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THE DIALYSIS PROCEDURE AS A TRIGGER FOR ATRIAL FIBRILLATION: NEW INSIGHTS IN THE DEVELOPMENT OF ATRIAL FIBRILLATION IN DIALYSIS PATIENTS

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ABSTRACT

Aims

Atrial fibrillation (AF) is common in dialysis patients and is associated with increased morbidity and mortality. The pathophysiology may be related to common risk factors for both AF and renal disease or to dialysis-specific factors. The purpose of this study was to determine whether and how AF onset relates to the dialysis procedure itself.

Methods

All dialysis patients enrolled in the ICD-2 trial until January 2012, who were implanted with an ICD, were included in this study. Using the ICD remote monitoring function the exact time of onset of all AF episodes was recorded. Subsequently the time of AF onset was linked to the timing of dialysis procedures.

Results

For the current study a total of 40 patients were included, follow-up was 28±16 months, 80% male, 70±8 years old. A total of 428 episodes of AF were monitored in 14 patients. AF onset was more frequent on the days of hemodialysis (HD) ($p<0.001$) and specifically increased during the dialysis procedure itself ($p=0.04$). Patients with AF had a larger left atrium ($p<0.001$), and a higher systolic blood pressure before and after HD ($p<0.001$) compared to patients without AF.

Conclusion

This study provides insight in the exact timing of AF onset in relation to the dialysis procedure itself. In HD patients, AF occurred significantly more often on a dialysis day and especially during hemodialysis. These findings might help to elucidate some aspects of the pathophysiology of AF in dialysis patients and could facilitate early detection of AF in these high-risk patients.

INTRODUCTION

The incidence of cardiovascular disease in dialysis patients is high, with an annual cardiovascular mortality rate 5 to 30 times higher than the general population.[1-3] Atrial fibrillation (AF), a major risk factor for ischemic stroke and an independent predictor of death, is very common in dialysis patients.[2-5] Furthermore, AF-related mortality in patients with end stage renal disease (ESRD) is estimated to be twice as high as in patients without kidney disease.[6] Despite our increasing knowledge about rhythm disorders, our knowledge about the relationship between AF and dialysis remains scarce.

In the general, non-dialysis population, risk factors for the development of AF include age, hypertension, obesity, diabetes, atrial enlargement and pre-existent cardiovascular disease.2,6-8 These risk factors are common in dialysis patients and could explain their high burden of AF. On the other hand, the dialysis procedure itself might provide unique risk factors for the onset of AF.8,9 Consequently, knowledge of the exact timing of AF onset in relation to the dialysis procedure itself could provide valuable information regarding the underlying pathophysiology.

The purpose of the present study was to determine the exact timing and characteristics of AF, in relation to the dialysis procedure in patients who received an implantable cardioverter defibrillator (ICD), as part of the ICD-2 study protocol.[10] The remote monitoring function of the ICDs in these patients provided a unique possibility to thoroughly relate onset of AF to the dialysis procedure itself.

METHODS

Study population

For this study all patients currently enrolled in the ICD-2 trial (ISRCTN20479861), receiving a dual-chamber ICD (Biotronik, Berlin, Germany) between 2008 and 2012 were included. This ongoing randomized controlled trial was designed to evaluate the effectiveness of ICDs in the prevention of sudden cardiac death in ESRD. The study-protocol has been described previously.[10] The study population consists of dialysis patients without a primary or secondary indication for an ICD. All patients provided informed consent and the trial design was approved by the local ethics committee.

Implantable cardioverter defibrillator

All ICDs were implanted transvenously. The ICD was programmed to evaluate all p-p intervals. Registration of an AF episode started if at least 36 out of 48 consecutive p-p intervals had a frequency higher than 180/min. An episode of AF was deemed terminated if 20 out of 24 consecutive p-p intervals had an AT/AF interval of less than 180/min. The atrial sensing threshold was programmed as 0.4 mV. Average p-wave sensing amplitude was calculated using the remote monitoring data. The implanted ICD contains an

integrated antenna that transmits a heart rhythm registration and data on the timing of arrhythmias to an external remote monitoring device (Biotronik, Cardiomessenger 2-S), which subsequently sends the data to a central database every day.

