Hemodiafiltration and hemodialysis differently affect P wave duration and dispersion of the surface electrocardiogram

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Short title: Effect of hemodiafiltration on P wave duration

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal failure. Several studies have confirmed that the incidence of atrial and ventricular arrhythmias is higher during hemodialysis [1-3]. Atrial fibrillation is one of the most commonly encountered arrhythmias in patients on chronic renal replacement therapy, with an incidence of approximately 10%. Independent risk factors for atrial fibrillation include age, gender, hypertension, diabetes mellitus, heart failure, and valvular heart disease. In patients with renal diseases, mortality caused by atrial fibrillation is primarily connected with thromboembolic consequences [4]. In addition, the hemodynamic deterioration caused by the arrhythmia leads to increased mortality rates, especially in patients with altered left ventricular systolic function [5,6]. In patients with paroxysmal atrial fibrillation during sinus rhythm, the intra- and interatrial conduction time of the sinus impulse lengthens, and the duration of the P wave measured on a surface electrocardiogram (ECG) is increased [7-12]. Furthermore, hemodialysis may lengthen P wave duration and dispersion [13]. Whereas conventional hemodialysis (HD) eliminates uremic toxins by diffusion depending on their molecular weights, hemodiafiltration (HDF) also eliminates toxic polypeptides (characterized by β-2 microglobulins) by convective transport [7,14]. The quality of life of patients undergoing HDF is superior to that of patients undergoing HD, and mortality rates in the former group are lower [8,15]. However, the effects of HDF on atrial arrhythmias are not well established, and the extent to which changes in arrhythmia substrates are responsible for the beneficial clinical results of HDF is still unknown. In the current study, we investigated the effects of HD and HDF on P wave duration and dispersion, two characteristics that characterize atrial arrhythmogenicity and are measured by a surface ECG.

Materials and methods

The studied population consisted of thirty patients (18 males, 12 females, mean age 60.57±13.62 years, range 23-85 years). First, we collected and analyzed data from the patients while they were undergoing HDF over a period of three months; the same patients were then treated with conventional HD for at least another three months, and another set of data was collected. Patients with end-stage kidney disease (Stage 5) participating in renal replacement programs in our clinic were enrolled in the study. The 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 that may have affected atrial and ventricular depolarization and repolarization (e.g., haloperidol, methadone, amiodarone, sotalol, selective serotonin reuptake inhibitors, macrolide antibiotics, antifungal agents) were excluded from our investigation. Likewise, because thyroid dysfunction and altered calcium metabolism may affect atrial pulse conduction, patients suffering from these endocrine disorders were excluded from the study. None of our patients had a history of atrial fibrillation. The causes of chronic renal failure in this patient population were 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), lupus nephritis (n=2), and vasculitis (n=4). Clinical data from the study population are shown in **Table 1**. All patients gave informed consent to participate in the study, and the Institutional Ethics Committee on Human Research approved the study protocol. The renal replacement therapies were performed three times a week during 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 HDF, 15.16±5 liters of ultrafiltrate was removed using a post-dilution technique. 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 HDF, the blood flow was 338±11.6 ml/min, which was not significantly different from that observed during HD ($p<0.05$). The bicarbonate dialysis solution contained the same ionic concentrations. We adjusted the dialysate bicarbonate concentration individually in each case in the range of 28-36 mmol/L for aiming at plasma bicarbonate concentration of 20-22 mmol/L. Dialysate bicarbonate concentration was not changed during the study. No drugs were administered during the sessions. The serum electrolyte levels were measured four times during the sessions and 2 hours afterwards. ECGs were performed five times in each case: at the beginning of the session, 15, 30, and 240 minutes into the session, and two hours after the end of the session. Electrocardiograms were recorded at a speed of 25 mm/sec (Hewlett Packard Page Writer 200i) while the patients were in the supine position breathing freely. Copies of the recordings were magnified by a factor of three. To avoid inter-observer variability, ECG parameters were measured by one examiner with calipers in a blinded fashion (with no information about the source of the ECG recording). The P wave duration was defined as the section beginning at the first sign of electrical activity after the T wave (or in some cases, the U-wave) and ending at the intersection of the P wave's descending branch and the isoelectric line. Three consecutive P waves were analyzed in every lead, and their average duration was calculated; the resulting value was designated the P wave duration in the given lead. In the statistical analysis, the longest P wave of the 12 leads was used as the P interval (Pmax). P dispersion (Pd) was determined as the difference between the longest and shortest P interval. Pmax and Pd were corrected to the heart rate (Pmaxc, Pdc) according to Bazett's formula ($Pmaxc = Pmax/\sqrt{RR\ (msec)}$, $Pdc = Pd/\sqrt{RR\ (msec)}$). Holter-ECGs (GE Medical SEER Light) were performed, with monitoring starting before the therapy and ending 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. Before and after the renal replacement therapies, a transthoracic echocardiography (M-mode, 2 D) was performed with pulsed and continuous wave and tissue Doppler technique (Philips ATL HDI 5000 imaging system with a 3.5 MHz transducer). During the examinations, the cross diameter of the left atrium, the thickness of the septal and the posterior wall, and the left ventricular systolic and diastolic diameters were measured from the parasternal long-axis view. Based on the apical four-chamber view, Simpson's method was used to determine the left ventricular ejection fraction. Statistical analysis of the data was carried out with SAS 8.2 for Windows. The variations in the investigated parameters over time and the differences between the two treatment modalities were determined using analysis of variance (ANOVA). The correlations between the parameters were analyzed by Pearson test when the distribution was normal and by Spearman's rank test in the case of abnormal distribution. Throughout the analysis, the $p<0.05$ probability level was considered to be statistically significant.

