The Effects of a Single Dialysis Session on Atrial Electromechanical Conduction Times and Functions

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Key Words
Atrial conduction time • Atrial fibrillation • Atrial mechanical functions • Atrial remodeling • Electromechanical delay • Hemodialysis

Abstract
Background/Aims: Abnormalities in atrial electromechanical delay (EMD) times and mechanical functions are considered as independent predictors of atrial fibrillation. However, to date, effects of a single hemodialysis (HD) session and acute volume-preload changes on atrial-EMD functions have not been investigated by Tissue Doppler Echocardiography (TDE). The aim of the present study was to evaluate atrial-EMD times and mechanical functions in HD patients.

Methods: Thirty-five non-diabetic, normotensive HD patients and 35 healthy control subjects were enrolled in the study. Standard and TDE performed before mid-week dialysis session for hemodialysis group and on admission for control group.

Results: Interatrial and left-right intraatrial-EMD intervals and left atrial mechanical volumes were significantly longer in hemodialysis group compared to controls (all p<0.01) and were reduced after HD session. Furthermore, removed ultrafiltration volume was associated with reduction in atrial-EMD intervals and functional volumes. LA-passive emptying volume, ultrafiltration volume, LV-E/E' ratio, and Vp were independent predictors of interatrial-EMD.

Conclusions: The present study confirms negative effects in HD patients of structural remodeling and reveals negative effects of electrical remodeling. Prolonged inter and intraatrial-EMD intervals should be the underlying pathophysiological factors of increased rate of atrial fibrillation in the HD population.

Introduction
Atrial fibrillation (AF) is the most common arrhythmia in hemodialysis (HD) patients [1]. The prevalence of AF is estimated about 7–23.4% [2, 3] in end stage renal disease (ESRD)
patients which is 10–20 folds higher than in the general population [4, 5]. AF is associated with increased cardiovascular mortality rate in these patients [6]. Therefore, determining the predisposing risk factors of AF in this population is crucial. Electrical and/or structural remodeling of the atria is the basic pathophysiological mechanism of AF [7]. Measurement of left atrial (LA) diameter and volume index are the most common diagnostic tools in the evaluation of atrial remodeling and functions. However, conventional echocardiographic parameters easily affected by acute preload changes and they do not allow to assess electromechanical functions of atria [8].

Tissue Doppler Echocardiography (TDE) is very useful diagnostic tool for determining atrial conduction intervals [9]. Electromechanical delay (EMD) intervals of different atrial regions should be obtained with high temporal resolution with this technique. LA volumes and mechanical functions have recently been identified as potential indicators of cardiac diseases and arrhythmias [10-12]. Unlike the size of LA, atrial electromechanical conduction times and mechanical volumes indicate both electrical and structural remodeling of the atria. Several electrophysiological parameters (inter and intra-atrial EMD) were considered as predictors of AF [13, 14].

Recently, it has been shown that paroxysmal AF, rheumatoid arthritis, systemic lupus erythematosus and subclinical hypothyroidism may impair LA functions and atrial conduction times [14-17]. However, to date, effects of a single HD session and acute volume-preload changes on atrial electromechanical conduction functions have not been investigated by TDE. The aim of the present study was to evaluate atrial electromechanical conduction times and mechanical functions before and after HD in ESRD patients.

Materials and Methods

Study Population

Thirty-five nondiabetic, nonhypertensive HD patients (16 women and 19 men) and 35 healthy control subjects (18 women and 17 men) enrolled the prospective study. We enrolled the study normotensive, euvolemic, non-edematous, well-controlled dry weight HD patients whose cardio-thoracic index lower than 0.5. All evaluations were performed on admission for the control group while on before and after midweek dialysis session to obtain volume standardization in HD group. All patients on HD group were on dialysis treatment for 4 hours 3 times a week in the same dialysis center. Same kind of low flux, hollow fiber dialyzers (composed of polysulfone) used for all patients. Patients with a Kt/V > 1.4 were enrolled to the study. All participants had normal sinus rhythm on electrocardiography (ECG). The study approved by the local ethics committee of Abant Izzet Baysal University. Informed consent obtained from all participants.

