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ORIGINAL ARTICLE

Echocardiographic associates of atrial fibrillation in end-stage renal disease

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ABSTRACT

Background. The prevalence of atrial fibrillation (AF) in end-stage renal disease (ESRD) patients is relatively high. The present study evaluated the association between left atrial (LA) remodelling, including an increased size and myocardial fibrosis, and slow LA conduction and the occurrence of AF.

Methods. In 171 ESRD patients enrolled in the Implantable Cardioverter Defibrillators in Dialysis patients (ICD2) trial, the LA dimensions, LA conduction delay [as reflected by the time difference between P-wave onset on surface electrocardiogram and A′-wave on tissue Doppler imaging (PA-TDI)] and LA function were compared between patients who exhibited AF versus patients without AF. Based on ICD remote monitoring or clinical records, the occurrence of AF was detected.

Results. Of 171 patients, 47 (27%) patients experienced AF. Despite comparable left ventricular ejection fraction and prevalence of significant mitral regurgitation, patients with AF had significantly larger LA volume index (mean ± standard deviation) (29 ± 11 versus 23 ± 10 mL/m^2, P = 0.001), longer PA-TDI duration (144 ± 30 versus 131 ± 27 ms, P = 0.010) and reduced late diastolic mitral annular velocity (A′) (7.1 ± 2.8 versus 8.2 ± 2.4 cm/s, P = 0.012) compared with patients without AF. On multivariable analysis, larger LA volume index [odds ratio (OR) 1.04, 95% confidence interval (CI) 1.01–1.08, P = 0.017], longer PA-TDI duration (OR 1.02, 95% CI 1.00–1.03, P = 0.025) and reduced A′ (OR 0.84, 95% CI 0.72–0.98, P = 0.025) were independently associated with AF after adjusting for age and left ventricle diastolic relaxation.

Conclusion. ESRD patients with AF show more advanced changes in the LA substrate than ESRD patients without AF.

Keywords: atrial fibrillation, echocardiography, end-stage renal disease, left atrium, tissue Doppler imaging

INTRODUCTION

Atrial fibrillation (AF) is very common in end-stage renal disease (ESRD) patients and the incidence of newly diagnosed AF in older patients initiating dialysis is 5-fold higher than in the general population [1–3]. Electrical and structural remodelling of the atrial myocardium serves as a substrate for AF [4]. In

patients with ESRD, the metabolic and haemodynamic disturbances associated with dialysis may modulate the AF substrate, contributing to the high incidence of AF [5]. However, the structural remodelling of the left atrium (LA) has not been characterized in this group of patients. Increased interstitial fibrosis that leads to slow conduction of the activation potential in the LA is one of the structural changes. PA-TDI duration, a parameter derived from echocardiography using tissue Doppler imaging (TDI), measures the delay between electrical conduction and mechanical activation of the LA myocardium and reflects the total atrial conduction time [6]. It is suggested that a longer PA-TDI duration reflects a higher burden of LA fibrosis [7]. The present study compares the LA substrate of patients with ESRD with and without AF.

MATERIALS AND METHODS

Patient population and protocol

The Implantable Cardioverter Defibrillators in Dialysis patients (ICD2) trial (ISRCTN20479861) is an ongoing prospective randomized controlled study evaluating the efficacy and safety of prophylactic ICD therapy in reducing sudden cardiac death rates in patients with ESRD treated with dialysis [8]. The study protocol has been described previously [8]. In brief, the inclusion criteria were: ESRD patients in dialysis at least 90 days prior to inclusion, aged between 55 and 80 years old. ESRD patients who fulfil current criteria for ICD implantation for primary or secondary prevention and with an expected survival of <1 year were not considered for inclusion. Eligible patients were randomized in a 1:1 fashion to receive an ICD or conventional therapy alone. All patients provided informed consent and the trial design was approved by the local ethics committee [8]. Baseline evaluations included a 12-lead electrocardiogram (ECG) and transthoracic echocardiogram. In this substudy, patients who were in sinus rhythm at the time of the 12-lead ECG and transthoracic echocardiography were included. Patients were divided into two groups according to the presence of AF (prior to, or after inclusion in the study). The echocardiographic associates of AF were investigated.