Results

Pmax and Pmaxc were significantly longer during HDF than during HD, even at the beginning of the sessions (Pmax 102 msec vs. 88.66 msec, $p=0.0036$; Pmaxc 114.83 msec vs. 99.4 msec, $p=0.0036$). Nevertheless, these parameters were found to be within the physiologic range. All investigated ECG parameters were significantly increased ($p<0.05$) during HD, whereas no significant changes were observed during HDF. Pmax, Pd, Pmaxc, and Pdc were significantly prolonged 30 minutes into the HD. The mean value of Pmax was 88.6 msec at the beginning of the HD; this value increased to 102 msec within 30 minutes ($p<0.05$) and reached its maximum value (111 msec ($p<0.05$)) 240 minutes into the session; Pmax then

decreased to 98 msec 2 hours after the end of the HD. The Pd was 37.3 msec before HD and 52 msec within the first half hour of the session ($p<0.05$). Pmaxc lengthened from a 99.4 msec baseline value to 115.5 msec and remained at that level until two hours after the treatment (115.3 msec). Pdc did not change in the first half hour of HD (44 msec); however, it decreased to 40.4 msec ($p<0.05$) 30 minutes into the treatment and increased to 48 msec by the end of the sessions ($p<0.05$). Two hours later, the Pdc was found to have reverted to its baseline value (43.9 msec). In contrast, the P wave parameters did not change significantly during HDF **(Figures 1/a. and 1/b.)**. Total calcium and ionized calcium levels significantly increased, whereas potassium, magnesium, and phosphate levels decreased during both modalities. During HDF, serum sodium levels did not change significantly; however, after 15 and 30 minutes of HD, sodium levels decreased ($p<0.05$) relative to baseline levels and increased by the end of the sessions **(Table 2.)**. During the different treatment modalities praedialytic serum bicarbonate values were also determined. However, regarding these parameters no significant differences were evaluated (HD: 19.6±2.1 vs. HDF: 20.7±2.8; $p=0.14$). We investigated whether the praedialytic bicarbonate levels correlate with the duration of P interval and Pd or not. According to our data there is a significant negative correlation between praedilalytic bicarbonate levels and Pmax, Pd, Pdc by the end of the sessions **(Table 3.)**. During HDF, the change in sodium levels was significantly positively correlated with both Pd and Pdc. Moreover, during conventional HD, the change in ionized calcium levels was positively correlated with both Pd and Pdc **(Table 3.)**. No additional significant correlations between the studied ECG markers and ionic parameters were found. Changes in the ventricular rate (characterized by the RR cycle length) increased from 798±102.65 msec to 852±104.3 msec ($p=0.0047$) after 30 minutes of HDF, indicating a transient decrease in the heart rate; the ventricular rate gradually decreased to its baseline rate after the sessions ended. With HD, the RR cycle length decreased significantly relative to the baseline length