Patients with diabetes mellitus, hypertension (blood pressure ≥ 140/90 mm Hg), cardiac arrhythmia such as atrial flutter or fibrillation (current presence or a previous history), valvular heart diseases, heart failure, coronary artery disease, chronic obstructive pulmonary disease, a history of cardiac surgery or implanted device, sick sinus syndrome and active infectious disease were excluded from the study. Finally, patients that not given informed consent and patients with poor echocardiographic image were excluded.

Standard Echocardiography

All patients were evaluated by transthoracic M mode, two dimensional (2D), pulsed-wave (PW), continuous wave (CW), colour flow and Tissue Doppler Echocardiography (TDE). All examinations were performed with the GE Vivid-7 system (GE Vingmed, Horten, Norway) with a 2–4 MHz transducer at a depth of 16 cm. Continuous single-lead ECG obtained from all patients during echocardiography. All patients were imaged in the left lateral decubitus position.

2D and conventional Doppler examinations were obtained in the parasternal and apical views, according to the guidelines of the American Society of Echocardiography [18]. LV diameters and wall thickness were measured by M-mode echocardiography. LV ejection fraction was calculated using apical two-and four-chamber views by Simpson’s method, according to the American Society of Echocardiography guidelines [18]. The mitral valve inflow pattern (E-wave, A-wave, E-wave deceleration time [Dt], E/A ratio and isovolumic relaxation time [IVRT]) was measured using pulsed wave Doppler. LV mass index was
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calculated using the formula with the Deveraux equation [19]. LA volumes were obtained via apical four and two chamber views by a disc method [18, 20]. LA maximum volume (V_max) at the end-systolic phase, LA minimum volume (V_min) at the end-diastolic phase, and LA volume before atrial systole (V_p) were measured and calculation indexed to body surface area. The LA function parameters were calculated as follows:

- LA passive emptying volume = V_max – V_p,
- LA passive emptying (%) = [(V_max – V_p) / V_max] × 100,
- LA active emptying volume = V_p – V_min,
- LA active emptying (%) = [(V_p – V_min) / V_p] × 100 [14, 21].

Tissue Doppler Echocardiography (TDE)

TDE was performed by transducer frequencies of 3.5 to 4.0 MHz, adjusting the spectral pulsed Doppler signal filters to acquire the Nyquist limit of 15 to 20 cm/s and using the minimal optimal gain. Myocardial TDE velocities (peak systolic [S'], early diastolic [E'] and late diastolic velocities [A']) were measured via spectral pulsed Doppler as of the LV-free wall from the apical four and two chamber view [18]. The ultrasound beam was positioned as parallel as possible with the myocardial segment to acquire the optimal angle of imaging.

Atrial electromechanical coupling (PA) is the time interval from the onset of P wave to the late diastolic wave on ECG. It has obtained from lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus and called as following: PA_lateral, PA_septum and PA_tricuspid respectively. Interatrial electromechanical delay (EMD) was measured by the difference between PA_lateral and PA_tricuspid. Left intraatrial EMD was measured by the difference between PA_lateral and PA_septum, and finally, right intra-atrial EMD was measured by the difference between PA_septum and PA_tricuspid [18, 21, 22]. An average measurement achieved after obtaining these values three times. Two cardiologist who were unaware of the patients were performed the echocardiologic measurements. We excluded the patients from the study if there was a difference greater than 5% between the measurements of the echocardiologists.

Statistical Analysis

SPSS software version 15.0 used for statistical analysis. Continuous variables were presented as mean ± standard deviation while categorical variables were presented as the percentage. Numerical variables of the groups were distributed normally, and variances were equal. Since the baseline demographics, laboratory and echocardiographic values were normally distributed; the Independent samples t-test was performed to compare these parameters between the HD and control groups. Paired Student’s test was used to compare the measurements at two time points (before and after HD) for LA mechanical functions and atrial conduction times measurements. Pearson’s and Spearman correlation tests used to determine the correlation between variables. A backward multiple regression analysis was used to recognize the significant determinants of interatrial EMD, which incorporated variables that correlated with a p value of less than 0.1 in the correlation analysis. A value of p<0.05 was considered statistically significant.