Clinical and electrocardiographic variables

Baseline clinical variables included demographics, cardiovascular risk factors, medication use and laboratory results. Residual renal function was calculated as the mean of creatinine and urea clearance adjusted for body surface area (mL/min/1.73 m^2). The mean of post- and pre-dialysis samples (if available) were used to estimate mean plasma creatinine and urea concentrations [9]. Baseline ECG variables included heart rate, P-wave duration, PR interval, QRS duration, QT interval and corrected QT interval calculated by Bazett's formula (corrected $QT = QT/\sqrt{RRinterval}$) [10].

Echocardiography

Patients were imaged in the left lateral decubitus position using commercially available systems (Vivid 7 or E9, General Electric Vingmed, Milwaukee, WI, USA). Standard 2-dimensional images were acquired using 3.5 MHz or M5S transducers adjusting depth and gain settings. Image acquisition was ECG-triggered and stored in cineloop format for off-line analysis (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). Linear dimensions of the left ventricle (LV) were measured from the parasternal long-axis view using M-mode [11]. LV end-diastolic and end-systolic volumes were measured on the apical 4- and 2-chamber views using the biplane Simpson's method and LV ejection fraction was derived [11]. LA volume was measured in the apical 4-chamber view using the disk summation technique and was indexed for body surface area. Tricuspid annular plane systolic excursion was measured in the focused apical 4-chamber view of the right ventricle applying anatomical M-mode to assess the right ventricular longitudinal function [11]. Mitral regurgitation severity was graded semi-quantitatively from colour-flow Doppler data by measuring the width of the vena contracta [12]. LV diastolic function was assessed by integrating the pulsed wave Doppler data of the mitral valve inflow, TDI data and LA volume [13]. Peak E (early diastolic) and A (late diastolic) wave velocities were measured on pulsed wave Doppler recordings of the mitral inflow. Lateral E′ and A′ were measured using colour-coded TDI at the lateral side of the mitral annulus in the apical 4-chamber view [13]. The tricuspid regurgitation gradient was measured on continuous wave Doppler tracings of the tricuspid valve. Pulmonary pressures were estimated by adding to the transtricuspid regurgitant gradient 5–15 mmHg depending on collapsibility of the inferior vena cava as previously described [14].

To assess the electromechanical delay of the LA, the PA-TDI duration was measured from colour-coded TDI data. The PA-TDI duration is a surrogate of the total atrial conduction time (which is considered a surrogate for LA fibrosis) and has been associated with the occurrence of AF in various cardiac diseases [6, 15–17]. To measure the PA-TDI duration, a sample volume is placed on the lateral wall of the LA just above the mitral annulus to provide the tracing of the mechanical activation in that area. The PA-TDI duration was assessed by measuring the time interval between the onset of the P-wave on the surface ECG and the peak of the A′-wave on colour-coded TDI tracing (Figure 1).

Atrial fibrillation

The occurrence of AF was detected based on ICD remote monitoring or clinical records. All ICDs were dual-chamber (Biotronik, Berlin, Germany), implanted transvenously and fitted with an external remote monitoring device (Biotronik, Cardiomessenger 2-S). The ICD evaluated all P-P intervals and was programmed to register an atrial episode if at least 36 out of 48 consecutive P-P intervals had a frequency higher than 180/min. An atrial episode was deemed terminated if 20 out of 24 consecutive P-P intervals had a frequency of <180/min. All atrial episodes were analysed using the remotely transmitted intracardiac electrogram and analysed to detect those that were AF. The type of AF was diagnosed according to current recommendations [18].