Dialysis procedure

For this study, we included both patients on peritoneal dialysis (PD) and hemodialysis (HD). HD patients were dialyzed 2-3 times a week with a dialysis time of 3-4 hours. Ultrafiltration rate and dialysate potassium concentrations were based on target weight, actual body weight and serum potassium of the individual patients. PD patients received continuous dialysis (24 hours a day,7 days a week) in which the interval of intraperitoneal fluid replacement, which was performed at home, depended on the patient preferences and characteristics of the peritoneal membrane.

Atrial fibrillation

All AF episodes registered by the ICD were analyzed using the intracardiac electrogram, stored in the central database. One of the authors (MSB) confirmed that the atrial episode recorded by the ICD were actually AF, while blinded for the relationship of the atrial episode with the dialysis procedure. The date and time of AF onset were recorded, as well as the episode duration. The days of the week were numbered such that the first day of the week, on which each individual patient underwent dialysis, was coded as day 1. Using this method, patients who performed dialysis on different days of the week were compared. For this particular analysis we used patients performing HD three times a week, or performing PD.

Subsequently, AF onset was related to the start of the HD procedure. Onset of AF was categorized in the seven hours before dialysis, the 3-4 hours during or the seven hours after HD. This window of seven hours was chosen because a larger time-window would result in crossover into the next day.

Clinical variables

Baseline parameters were compared between dialysis patients with and without AF. As part of the ICD-2 protocol, all patients underwent 2-dimensional transthoracic echocardiography (M3s probe, Vivid 7, GE Vingmed, Horton, Norway) at the time of inclusion. Left atrial (LA) diameter, left ventricular mass index (LVMI), and the presence of mitral valve regurgitation were assessed.[11]

If a HD patient developed AF on a dialysis day, the associated dialysis volume, potassium concentrations and blood pressures before and after the procedure, were collected from an electronic patient database (Diamant, Diasoft, The Netherlands). Since serum potassium concentrations were only measured on a monthly basis, dialysate potassium concentration was used as an approximation of potassium shifts.

For patients on HD, there is an inverse relation between the prescribed dialysate potassium concentration and the serum potassium concentration in order to remove sufficient amounts of potassium. Therefore, low potassium concentrations in the dialysate causes a high potassium shift from the serum during HD.

A single dialysis procedure from every single month of follow-up in patients without AF was randomly selected to compare dialysis procedures between patients with and without AF. In an effort to distinguish between patient-related and dialysis-related factors, additional data on HD procedures, that were not associated with AF, were collected from the patients who developed AF.

Follow-up

The primary outcome of this analysis was the onset of AF and all episodes of AF were measured until the end of follow-up. If AF was recorded by the ICD during follow-up, the treating nephrologist and cardiologist of that particular patient were informed and treatment was started at their discretion.

Statistics

Continuous data were described by their mean (±SD) or as a median (25^{th}-75^{th} percentile) if data was skewed, and compared using an independent Student t-test. Categorical data was presented as a percentage and compared using a Chi-square test, or the Fisher's Exact Probability test if appropriate.

All AF episodes where classified by the different days of the week (1-7). A repeated measures logistic regression generalized estimating equations(GEE) was used to compute the probability that AF developed on a dialysis day, thereby taking into account the within-patient correlation.

Subsequently, all AF episodes that occurred on a dialysis day were analyzed. AF onset was categorized in the period before, during and after HD. Incidence rates between these periods were compared as rate-ratios using Poisson regression, again taking into account the within-patient repeated measured nature of the data. A GEE model with robust variance estimator was used.

The within-patient correlation was taken into account in both the analyses. However, since the number of AF episodes was not distributed evenly among patients, characteristic of patients who provided many AF episodes might still influence our outcomes. Therefore, both analyses were performed multiple times, each time excluding one single AF patient.