(800.6±96.2 vs. 746.6±125.5 msec, p=0.024) only 2 hours after the end of the sessions. At the beginning of the sessions, there were no significant differences in left atrial diameter between the two treatment modalities; however, by the end of the sessions, a significant decrease was observed in the case of HDF (p=0.00017). In contrast, no significant changes in left atrial diameter were found during HD (p=0.12) **(Figure 2.)**. No significant difference in atrial diameter between men and women was observed (p=0.56). The ratio between the baseline left atrial diameter and the number of supraventricular premature beats was also determined. With HDF, the left atrial cross diameter measured at the beginning of the sessions was positively correlated with the incidence of supraventricular premature beats (r=0.4556, p=0.011) **(Figure 3/a**.). Furthermore, the decrease in the left atrial diameter was negatively correlated with the incidence of supraventricular premature beats (r=-0.43, p=0.016) during HDF **(Figure 3/b.)**. The body weight and the body mass index (BMI) of the patients decreased significantly during both modalities (BMI HD: 24.39±4.19 kg/m^2 to 23.59±4.2 kg/m^2; BMI HDF: 24.37±4.12 kg/m^2 to 23.6±4.14 kg/m^2). Importantly, the difference between the volume removals did not prove to be significant (p= 0.34). Atrial fibrillation did not occur during any of the renal replacement therapies; however, the frequency of supraventricular premature beats was high in both treatment modalities (HD: 363 beats/24 h; HDF: 350 beats/24 h). Although the Holter ECG recordings of the hemodialyzed patients showed a more frequent occurrence of supraventricular premature beats, the difference in the frequency of these beats for the two modalities was not statistically significant (p=0.14). In both treatment modalities, there was a rapid decrease in blood pressure to levels comparable to baseline values after the start of the sessions; within 15 minutes of treatment, the levels significantly decreased. The systolic blood pressure did not change significantly after this; however, the diastolic values increased after the treatments. During HDF, the systolic and diastolic values were higher even during the initial stages of the sessions **(Figures 4/a. and 4/b.)**. The end systolic and diastolic

left ventricular diameters, the left ventricular mass index, and the left ventricular ejection fraction were not significantly different or altered in either of the treatments **(Table 4.).**

Discussion

The structural and electrophysiological heterogeneity of the atrial myocardium may result in inhomogeneous atrial depolarization and/or repolarization and unidirectional conduction block. These abnormalities play an important role in creating atrial premature beats and reentry, an electrophysiological prelude to atrial fibrillation. The duration and dispersion of the P wave have been shown to be prolonged in patients with paroxysmal atrial fibrillation during sinus rhythm [10-12]. Recent studies have also reported that the mortality rate of patients participating in HDF programs is 35% lower than that of patients receiving conventional treatment [7,8,14]. This phenomenon may be the result of the more effective removal of small- and medium-molecular weight substances during HDF, which might be related to high-flux membranes and a more appropriate convective volume [16]. The concentrations of acute phase proteins and inflammatory mediators do not rise during or after HDF. The reduction in beta-2 microglobulin concentrations achieved with HDF can reduce the incidence of amyloidosis by approximately 50% [17-21]. In addition to these known factors, it could also be hypothesized that patients receiving convective treatment for their renal diseases may benefit from a reduction in the incidence of arrhythmias and from the slower progression of damage to the heart [22,23]. Previously, we have demonstrated the beneficial effects of hemodiafiltration on ventricular repolarization, but the possible influence of this treatment modality on atrial rhythm disturbances has remained to be elucidated [24]. To clarify this hypothetical relationship between convective treatment and atrial arrhythmogeneity we decided to investigate atrial electrocardiographic arrhythmia