Statistical analysis

All continuous variables were tested for a normal distribution using the Kolmogorov–Smirnov test. Categorical variables

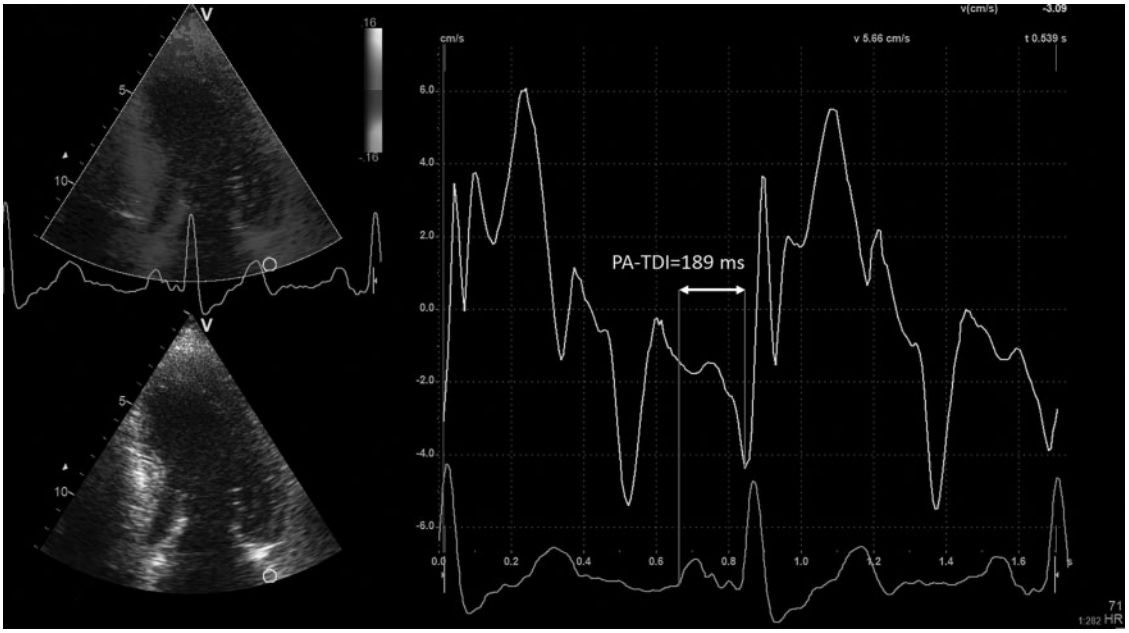

FIGURE 1: Measurement of PA-TDI (tissue Doppler imaging) duration in a patient with end-stage renal disease. The sample volume is placed on the lateral wall of the left atrium just above the mitral annulus and the PA-TDI duration is measured as the time interval between the onset of the P-wave (derived from the ECG tracing) and the peak of the A′-wave on colour-coded TDI. The PA-TDI duration in this patient was 189 ms. This patient developed atrial fibrillation during follow-up.

are presented as numbers and percentages. Continuous variables with a normal distribution are presented as the mean ± standard deviation and those without a normal distribution are presented as the median and interquartile range. Differences between patients with and without AF were evaluated using the unpaired Student's *t*-test or Mann–Whitney *U*-test, as appropriate for continuous data. For categorical data, the chi-square test was used and for small numbers, the Fisher's exact test. Binary logistic regression was applied in a multivariate model to explore independent correlates of AF in this population. Statistical analyses were performed using the SPSS software (Version 20.0. IBM Corp., Armonk, NY, USA). All statistical tests were two-sided and a P-value of <0.05 was considered significant.

RESULTS

A total of 171 patients were included [129 men (75%), mean age 67 ± 7 years]. Fourteen patients were excluded due to the absence of sinus rhythm during the echocardiographic examination. Among the included patients, 47 (27%) experienced AF. Differences in clinical and ECG characteristics between patients with and without AF are listed in Table 1. Patients with AF showed significantly higher use of sotalol [7 (15) versus 1 (1) %, P = 0.001] and oral anticoagulation [12 (26) versus 9 (7) %, P = 0.001], higher plasma levels of sodium (140 ± 3 versus 139 ± 3 mmol/L, P = 0.008), lower heart rate (67 ± 10 versus 72 ± 12 beats/min, P = 0.005), longer QT interval (417 ± 52 versus 394 ± 37 ms, P = 0.002) and corrected QT interval [418 (409–452) versus 412 (399–433) ms, P = 0.033] compared with the group without AF. Among the patients with AF, 31 patients (66%) had paroxysmal AF, 11 persistent AF (23%) and 5 permanent AF (11%). Twenty-two patients (47%) experienced AF before study entry.