All statistical analyses were performed using SPSS (version 18.0, IBM Corp, Amonk, NY, USA).

RESULTS

Inclusion

Forty patients were included in this study. Average follow-up was 28±16 months. Patients were predominantly male (80%) and the majority was treated with HD (65%). Average time on dialysis was 54±28 months and average left ventricular ejection fraction was 54%.

Patients on PD were younger (67±7 vs. 72±7 years, p=0.045), had a smaller LA-diameter (39±6 vs. 44±6mm, p=0.01) and a lower LVMI (105±28g/m^2 vs. 144±39g/m^2, p=0.002), than HD patients.

Incidence of AF

In 14 patients, at least one episode of AF was recorded during follow-up (34%). Nine of these patients (64%) were not diagnosed with paroxysmal AF previously. Patients that developed AF had a significantly larger LA-diameter (46±2 vs. 40±6mm, p<0.001). Further baseline characteristics did not differ between both groups (table 1).

Table 1: Baseline characteristics

Total cohort	AF (n=14)	No AF (n=26)	p-value
Follow up, months	28±14	28±17	1.0
Age, years	72±7	69±8	0.2
Male gender, nr (%)	12 (86%)	20 (77%)	0.5
Dialyse type (HD), nr (%)	11 (79%)	15 (58%)	0.3
Urine production, mL/24hours	1387±1272	1017±836	0.3
Dialysis Vintage, months	56±31	53±26	0.8
Hypertension, nr (%)	12 (86%)	22 (85%)	1
Diabetes, nr (%)	7 (50%)	6 (23%)	0.2
Coronary artery disease, nr (%)	4 (29%)	10 (39%)	0.7
LVEF, %	54±6	53±6	0.8
Left atrial diameter, mm	46±5	40±6	<0.01
Mitral valve regurgitation	2(14%)	0	0.1
LVMI g/m^2	137±38	127±41	0.5
Beta-Blocker, nr (%)	9(64%)	16(62%)	1.0
Calcium antagonist, nr (%)	9 (64%)	9 (38)	0.1
ACEi, nr (%)	7(50%)	5(19%)	0.1
ARB, nr (%)	6 (43%)	7 (27%)	0.5
Diuretics, nr (%)	8 (57%)	16 (62%)	1

AF; Atrial Fibrillation, HD; Hemodialysis, LVEF; Left ventricular ejection fraction, Mitral valve regurgitation; grade III or IV, LVMI; Left ventricular mass index, ARB; Angotensin receptor blocker

In the 14 patients who developed AF, the ICD monitored a total of 10,196 days. In the HD group (n=11) a total of 8,190 days were monitored, of which 1,594 days (19%) were spent in AF (386 AF episodes). In the PD group (n=3) a total of 2,006 days were monitored, including 64 days (3%) of AF (42 AF episodes). Median duration of the AF episodes was 212 min (42- 441min, table 2). Eighteen percent of episodes lasted less than 6 min. The distribution of AF episodes ranged from 1 to 213 episodes per patient (table 2).

AF in relation to the dialysis procedure

In the 11 HD patients, 10 received dialysis 3 times a week. One patient switched from HD twice a week to three times a week and in this patient only the latter period was used. After AF onset was scored according to the days of the HD procedure, it was shown that the frequency of AF development on a dialysis day was approximately 3 times higher than on a non-dialysis day (282 vs. 87 episodes, p=0.001, figure 1A). No significant difference in AF onset between days of the week was observed in PD patients (figure 1B).

Out of the 296 AF episodes that occurred on a dialysis day, 236 episodes had both the start of the dialysis procedure and the exact timing of AF onset recorded. In the period between 7 hours before and 7 hours after HD, 205 AF episodes occurred. Eight percent of these AF events commenced before the dialysis procedure, 48% began during HD and 43% of AF episodes started afterwards (figure 2).

