial conduction durations were shown to be increased by age and many systemic sicknesses such as diabetes and hypertension which were exposed to be conventional risk factors for AF (Emiroglu et al., 2011); however, effects of ESRD on atrial electromechanical functions were not investigated adequately. The aim of our study was to evaluate AEMD durations measured by echocardiography in patients with ESRD.

2. Methods

Study population

A total of 46 patients with Group 1, aged over 18 years, who were on a regular haemodialysis program at the nephrology clinic of Kırşehir Ahi Evran University. Healthy people who were admitted to the cardiology outpatient due to any symptom matched for age and sex were involved in this study as Group 2. ESRD patients getting haemodialysis treatment 3 times a week for at least 1 year in our institution. These patients had been experiencing an average haemodialysis program (500 mL/min dialysate flow; 250 mL/min blood flow; 4 hours of per treatment session). The study was shown in agreement with the ethical principles described by the Declaration of Helsinki (Williams, 2008)

Exclusion criteria of this study were as follows: patients having diabetes mellitus (DM), documented coronary artery disease (CAD), valvular heart disease of moderate severity, myocarditis, pericarditis, any cardiovascular drug use, rhythms other than sinus, significant valvular heart disease, chronic obstructive pulmonary disease, hepatic dysfunction, hyperthyroidism.

Investigation planning and measurements:

Firstly, demographic data of patients who were entitled to be involved in the study and signed an knowledgeable agreement form were noted. Group 1 examinations were conducted on the days when they did not receive haemodialysis to get volume standardization.

Echocardiographic evaluation

Echocardiography was achieved by a GE VingMed Vivid 7 (GE VingMed Ultrasound, Horten, Norway) Parasternal long-axis, short-axis, and apical four-chamber and two-chamber images were occupied and the calculation was completed using M-mode, 2D, continuous wave Doppler, pulsed wave Doppler, and tissue Doppler methods (Quinones et al., 2002). Posterior wall (PW) thickness, interventricular septum (IVS) thickness, left ventricular end-diastolic diameter (LVEDD) and left ventricular diameter (LVESD) were considered using M-mode method. The modified Simpson method was used to calculate left ventricular ejection fraction (EF)

Evaluating left atrial (LA) mechanical functions by echocardiography

The LA volumes were intended from the four- and two-chamber views, using Simpson's rule. LA maximum volume (Vmax) was noted just when the mitral valve was opened and LA minimum volume (Vmin) was noted just when the mitral valve was closed; LA presystolic volume (Vp) was noted at the opening of atrial systole p wave on ECG. All LA volumes were modified for body surface area (BSA).

LA emptying functions were intended as follows:

LA passive emptying volume (LAPEV): Vmax-Vp

LA passive emptying fraction (LAPEF): LAPEV/ Vmax

LA active emptying volume (LAAEV) Vp-Vmin

LA active emptying fraction (LAAEF): LAPEF / Vp

LA total emptying volume (LATEV)=Vmax-Vmin

(Aydın et al., 2004).

Interatrial and intraatrial electromechanical delay

All EMD times used to measure interatrial and intraatrial electromechanical delay was determined by the tissue Doppler imaging (TDI) method and simultaneous electrocardiographic rhythm traces. Atrial systole was measured to be the A wave (A), which was the second negative deviation at diastole. The time interval between the start of the P wave in the superficial ECG and the highest of late diastolic wave (Am wave) was distinct as atrial electromechanical coupling (PA), although the measurements were occupied from the lateral mitral annulus (lateral PA), septal annulus (septal PA), and right ventricular tricuspid annulus (tricuspid PA). Interatrial and intraatrial electromechanical delays were calculated (Dabrowska-Kugacka et al., 2009):

- Interatrial electromechanical delay (Interatrial EMD): Time difference between lateral PA and tricuspid PA; and
- Intraatrial electromechanical delay (Intraatrial EMD): Time difference between septal PA and tricuspid PA.

Statistical analysis

All data were analysed using SPSS for Windows version 15.0 software (Chicago, IL, USA). Categorical variables were obtainable as frequencies and percentages; continuous variables were expressed as means and SD. The normal distribution of continuous variables was tested with the Kolmogorov-Smirnov test. Continuous variable differences between groups were examined by the Mann-Whitney U test. Correlation

analyses were performed using Spearman's coefficient of correlation. The comparison of categorical values was carried out with the chi-square test. p<0.05 was considered significant.