Results

Patient Characteristics

The clinical, laboratory characteristics and echocardiographic findings of HD patients and control subjects shown in Table 1. The mean HD duration, interdialytic weight gain, ultrafiltration volume and kT/V were 4.2 ± 3.1 years, 2.52 ± 1.14 kg, 2.38 ± 1.03 kg and 1.63, respectively, in HD group. Age, sex, smoking status, heart rate, lipid profiles, glucose and thyroid stimulant hormone levels, systolic and diastolic blood pressure, and left ventricular (LV) end-systolic diameter were similar between two groups (p>0.05). Hemoglobin levels (p<0.01), LV ejection fraction (p=0.043), LV E/A ratios (p=0.015) were significantly lower in HD patients than the controls. Septum (p=0.037) and posterior wall thickness (p=0.029), E (p=0.024) and A (p=0.018) wave, LV end-diastolic diameter (p=0.023), LV mass index (p=0.014) and E/E’ ratios (p<0.01) were significantly increased in HD patients than the control group.
LA mechanical functions

Table 2 shows measurements of LA volumes, mechanical functions and variabilities of these parameters between groups. Measurements of LA diameter, \(V_{\text{max}}\), \(V_{\text{min}}\), conduit volume, LA passive emptying volume, LA active emptying volume were elevated in HD group compared to controls (all \(p<0.01\)). LA passive (\(p<0.01\)) and active (\(p<0.01\)) emptying (%) were significantly lower in HD group than the control group.

\[ V_{\text{max}} (p<0.01), V_{\text{min}} (p<0.01), V_p (p<0.01), \] LA passive emptying volume (\(p<0.01\)), LA diameter (\(p<0.01\)), and conduit volumes (\(p=0.015\)) were significantly reduced in HD patients before HD session compared to after HD measurements. There was no significant difference
before and after HD measurements in terms of LA passive and active emptying (%), LA active emptying volume parameters (all p>0.05).

The difference of $V_{\max}$, $V_p$, LA passive emptying volume, LA diameter measured before and after HD session was positively correlated with ultrafiltration volume ($r=0.403$, $p=0.04$; $r=0.686$, $p=0.027$; $r=0.505$, $p=0.036$; $r=0.761$, $p=0.019$; respectively, Pearson correlation test), but there was no difference in terms of $V_{\min}$, conduit volume, LA passive and active emptying (%), LA active emptying volume parameters (all p>0.05).

### Table 3. Atrial electromechanical interval findings measured by Tissue Doppler Echocardiography (TDE)

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=35)</th>
<th>Before HD (n=35)</th>
<th>After HD (n=35)</th>
<th>$p^1$ Control group vs before HD</th>
<th>$p^2$ Before HD vs after HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA lateral (ms)</td>
<td>54.6 ± 4.1</td>
<td>72.5 ± 8.0</td>
<td>64.8 ± 6.5</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<tr>
<td>PA septum (ms)</td>
<td>42.1 ± 5.3</td>
<td>51.3 ± 5.5</td>
<td>46.1 ± 4.5</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PA tricuspid (ms)</td>
<td>37.7 ± 3.9</td>
<td>39.4 ± 6.2</td>
<td>38.7 ± 5.3</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PA lateral − PA tricuspid (ms)$^a$</td>
<td>17.4 ± 3.8</td>
<td>32.2 ± 6.5</td>
<td>26.1 ± 6.5</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PA lateral − PA septum (ms)$^b$</td>
<td>11.6 ± 3.4</td>
<td>22.8 ± 7.2</td>
<td>17.3 ± 8.3</td>
<td>&lt;0.01</td>
<td>0.013</td>
</tr>
<tr>
<td>PA septum − PA tricuspid (ms)$^c$</td>
<td>7.2 ± 1.7</td>
<td>14.4 ± 5.3</td>
<td>11.7 ± 4.8</td>
<td>&lt;0.01</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation. HD: Hemodialysis, PA: The interval measured by tissue Doppler imaging from the onset of the P wave on the surface electrocardiogram to the beginning of the late diastolic (Am) wave. $^a$Interatrial electromechanical delay; $^b$Left intra-atrial electromechanical delay; $^c$Right intra-atrial electromechanical delay