In the 7 hours before the HD procedure, the rate of AF onset was approximately 0.003/person-hours, compared to a 0.04/person-hours during the HD procedure (rate ratio (RR) 0.075). Thus, the risk of developing AF during HD was approximately 13 times higher than before HD (p=0.03). The rate of AF onset in the 7 hours after the HD procedure was 0.02/person-hours (RR 0.5) and the risk of developing AF during HD was approximately twice as high. (p=0.001).

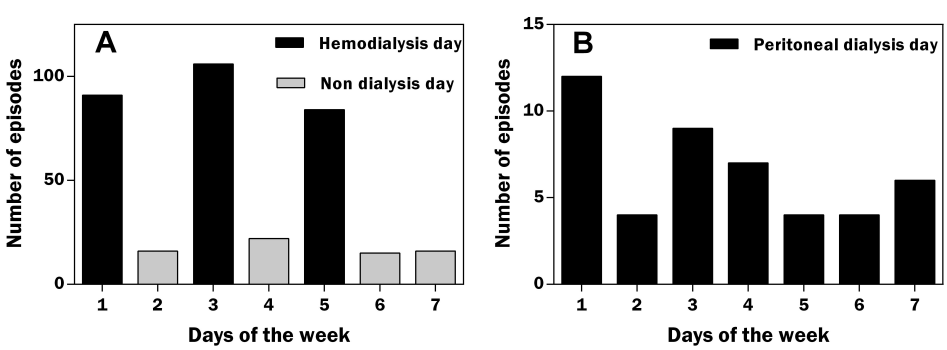

Figure 1: Onset of atrial fibrillation on different days of the week for hemodialysis (A) and peritoneal dialysis (B).

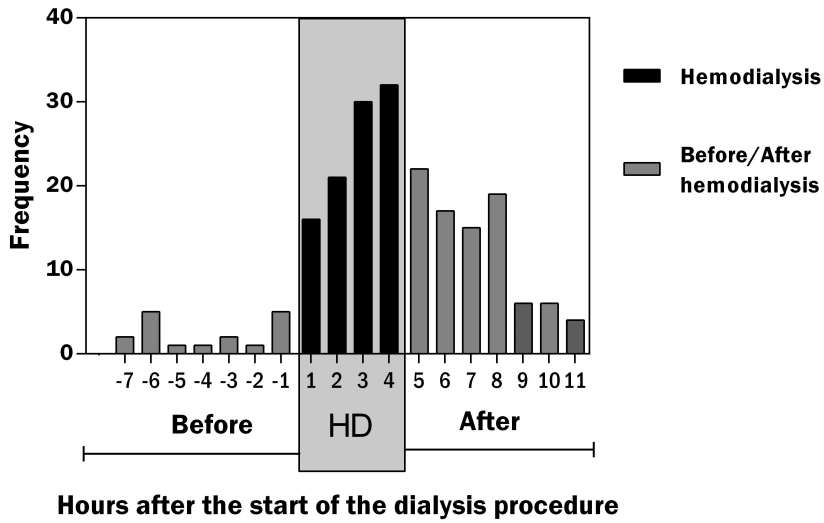

Figure 2: Onset of atrial fibrillation episodes in relation to the start of the dialysis procedure.

The distribution of AF onset around the HD procedure changed after excluding individual patients. After exclusion of patient #2 (table 2), the risk of developing AF during HD remained significantly higher than before HD (RR=0.5, p=0.001) but there was no statistical difference between the risk of AF onset during and after HD (RR=1, p=0.45). After exclusion of patient #7, the increased chance to develop AF during HD compared to before dialysis lost statistical significance (RR=0.06, p=0.07), whereas the chance to develop AF during HD remained 2 times higher than after HD (RR=0.5, p=0.001). Exclusion of the other patients had no significant effect. Furthermore, AF onset remained more frequent on a dialysis day compared to a non-dialysis day, after exclusion of individual patients.

Dialysis characteristics

Patients with AF developed AF episodes more frequently around HD procedures with a higher extracted volume (2,120 vs. 1,611 mL, p<0.001) and a lower dialysate potassium concentration (1.6 vs. 2.0 mEq/L, p<0.001). Furthermore, AF-patients had a higher extracted volume during HD (2,120 vs. 1,843 mL, p=0.01) and a lower dialysate potassium concentration (1.6 vs. 1.9 mmol/L, p≤0.001) than patients who never developed AF (table 3).