3. Results

Clinical and laboratory findings are revealed in table 1. There were important differences in mean diastolic blood pressure, haemoglobin, creatinine, serum glucose, uric acid, phosphor, potassium between the groups (p<0.05) (Table 1). Systolic and diastolic blood pressures were significantly higher in the ESRD group. Echocardiographic dimensions, there were significant differences IVS thickness(12.7±1.5mm vs. 10.4±1.5mm, p<0.001) PW thickness (12.6±1.6mm vs. 10.1±1.9mm, p<0.001), LA dimension (40.9±5.3 vs. 34.6±2.6, p<0.001), DT (222.5±44.8 vs. 199.9±28.9, p=0.008), IVRT (116.1±18.8 vs. 105.8±12.8, p=0.004), E/A ratio (1.0±0.4 vs. 1.2±0.3, p=0.04) and tissue Doppler early diastolic flow (0.7±0.2 vs. 0.9±0.2, p=0.001) between groups (p>0.05) (Table 2).

Table 1. Baseline clinical and laboratory characteristics of study population and comparison between groups

	Group 1 (n=46)	Group 2 (n=40)	*p* value
Age (years)	57.6 ± 13.6	52.8 ± 8.9	0.061
Male sex % (n)	21	22	0.387
Mean systolic blood pressure (mmHg)	121.7 ± 20.0	117.3 ± 12.2	0.221
Mean diastolic blood pressure (mmHg)	77.3 ± 13.4	70.9 ± 9.9	0.015
Hemoglobin (g/L)	10.9 ± 1.2	14.1 ± 1.4	<0.001
White blood cell (10^3 µL)	7.4 ± 2.8	6.6 ± 1.8	0.146
Creatinine (mg/dL)	7.9 ± 2.5	0.8 ± 0.1	<0.001
Serum glucose (mg/dL)	106.2 ± 30.8	87.2 ± 8.7	<0.001
Uric acid (mg/dL)	6.4 ± 1.1	4.7 ± 1.1	<0.001
Phosphor (mg/dL)	5.1 ± 1.3	3.5 ± 0.6	<0.001
Calcium (mg/dL)	8.9 ± 0.7	9.1 ± 0.3	0.278
Potassium (mmol/IL)	4.8 ± 0.6	4.3 ± 0.3	<0.001

The LA volume indices are shown in Table 3. There were no significant differences in LATEV, LAAEF, LAAEV, LAPEV between the ESRD and Group 2 (p>0.05). Atrial electromechanical coupling parameters at different sites measured via tissue Doppler imaging are shown in Table 4. PA lateral (144.1±13.5 vs. 126.3±10.6, p<0.001), PA septal (129.4±13.1 vs. 116.8±9.7, p<0.001), PA tricuspid (110.9±10.9 vs. 103.1±9.1, p=0.001), IA-EMD (33.2±9.1 vs. 22.7±7.7, p<0.001), IRight-EMD (18.5±7.7 vs. 13.2±6.4, p=0.001) and ILeft-EMD (18.5±7.7 vs. 13.7±5.7, p=0.002) durations were significantly longer in the ESRD group than in the control group There was a significant correlation between ferritin levels and AEMD durations (Fig. 1).

Table 2. Conventional echocardiographic parameters and Comparison Between Groups

	Group 1 (n=46)	Group 2 (n=40)	*p* value
IVS thickness (mm)	12.7 ± 1.5	10.4 ± 1.5	<0.001
PW thickness (mm)	12.6 ± 1.6	10.1 ± 1.9	<0.001
LVEDD (mm)	46.1 ± 4.9	46.9 ± 4.6	0.436
LVESD (mm)	30.7 ± 4.8	31.6 ± 4.3	0.476
LA dimension (mm)	40.9 ± 5.3	34.6 ± 2.6	<0.001
LVEF (%)	58.0 ± 9.0	59.9 ± 5.8	0.256
DT (ms)	222.5 ± 44.8	199.9 ± 28.9	0.008
IVRT (ms)	116.1 ± 18.8	105.8 ± 12.8	0.004
E (m s–1)	0.71 ± 0.2	0.79 ± 0.18	0.121
A (m s–1)	0.76 ± 0.22	0.69 ± 0.11	0.076
E/A	1.0 ± 0.4	1.2 ± 0.3	0.040
E'	0.7 ± 0.2	0.9 ± 0.2	0.001