### Atrial conduction times

Table 3 shows the measurements of atrial electromechanical conduction time intervals and variations of these measurements between groups. PA lateral, PA septum durations of the HD group were significantly prolonged compared to controls (72.5 ± 8.0 vs 54.6 ± 4.1, 51.3 ± 5.5 vs 42.1 ± 5.3; p<0.01). There was no statistically significant difference between groups in terms of PA tricuspid (p>0.05). Interatrial, left intraatrial and right intratrial EMD intervals were significantly longer in HD group compared to controls (32.2 ± 6.5 vs 17.4 ± 3.8, p<0.01; 22.8 ± 7.2 vs 11.6 ± 3.4, p=0.013; 14.4 ± 5.3 vs 7.2 ± 1.7, p=0.036, respectively).

PA lateral and PA septum durations significantly reduced after HD compared to before HD period (72.5 ± 8.0 vs 64.8 ± 6.5, 51.3 ± 5.5 vs 46.1 ± 4.5; both p<0.01); however, no difference determined on PA tricuspid intervals (39.4 ± 6.2 vs 38.7 ± 5.3; p>0.05). Both left and right intraatrial and interatrial EMD intervals significantly reduced on after HD session compared to before HD period (22.8 ± 7.2 vs 17.3 ± 8.3, p=0.013; 14.4 ± 5.3 vs 11.7 ± 4.8, p=0.036; and 32.2 ± 6.5 vs 26.1 ± 6.5, p=0.01, respectively).

We found a correlation between UF volume and the difference of inter and left intraatrial EMD interval measurements before and after HD period. (Pearson correlation test, r=0.814, p<0.01; r=0.502, p=0.011; respectively). However, no such correlation found between right intraatrial EMD difference and UF volume. (Pearson correlation test, r=-0.318, p=0.290).

A backward linear regression analysis demonstrated that, LA passive emptying volume, ultrafiltration volume, LV E/E’ ratio, and $V_p$ are independent predictors for interatrial EMD (Table 4). But, there were no relation between interatrial EMD and age, HD duration, Kt/V, hemoglobin level, LA diameter, $V_{max}$, $V_{min}$, conduit volume, LA passive and active emptying (%), LA active emptying volume, LV end-diastolic diameter, LV E/A ratio, LV ejection fraction, and LV mass index.

### Discussion

To our knowledge, this is the first study observed the changes on electromechanical conduction intervals measured by TDE of HD patients. We demonstrated a prolongation in inter and intraatrial conduction intervals in HD patients compared to healthy subjects.
Furthermore, removed ultrafiltration volume was associated with reduction in atrial electromechanical conduction intervals. Another important result of the present study is that not only LA diameter but also LA mechanical volumes and function parameters are impaired in HD patients, and they reduce after HD session.

Many risk factors have been defined in several studies that performed to determine clinical and echocardiographic predictors of AF in dialysis patients [2, 23-25]. Independent risk factors of AF are age, gender (male), hypertension, diabetes mellitus, heart failure, valvular heart diseases, and LA enlargement as listed in Framingham and same other studies [26-28]. Risk factors for AF in HD population are age, HD duration, heart diseases and LA enlargement [5]. We designed this study on nondiabetic nonhypertensive HD population to avoid the effects of these conditions which are AF predictors on atrial EMD measurements. Study cohort was consisted of relatively younger, and clinically well patients whose HD duration was relatively shorter.

In recent studies, authors obtained indirect data about atrial conduction intervals by simulating human atrial myocytes or by using the averaged P wave signals. Conduction velocity and effective refractory period on after HD sessions is reduced in the Courtemanche simulated human atrial myocytes model [29]. Authors evaluated HD patients with digital ambulatory P signal averaged electrocardiography, recently [30] and they found an increase in P wave duration and a reduction in root mean square voltages for the last 20 ms of the P wave (RMS20), which are considered as predictors for AF. Those electrocardiographic changes were associated with HD duration and the volume removed by HD. Electrophysiological studies have shown that paroxysmal AF is associated with longer interatrial and intraatrial conduction times of sinus impulses, which results in prolongation of the P wave in ECG [31]. An association between AF development and inter and left intra atrial conduction delay with TDE has been described [22]. Inter and intraatrial conduction delays determined by TDE in rheumatological diseases such as rheumatoid arthritis [14] and SLE [15] and suggested that these would be early manifestations of subclinically cardiac involvement.