DISCUSSION

This study demonstrates a distinct relationship between AF and the HD procedure. AF onset was more frequent on the days of the HD procedure and AF occurred mainly during the dialysis procedure itself. Furthermore, patients receiving PD showed

Table 2: Number of AF episodes per patient

Patient #	Dialysis Type	Days of AF	Nr. Eps	Duration, min (25th-75th percentile)
1	HD	134	1	
2	HD	240	213	229 (73-424)
3	HD	36	17	71 (2-985)
4	HD	4	1	
5	HD	22	17	16 (1-92)
6	HD	607	1	
7	HD	114	68	18 (145-349)
8	HD	205	7	118 (3-711000)
9	HD	207	37	348 (125-1064)
10	HD	23	22	2 (1-4)
11	HD	2	2	7
12	PD	16	9	130 (19-1292)
13	PD	7	4	5 (3-77)
14	PD	41	29	660 (413-867)

AF; Atrial Fibrillation, HD; Hemodialysis, PD; Peritoneal Dialysis

Table 3: Dialysis characteristics

	Patients with AF			Patients without AF	
HD Characteristics	**HD with AF**	**HD without AF**	**p-value (1)**	**HD**	**p-value (2)**
Extracted volume, mL	2,120±1,278	1,611±1,248	0.001	1,843±1,189	0.01
SBP before HD, mmHg	159±23	155±22	0.01	146±25	<0.001
DBP before HD, mmHg	70±12	71±45	0.7	70±12	0.6
SBP after HD, mmHg	139±31	145±25	0.01	130±24	0.001
DBP after HD, mmHg	65±14	68±15	0.01	69±37	0.1
Potassium, mEq/L	1.6±0.6	2.0±0.7	0.001	1.9±0.6	0.001

(1) Comparing HD with AF to HD without AF within patients with AF
(2) Comparing HD with AF to patients without AF
SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure. AF; Atrial Fibrillation, HD; Hemodialysis

significantly less episodes of AF. These findings might help to elucidate some aspects of the pathophysiology of AF in dialysis patients and might facilitate early diagnosis.

Although an association between HD and the onset of AF has previously been described, data on this relationship and its etiology remains scarce.[8,12] *Ansari et al* described that 9 out of a total of 10 monitored episodes of atrial arrhythmia started in the last hour of HD, based on patient complaints.[13] A relationship between dialysis and

arrhythmia was also described by *Korzets et al*, although no actual data supporting this claim was provided.[14] Although the number of included patients was relatively small, the current analysis of 417 episodes of AF in 14 dialysis patients, based on continuous ICD telemonitoring, provides the largest analysis on the relationship between AF onset and the HD procedure currently available.

Dialysis-specific factors in the occurrence of AF

The current data shows that the dialysis procedure itself is associated with the development of AF. Two pathways have been suggested as important in this relationship. The volume hypothesis postulates a major role for either volume overload or intravascular volume depletion in the development of AF, whereas a second hypothesis suggests an important role for electrolyte shifts in AF development.[15-17]

The volume hypothesis

Volume overload causes atrial stretch, left ventricular hypertrophy and neurohumeral alterations.[17,18] This pathway would lead to a relatively high incidence of AF onset between dialysis days and just prior to the HD procedure, when fluid overload is at its largest. Since there was no increased incidence in the 7 hours before the start of the HD procedure, volume overload seems to be an unlikely explanation for the increased incidence of AF in HD patients.

Previous studies have shown a profound drop in intracardiac diastolic and systolic pressure during HD.[19,20] This suggests that the HD procedure might result in intravascular volume depletion, which inhibits the baroreflex, causing sympathetic activation and catecholamine release, which increases susceptibility to AF.[21-23] In the current study, AF onset occurred most frequently during the HD procedure and the incidence of AF onset increased continuously during HD. Furthermore, higher ultrafiltration volumes in dialysis sessions as well as lower diastolic pressure after dialysis were associated with the occurrence of AF. These factors suggest a role for intravascular volume depletion, in the development of AF in HD patients.