Regarding the echocardiographic characteristics, patients with AF had significantly larger LV end-diastolic and end-systolic diameters and larger end-diastolic volume compared with their counterparts (Table 2). Furthermore, patients with AF had significantly larger LA volume index (29 ± 11 versus 23 ± 10 mL/m^2, P = 0.001), reduced late diastolic mitral annular velocity (A′) (7.1 ± 2.8 versus 8.2 ± 2.4 cm/s, P = 0.012) and longer PA-TDI duration (144 ± 30 versus 131 ± 27 ms, P = 0.010) compared with patients without AF. There were no differences in LV ejection fraction or presence of mitral regurgitation.

Correlates of AF

On multivariable analysis, larger LA volume index [odds ratio (OR) 1.04, 95% confidence interval (CI) 1.01–1.08, P = 0.017], longer PA-TDI duration (OR 1.02, 95% CI 1.00–1.03, P = 0.025) and reduced late diastolic mitral annular velocity (OR 0.84, 95% CI 0.72–0.98, P = 0.025) were independently associated with AF after adjusting for age and LV diastolic relaxation (Table 3).

DISCUSSION

The present study demonstrated that ESRD patients with AF versus patients without AF have significantly larger LA volume index, reduced late diastolic mitral annular velocity (A′, reflecting atrial booster pump function) and longer PA-TDI duration. These echocardiographic differences suggest that patients with ESRD and AF have LA structural changes (i.e. LA dilatation, and possibly fibrosis—as reflected by increased PA-TDI) that

Table 1. Characteristics of end-stage renal disease patients with and without AF

	AF ($n = 47$)	No AF ($n = 124$)	P-value
Clinical characteristics			
Age (years)	68 ± 7	67 ± 7	0.285
Male gender, *n* (%)	39 (83)	90 (73)	0.158
Dialysis type (haemodialysis), *n* (%)	35 (75)	86 (69)	0.512
Dialysis vintage (months)	17 (11–32)	14 (7–26)	0.159
Body mass index (kg/m^2)	28 ± 5	27 ± 4	0.066
Smoking, *n* (%)	31 (66)	83 (67)	0.904
Diabetes mellitus, *n* (%)	20 (43)	43 (35)	0.341
Hypertension, *n* (%)	38 (81)	100 (81)	0.976
Hypercholesterolaemia, *n* (%)	25 (53)	61 (49)	0.641
Previous myocardial infarction, *n* (%)	12 (26)	37 (30)	0.578
Previous CABG or PCI, *n* (%)	10 (21)	36 (29)	0.294
Medication			
ACE inhibitor/ARB, *n* (%)	28 (60)	59 (48)	0.161
Calcium antagonist, *n* (%)	17 (36)	45 (36)	0.988
β Blocker, *n* (%)	28 (60)	72 (58)	0.858
Sotalol, *n* (%)	7 (15)	1 (1)	0.001
Amiodarone, *n* (%)	1 (2)	1 (1)	0.475
Oral anticoagulation, *n* (%)	12 (26)	9 (7)	0.001
Statin, *n* (%)	28 (60)	80 (65)	0.550
Laboratory results			
RRF (mL/min/1.73 m^2)	2.1 (1.2–2.7)	1.6 (0.0–2.7)	0.094
Sodium (mmol/L)	140 ± 3	139 ± 3	0.008
Potassium (mmol/L)	4.8 (4.4–5.4)	4.7 (4.2–5.2)	0.660
Phosphate (mmol/L)	1.5 ± 0.4	1.5 ± 0.4	0.864
Corrected calcium (mmol/L)	2.3 ± 0.2	2.3 ± 0.2	0.578
Parathyroid hormone (pmol/L)	26 (15–57)	24 (14–40)	0.544
Haemoglobin (mmol/L)	7.5 ± 0.7	7.6 ± 0.8	0.466
Electrocardiogram			
Heart rate (beats/min)	67 ± 10	72 ± 12	0.005
P-wave duration (ms)	106 ± 21	106 ± 17	0.908
PR interval (ms)	178 (162–201)	171 (160–189)	0.147
QRS duration (ms)	101 ± 19	101 ± 15	0.850
QT interval (ms)	417 ± 52	394 ± 37	0.002
Corrected QT interval (ms)	418 (409–452)	412 (399–433)	0.033