IVS: Ventricular septal thickness; **PW:** Posterior wall thickness; **LVEDD:** Left ventricular end-diastolic dimension; **LVESD:** Left ventricular end-systolic dimensions; **LA:** Left atrium; **LVEF**: Left ventricular ejection fraction; **E:** Early diastolic flow; **A:** Atrial contraction signal; **DT;** Deceleration time; **IVRT**: Isovolumetric relaxation time; **E':** Early tissue doppler flow

Table 3. LA Electromechanical Functions and Comparision Between Groups

	Group 1 (n=46)	Group 2 (n=40)	*p* value
LA Vmax (mL m²)	44.9 ± 14.7	34.9 ± 6.6	<0.001
LA Vmin (mL m²)	23.5 ± 8.5	15.9 ± 4.3	<0.001
LA Vp (mL m²)	33.0 ± 10.9	24.9 ± 4.5	<0.001
LA EF (%)	47.5 ± 8.1	53.8 ± 10.4	0.002
LATEV (mL m²)	21.5 ± 7.8	19 ± 5.9	0.108
LAAEF (%)	28.8 ± 8.1	36.1 ± 10.1	<0.001
LAAEV(mL m²)	9.5 ± 3.9	8.9 ± 3.0	0.505
LAPEF (%)	26.3 ± 6.9	30.7 ± 10.5	0.024
LAPEV(mL m²)	11.9 ± 5.6	10.9 ± 4.6	0.346

LA Vmax: Left atrium maximum volume; **LA Vmin:** Left atrium minimum volume; **LA Vp:** Left atrium volume before atrial systole; **LAEF:** Left atrium ejection fraction; **LATEV:** Left atrium total emptying volume; **LAAEF:** Left atrium active emptying fraction; **LAAEV:** Left atrium active emptying volume; **LAPEF:** Left atrium passive emptying fraction; **LAPEV:** Left atrium passive emptying volume

4. Discussion

In this study, we observed deterioration of LA mechanical functions and increase of AEMD durations in patients with ESRD in comparison to the Group 2. Also, we detected a correlation between AEMD durations and serum ferritin levels.

Patients with ESRD were shown to have a higher risk of cardiac arrhythmias and sudden cardiac death in previous studies. About half of cardiovascular deaths of patients with ESRD are due to cardiac arrhythmias and sudden death (Chan et al., 2010). Furthermore, to the pro-arrhythmogenic effect of HD, increasingly decreasing kidney functions cause electrolyte imbalance. Similarly, coronary artery disease, hypertension, heart failure and ventricular hypertrophy, which are seen often as co-morbidities with ESRD, contribute to development of arrhythmias. AF is the most often seen arrhythmia in daily practice,

Table 4. Electrocardiographic and tissue Doppler echocardiographic findings

	Group 1 (n=46)	Group 2 (n=40)	*p* value
PA Lateral (ms)	144.1 ± 13.5	126.3 ± 10.6	<0.001
PA Septal (ms)	129.4 ± 13.1	116.8 ± 9.7	<0.001
PA Tricuspid (ms)	110.9 ± 10.9	103.1 ± 9.1	0.001
IA-EMD (ms)	33.2 ± 9.1	22.7 ± 7.7	<0.001
IRight-EMD (ms)	18.5 ± 7.7	13.2 ± 6.4	0.001
ILeft-EMD	18.5 ± 7.7	13.7 ± 5.7	0.002

PA: Time interval from the on set of the P-wave on the surface ECG to the peak of the late diastolic wave (A wave); **IA-EMD:** Inter-atrial electromechanical delay; **IRight-EMD:** Intra-right electromechanical delay; **ILeft-EMD:** Intra-left electromechanical delay

it increases the risk of stroke five times (Hart, 2000). The risk of AF is known to be increased in patients with ESRD. Alvaro et al. (2011) have followed up 10358 patients for a mean duration of 10.1 years in their ARIC study and detected a strong association between CRD and AF, independent of other risk factors. Winkelmayer et al (2011) have found a two-fold increase in one-year mortality in patients with AF in their study on 2.5 million patients with HD (38.9% vs. 19.3%). Defining the risk factors causing atrial fibrillation (AF) are very important for decreasing the morbidity and mortality. In addition to conventional risk factors such as diabetes, hypertension, a number of echocardiographic and clinical factors were found in recent years (To et al., 2007), but some of these techniques are not suitable for clinical practice, as they are invasive. P wave dispersion at ECG and dimension of LA dilatation at echocardiography have low prognostic value. AEMD durations measured echocardiographically, which were technologically advanced recently are used in determination of AF risk and these were revealed to be correlated with invasive methods.