Main outcomes of present study are prolongation in both interatrial and left-right intra atrial EMD intervals in HD cohort and reduction of these intervals after HD session. Prolonged PA lateral and PA septum durations reflects the delay of the electrical impulse based from synoatrial node to lateral and septal mitral annuluses. However, delay in this duration may be an electrophysiological consequence of prolongation in signal conduction ways caused by atrial enlargement. Because the distance between synoatrial node and right ventricular tricuspid annulus, where the electrodes have been placed, is very short, it is not surprising we
could not detect a significant difference in PA\(_{\text{tricuspid}}\) intervals. Moreover, manually recording throughout an ECG of current devices instead of digitally recording systems and relatively small study population may also contribute this insignificant difference in PA\(_{\text{tricuspid}}\) intervals.

TDE studies in HD population were accumulated on ventricular volumes, and there are few reports about LA mechanical functions. Tissue velocity and strain rate on late diastolic phase correctly predicts LA contractile functions independently from preload in evaluation of ESRD patients with TDE [32]. Early diastolic velocity (E') was found as an independent predictor of LV diastolic functions in ESRD patients in a study evaluated mitral annulus with TDE [8]. Preload reduction after fluid removal by HD results a reduction in LA diameter and LA volumes in same study. Our results are very important reporting the deterioration in atrial mechanical functions in non-diabetic, normotensive HD cohort compared to normal subjects. Overvolemia may explain the elevation in the parameters of LA and passive emptying volumes in ESRD patients. In addition, increase in LA active emptying volume in HD patients may be explained not only with atrial remodeling caused by chronic hypervolemia but also with secondary effects of ventricular diastolic dysfunction and LV hypertrophy (ventricular remodeling) in the present study. This hypothesis is compatible with the results of previous reports in the literature. Deterioration of myocardial diastolic functions in ESRD patients cause an increase in LV filling pressure and subsequently, in LA pressure and finally, may cause LA dilatation [33]. An increase in atrial size most commonly is related to increased wall tension as a result of increased filling pressure. Also increased filling pressure may be related to LV diastolic dysfunction in ESRD patients. Previous reports suggest impaired LA measurements reflects both magnitude and duration of LV diastolic dysfunction [34, 35]. This hypothesis is strongly suggested by HD patients in our study had lower E/A ratios, more increased LV end diastolic diameters and E/E' ratios compared to control subjects. In regression analyse, beside removal ultrafiltration volume, V\(_{\rho}\) passive emptying volume, and high E/E' ratio; which is the marker of diastolic dysfunction, are both found to be independent predictors of interatrial EMD. It is concluded that, atrial remodeling should not be understood apart from ventricular remodeling in terms of mechanical functions.

Study Limitations

Relatively small population is the major limitation of this study. As diabetes mellitus and hypertension considered conventional risk factors for AF, difficulties in selecting non diabetic and normotensive HD patients limited the study cohort. Another important limitation of our study is we could not followed up patients in terms of arrhythmic episodes. Therefore, more studies with a larger population are needed to identify intra and inter-atrial conduction delay in HD patients. Especially, studies investigating the association between parameters related to volume condition and electromechanical conduction time, are necessary.

Conclusions

Results of the present study reflects not only negative effects of structural remodeling, which has been mentioned in previous studies in literature, but also negative effects of electrical remodeling. This study demonstrated that, LA passive emptying volume, LA volume before atrial systole, ultrafiltration volume, and LV E/E' ratio are independent predictors of interatrial EMD. Prolonged inter- and intra-atrial EMD intervals should be the underlying pathophysiological factors of increased rate of AF in patients undergoing HD. Further studies evaluating the value of our findings in predicting the occurrence of atrial fibrillation will be needed to establish the clinical significance of our results.

Conflict of Interest

None declared.
References

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