Electrolyte shifts

Trans-membranous fluxes of electrolytes , especially potassium, may be potentially arhythmogenic.[15,16] During HD, supraventricular ectopy and heart rate increases, whereas both intra-atrial conduction velocity and repolarization duration decreases, all influenced by potassium concentration.[15,24,25]

We used dialysate potassium concentration as a surrogate for potassium flux. When dialysate potassium concentrations were compared between HD procedures, the development of AF was associated with a significantly lower potassium dialysate concentration, suggesting a possible role for potassium flux. However, if potassium

flux would be the main culprit in the development of AF, one would expect a higher incidence of AF onset at the start of the HD procedure and a more even distribution of onset during the procedure, than found in our data. In other words, the current data suggests an association of AF development with potassium concentration in the dialysis fluid . Although, whether this association is due to potassium flux, is unclear.

An alternative explanation could be that low dialysate potassium concentrations lead to hypokalemia at the end of HD, which subsequently causes arrhythmia. This would explain the gradual increase of AF onset during the HD procedure and the gradual decrease of AF onset in the hours after dialysis, when potassium redistributes and serum potassium concentration normalizes. Unfortunately, we were not able to collect data on the actual serum potassium concentration, before and after, the HD session.

Peritoneal dialysis

Patients performing PD showed significantly less episodes of AF than HD patients, and the episodes did not appear to be related to the days of the week. This could be explained by the fact that PD is a dialysis modality in which solutes and water are being removed continuously. Therefore, electrolyte and volume shifts are more gradual when compared to patients on HD. Furthermore, PD patients in the present population might represent a younger and healthier patient group. However, the number of PD patients in our analysis was too small to draw definite conclusions.

Clinical implications

Recent literature showed that atrial arrhythmias, as recorded by an ICD, lasting for more than 6 minutes, were associated with an increased risk of ischemic stroke and systemic embolism.[26] In our data, AF duration was more than 6 minutes in 82% of the cases, thus implicating an increased thromboembolic risk. Stroke prevention is difficult in HD patients, since ESRD is associated with an elevated bleeding risk as well.[27] Therefore, the current opinion is to refrain from routine use of oral anticoagulants as primary prevention of stroke in HD patients and to evaluate on a single patient basis.[28] This evaluation might be facilitated by a 12-lead ECG at the end of dialysis sessions at a regular basis, especially since 64% of the patients with AF found in our analysis, were newly diagnosed.

The possible role of intravascular volume depletion as an instigator for AF might suggest (1) a benefit of more frequent dialysis procedures, or (2) the recommendation of a lower dietary fluid intake. Frequent HD procedures (5-6 times a week) have already been shown to decrease mortality and LV-mass, associated with a positive effect on electrolyte metabolism.[29]

Further studies on the association between AF and the dialysis procedure are needed. More insights in the association between serum potassium concentration around the time of dialysis and AF development might benefit future AF prevention. Furthermore,

novel diagnostic tools such as the body composition monitor, might be useful to thoroughly relate fluid state and AF development in ESRD.[30]

Limitations

This study is limited by the relatively small patient population, which is partly compensated by the large number of AF episodes monitored. Despite remote monitoring, AF episodes may be missed due to undersensing or overwriting of earlier episodes, by the remote monitoring system. The aim of this study was to analyze AF onset in relation to the dialysis procedure, the number of patients was insufficient to allow evaluation of clinical consequences of the presence of AF, in our patient group. Furthermore, data on potassium levels, before and after the dialysis procedure, were not available.

Conclusions

This study provides insight in the exact timing of AF onset in relation to the dialysis procedure itself. In HD patients, AF occurred significantly more often on a dialysis day and especially during hemodialysis. These findings might help to elucidate some aspects of the pathophysiology of AF in dialysis patients and could facilitate early detection of AF, in these high-risk patients.

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