Continuous data are presented as mean ± standard deviation or median (interquartile range). Categorical data are presented as numbers and percentages.
ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; RRF, residual renal function.

lead to reduced LA function (A′ reflecting active atrial contribution to LV filling) as compared with ESRD patients without AF.

Prevalence of AF in ESRD patients

Similar to the general population, AF is the most common arrhythmia among patients with ESRD. In a recent meta-analysis including 253 589 ESRD patients across 25 studies, the prevalence of AF was 11.6% (range 5.4–27%) [1]. The wide range in prevalence of AF across the different studies may be explained by the different study designs (i.e. retrospective versus prospective), classification of AF (i.e. paroxysmal versus persistent AF, valvular versus non-valvular) and detection of AF (self-reported episodes of AF versus documentation of AF with ECG, Holter recordings or remote monitoring device). A recent study including 63 884 ESRD patients from Medicare and Medicaid populations who were selected based on the presence of chronic AF documented for at least 3 months during a 2-year window (paroxysmal AF, patients with valvular heart disease, hyperthyroidism or who underwent cardiac surgery were excluded) reported a prevalence of chronic AF of 7% [19], a rate 10-fold higher than that observed in the general population [20]. In the present study, the prevalence of AF was 27%, compatible with 2 of the 25 studies included in the meta-analysis by Zimmerman *et al.* [21, 22]. The inclusion of any type of AF and the methodology used in the current study to detect AF episodes, including remote monitoring devices, which provide the most sensitive approach to detect even asymptomatic episodes of AF, may have contributed to the higher prevalence compared with those reported in previous studies [1, 19]. Furthermore, several demographic and clinical characteristics associated with increased risk of AF may be different across the studies, explaining the differences in AF prevalence. Age, hypertension and diabetes mellitus are important risk factors for AF development in ESRD, which were highly prevalent in the present study population. In addition, the present study included a significant proportion of patients with moderate and severe mitral valve regurgitation, which is associated with AF.

These risk factors contribute to LA structural remodelling and pave the substrate for AF [4]. In addition, AF itself may induce structural remodelling of the LA, perpetuating the arrhythmia [23]. The haemodynamic and metabolic disturbances that may occur in ESRD patients, such as increased

Table 2. Echocardiographic characteristics of end-stage renal disease patients with and without AF

	AF ($n = 47$)	No AF ($n = 124$)	Normal reference range [11, 14]	P-value
IVSTd (mm)	12 ± 2	12 ± 3	6–10	0.787
PWTd (mm)	11 ± 2	11 ± 2	6–10	0.321
LVEDD (mm)	52 ± 6	49 ± 7	38–58	0.009
LVESD (mm)	37 ± 8	34 ± 7	22–40	0.017
LVEDV (ml)	133 ± 47	114 ± 39	48–185	0.008
LVESV (ml)	54 (43–73)	46 (37–64)	12–78	0.117
LVEF (%)	56 ± 8	54 ± 8	46–78	0.115
LAVI (mL/m^2)	29 ± 11	23 ± 10	16–34	0.001
TAPSE (mm)	22 ± 3	21 ± 4	>17	0.084
Moderate/severe MR, *n* (%)	8 (17)	12 (10)		0.165
Tricuspid regurgitation peak gradient (mmHg)	25 ± 8	25 ± 8	<32	0.813
Maximal E-wave velocity (m/s)	0.8 ± 0.3	0.7 ± 0.2		0.220
Maximal A-wave velocity (m/s)	0.8 ± 0.3	0.9 ± 0.2		0.069
Lateral E′ (cm/s)	6.2 ± 2.5	5.9 ± 2.1		0.459
Lateral A′ (cm/s)	7.1 ± 2.8	8.2 ± 2.4		0.012
PA-TDI (ms)	144 ± 30	131 ± 27		0.010

Continuous data are presented as mean ± standard deviation or median (interquartile range). Categorical data are presented as numbers and percentages.
AF, atrial fibrillation; IVSTd, interventricular septum width; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; MR, mitral regurgitation; PWTd, posterior wall width; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging.