The effect of ESRD on AEMD was investigated in few studies. In the study by Karavelioğlu et al. (2014), atrial electromechanical coupling times were shown to be increased in haemodialysis patients, and also left atrial diameter and left ventricular end-diastolic pressures were found to be associated with AEMD durations. In the study by Tekcea et al. (2013) AEMD durations which were shown to be increased in patients with ESRD before haemodialysis were shown to decrease after dialysis, and dialysis was found to have positive effects not only on structural remodelling, but also on electrical remodelling. In a study by Turkmen et al. (2015) increased left intra-atrial EMD time in patients with HD was found to increase 2-year mortality due to combined cardiovascular events and all-cause mortality.

It was shown that ESRD affects LA mechanical functions in studies and various mechanisms were proposed. The risk of HT development is increased in patients with CKD and these patients have weaker blood pressure control (Sarnak et al., 2003). CKD likewise activates the renin, angiotensin, aldosterone system, which cause atrial fibrosis and electrical remodelling (Siragy and Carey, 2010). The cause of deteriorated LA mechanical functions and increased AEMD durations in patients with ESRD may originate from interrelations between these various mechanisms mentioned above.

Another interesting point in the present study, is the

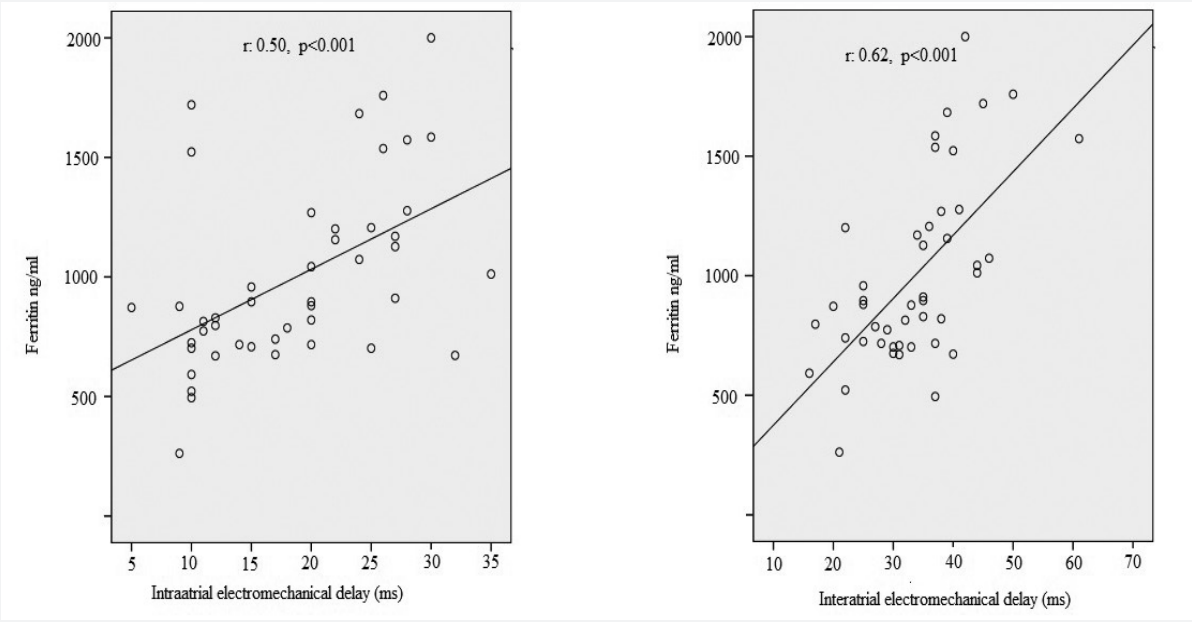

Fig. 1. Correlation graphs of atrial electromechanical delays with Ferritin levels

correlation between serum ferritin levels and AEMD durations. It is known that oral and intravenous iron treatment are given to dialysis patients for optimal response to human erythropoietin treatment. However, long-term iron treatment may cause oxidative stress, and inflammatory effects may disturb endothelial functions (Borawski et al., 2004) and iron was revealed to increase oxidative stress, thus producing deterioration in endothelial functions in disorders for example ESRD and thalassemia, in which iron load is increased (Bishu and Agarwal, 2006). The standing of inflammation in AF development was revealed in many illnesses where there is systemic inflammation. Also, iron overload in which primary and secondary hemosiderosis may also be seen, increases inflammation. The cause of the correlation between ferritin and AEMD durations may be due to increased iron levels affecting atrial conduction.

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