markers during hemodiafiltration and hemodialysis. Our present results show that the electrocardiographic changes observed during conventional HD were not observed during HDF. However, the reasons for the differences in Pmax and Pmaxc during the different modalities are not well understood, and further investigations are needed to understand this phenomenon. Importantly, no significant differences in the effective volume removals between the two treatment modalities were observed. The larger decrease in left atrial diameter indicates a more effective intracardiac volume, which decreases the potential of HDF to contribute to a considerable reduction in atrial wall stress during the convective treatment. Consequently, the amplified decrease in atrial volume can result in a lower incidence of supraventricular premature beats. Our data obtained from the 24-hour Holter ECG recordings show that supraventricular premature beats appeared often in both treatments, even though atrial fibrillation was not observed during either modality. Although, supraventricular premature beats were more frequent during HD, the difference in the number of these beats between the two treatment modalities in our study population was not statistically significant. The altered behavior of the ventricular frequency (characterized by RR cycle length) could be the result of the differences in intravascular and intracardiac dynamics of volume and pressure conditions resulting from HD and HDF. The changes in blood pressure can also highlight the role of volume and pressure load alterations. However, the systolic and diastolic values of the patients were higher during HDF, even at the beginning of the sessions, which may have affected our results. Because no significant differences in serum potassium, magnesium, and phosphate levels were observed between the two modalities, we conclude that the altered electrocardiographic activity during the different renal replacement therapies is not likely to be caused by the changes in these electrolyte levels. The significant correlations between serum sodium levels and Pd and Pdc observed during HDF and the correlations between the serum ionized calcium levels and Pd and Pdc

observed during HD indicate that these changes in electrolyte concentrations must play an important role in atrial arrhythmogenesis. Moreover, we found that the praedialytic bicarbonate levels may affect atrial arrhythmogeneity. Most importantly, our results also suggest that the alterations in these atrial arrhythmia markers may be the result of the simultaneous occurrence of certain electrolyte imbalances and renal replacement methods. Accordingly, we emphasize the need for and potential benefit of careful monitoring and control of these electrolytes during the sessions to prevent electrocardiographic changes and lower the risk of atrial arrhythmias.

Conclusion

Our data suggest that the electrocardiographic markers of atrial depolarization and repolarization do not change significantly during HDF. This finding might be the result of the more balanced but increased intracardiac and intravascular volume reduction, the more effective balancing of sodium serum concentrations, the already proven powerful antioxidant/anti-inflammatory effect of HDF, and the more efficient removal of the small- and medium-molecular weight substances and uremic toxins during HDF. Further studies are needed to analyze the impact of HDF on atrial arrhythmias.

Competing Interests

None of the authors have a relationship with companies that may have a financial or non-financial interest in the information contained in the manuscript. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

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Figure Legends

Figures 1/a. and 1/b. Changes in P interval (Pmax) and corrected P interval (Pmaxc), P dispersion (Pd), and corrected P dispersion (Pdc) during hemodialysis (HD) and hemodiafiltration (HDF) (*p<0.05). All investigated parameters significantly increased during HD. No such changes were observed during HDF.

Figure 2. Changes in left atrial diameter during hemodiafiltration (HDF) and hemodialysis (HD). The left atrial diameter decreased significantly during HDF. (*p<0.05)

Figure 3/a. The correlation between the left atrial cross diameter (DLA), as measured at the beginning of the hemodiafiltration (HDF), and the rate of supraventricular premature beats (SVPB). The DLA measured at the beginning of the sessions was positively correlated with the incidence of supraventricular premature beats. (*p< 0.05)

Figure 3/b. Correlation between the changes in the left atrial diameter (ΔDLA) and the rate of supraventricular premature beats (SVPB) during hemodiafiltration (HDF). The decrease in left atrial diameter was negatively correlated with the incidence of supraventricular premature beats during HDF. (*p< 0.05)

Figure 4/a. Changes in systolic blood pressure during the different methods of renal replacement therapy (*p<0.05). In both treatment modalities, systolic blood pressure rapidly decreased after the start of the sessions and became significantly different from the baseline level within 15 minutes.

HD: hemodialysis, HDF: hemodiafiltration, BP: blood pressure, sys: systolic

Figure 4/b. Changes in diastolic blood pressure during the different methods of renal replacement therapy (*p<0.05). The diastolic blood pressure rapidly decreased after the start of the sessions in both treatment modalities and became significantly different from the baseline level within 15 minutes. The diastolic pressure increased after the treatments.

HD: hemodialysis, HDF: hemodiafiltration, BP: blood pressure, dia: diastolic