Table 3. Significant correlates of atrial fibrillation in all end-stage renal disease patients

	OR (95% CI)	P-value
Age (years)	1.03 (0.98–1.09)	0.272
PA-TDI (ms)	1.02 (1.00–1.03)	0.026
Left atrium volume index (mL/m^2)	1.04 (1.01–1.08)	0.017
Lateral A′ (cm/s)	0.84 (0.72–0.98)	0.025
Lateral E′ (cm/s)	1.19 (0.995–1.42)	0.057

CI, confidence interval; OR, odds ratio; TDI, tissue Doppler imaging.

sympathetic tone, renin–angiotensin–aldosterone system activation, changes in volume and pressure overload, oxidative stress and inflammation, may lead to atrial remodelling and modulate the LA arrhythmogenic substrate, enhancing the risk of AF [5, 24]. Echocardiography permits thorough evaluation of the LA structural and functional changes that may lead to AF. However, the association between echocardiographic LA parameters and AF in ESRD patients remained unexplored.

LA remodelling in ESRD patients with versus without AF

Large LA volume, the extent of LA fibrosis and reduced LA function reflect the LA remodelling process that may lead to development and perpetuation of AF. Increased LA dimensions (linear or volumetric measurements) have been consistently associated with high risk of new onset AF and progression to permanent AF [25, 26]. Furthermore, LA dilatation is accompanied by interstitial myocardial fibrosis and increased collagen content, which is the hallmark of the LA structural remodelling leading to AF.

Importantly, ESRD patients have additional risk factors that promote myocardial interstitial fibrosis and perivascular fibrosis such as uraemia, chronic anaemia and hyperparathyroidism [27–29]. In the current study, echocardiographic variables reflecting LA dilatation, fibrosis and reduced function were all significantly altered in ESRD patients with AF versus patients without AF. Echocardiographic assessment of LA dilatation is most often measured with 2-dimensional linear diameters. However, the dilatation of the LA is a 3-dimensional process and therefore in the current study volumetric assessment of the LA was applied, which may better reflect the LA dilatation [26]. This approach has better correlation with other imaging modalities (magnetic resonance imaging), which measure the LA size in 3-dimensions [30]. In addition, LA fibrosis was assessed by measuring the PA-TDI duration, a parameter that estimates the electrical-mechanical conduction delay [31]. In a study including 495 heart failure patients treated with an ICD, 29% of patients experienced AF during a mean follow-up of 16 months and showed significantly longer PA-TDI duration as compared with patients without AF occurrence (154 ± 27 versus 135 ± 24 ms, respectively; $P < 0.001$) [16]. In the present study, ESRD patients who presented with AF had significantly longer PA-TDI duration compared with patients who remained in sinus rhythm, suggesting that more advanced LA fibrosis is present in this subgroup of patients.

LA dilatation and fibrosis lead to impaired LA function [32, 33]; in the current study LA function was measured with load-independent TDI-derived A′, which reflects the contraction of the LA during late diastole. This parameter may be a better measure of the function of the LA, rather than volumetric measures in ESRD patients [34]. The clinical implications of assessment of A′ have been demonstrated in several studies [35, 36]. In 518 patients (68% of patients with various cardiac diseases), a value of A′ ≤4 cm/s was significantly associated with increased risk of cardiac death (hazard ratio 5.2, 95% CI 2.48–10.2) on univariate analysis [35].

CONCLUSION

ESRD patients with AF have more advanced changes in the LA substrate, comprising LA dilatation, increased LA fibrosis and reduced LA function.

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CONFLICT OF INTEREST STATEMENT

V.D. received speaking fees from Abbott Vascular. The other authors have no conflict of interest to declare.

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