Original Article

Atrial Fibrillation linked to Vascular access Thrombosis in Chronic Hemodialysis Patients

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Aim: **Atrial fibrillation (AF) is characterized by the development of thromboembolic events and is more prevalent among end-stage renal disease patients than in the general population. Vascular access thrombosis (VAT) is a major morbidity in chronic hemodialysis (HD) patients; however, the association between AF and VAT is unknown.**
Methods: **We retrospectively reviewed chronic HD patients with functional vascular access between 1997 and 2006. The association between AF and the development of VAT was analyzed using Kaplan-Meier analysis and multivariate Cox proportional hazards regression.**
Results: **A total of 568 chronic HD patients, including 55 (9.7%) patients with AF, were reviewed and 154 (27.1%) patients developed at least one episode of VAT. Patients with AF had worse VAT-free survival than patients without AF ($p<0.001$). In Cox regression, age, type of vascular access, atrial fibrillation, diabetes, hypertension, and C-reactive protein were independently linked to the development of VAT ($p=0.049$, <0.001, <0.001, 0.001, 0.028 and 0.045). The hazard ratios were 2.1 (95% CI: 1.00-1.03) for arteriovenous graft, 2.47 (95% CI: 1.66-3.69) for AF, 1.72 (95% CI: 1.25-2.39) for diabetes and 1.09 (95% CI: 1.00-1.18) for serum C-reactive protein (every 1 mg/dL increase), respectively.**
Conclusion: **Atrial fibrillaiton is linked to the development of vascular access thrombosis in chronic hemodialysis patients and is independent of traditional VAT risk factors.**

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Key words; AF, VAT, HD, ESRD

Introduction

Vascular access thrombosis (VAT) is one of the most common morbidities and the major cause of hospitalization in chronic hemodialysis (HD) patients[1)]. The development of VAT is characterized by neointimal hyperplasia and luminal stenosis[1)]. Increasing evidence suggests that VAT is associated with an increase of systemic inflammation markers, such as C-reactive protein (CRP)[2)] and homocysteine[3-4)], in chronic HD patients. Increases of inflammatory markers, such as interleukin-6, were also identified in vascular access stenotic lesions[5)].

The incidence of AF in chronic HD patients is higher than that of the general population and the development of AF was associated with the duration of HD history, age, heart disease, and left atrial dilatation[6)]. AF patients are also characterized by an increase of inflammation markers, such as rising CRP[7)] and interleukin-6[8)], indicating the role of inflammation in the pathogenesis of AF. It is unknown if AF is associated with increasing VAT risks among chronic HD patients. Based on the underlying chronic inflammation in AF and VAT, we hypothesis that chronic HD

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patients with AF are more at risk for the development of VAT than those without AF. We conducted this study to determine if AF is linked to the development of vascular access thrombosis events in chronic HD patients with primary functional vascular access.

Subjects

All chronic HD patients (dialyzed for more than 3 months, thrice weekly, 4 hours) were dialyzed via the primary functional native ateriovenous fistula between 1997 and 2006 in China Medical University Hospital.

Methods

The duration of functional primary vascular access was recorded from the initiation of HD treatment via functional vascular access to the date of the first VAT episode or December 2006, censored by death, shifting to peritoneal dialysis, undergoing kidney transplantation, and transfer to other HD center. A VAT event was defined as the sudden cessation of function of the vascular access, rendering HD impossible and requiring thrombectomy, thrombolysis, or acute placement of another HD access[2].

Blood pressure (systolic blood pressure, SBP; diastolic blood pressure, DBP) at the beginning (PreHD) and end of HD (PostHD) in the supine position, measured by an automated oscillometric blood pressure device, was recorded every month on the blood sampling day. Changes in SBP (ΔSBP) during HD were calculated by PostHD SBP minus PreHD SBP and changes in DBP (ΔDBP) were calculated by PostHD DBP minus PreHD DBP. Biomarkers, including hematoglobin, serum albumin, creatinine, potassium, total serum calcium, phosphate, cholesterol and triglyceride, were recorded every month. CRP was recorded at the initiation of HD and every year. For patients with more than two biomarker values available, the average value was used for analysis.

Atrial fibrillation (AF) was defined as paroxysmal (PAF) for spontaneous resolution of the arrhythmia, and persistent and permanent (CAF) when it could not be interrupted either spontaneously, by using drugs, or by cardioversion[9]. Hypertension (HTN) was defined as a history of hypertension (blood pressure $>140/90$ mm Hg) for >2 years that required the initiation of antihypertensive therapy by the primary physician[10]. Diabetes mellitus (DM) was defined as a fasting glucose concentration of 126 mg/dL (7 mmol/L) or higher, self-reported diagnosis of DM, or self-reported use of antidiabetic medication[11]. Coronary vascular diseases (CVD), self-reported or included in the medical records, included myocardial infarction, coronary artery bypass graft, percutaneous transluminal angioplasty, coronary stenosis greater than 50%, and ischemic stroke at the beginning of HD[12].

Statistical analysis

All data were analyzed using a standard statistical package (SPSS for Windows, version 12; SPSS Inc., Chicago, IL, USA).The clinical and demographic data are reported as the mean ± SD or percent frequency, as appropriate. Student's *t*-test or the Mann-Whitney *U* test was used for continuous variables and the chi-square test for categorical variables. The VAT-free survival curve of patients with and without AF was analyzed using Kaplan-Meier estimates. Possible VAT risk factors were analyzed using univariate Cox regression and factors with $p<0.05$ were further analyzed using multivariate Cox regression. A p value <0.05 was considered significant.

Results

A total of 568 chronic HD patients, including 260 men and 308 women with a mean age of 56.7 ± 14 years old, were reviewed. Fifty-five (9.7%) patients had AF at the beginning of HD and 154 (27.1%) patients had at least one episode of VAT over an average of 58 months. The demographic characteristics of the entire study population are shown in **Table 1**. Patients with AF were older ($p<0.001$), had a higher percentage of hypertension ($p=0.007$) and a CVD history ($p=0.001$) than patients without AF. The serum albumin levels were significantly lower among patients with AF ($p=0.005$). Of 89.3% patients without AF, had a primary native-arteriovenous fistula (nAVF), significantly higher than 74.5% of patients with AF ($p=0.001$). In biomarkers, CRP was significantly higher in AF patients than in patients without AF ($p=0.002$).

As shown in **Table 2**, patients who developed VAT events were older ($p=0.04$), and had a higher percentage of AF ($p<0.001$), DM ($p=0.005$) and HTN ($p=0.038$). Of patients who developed VAT events, 34% had an arteriovenous graft (AVG) as primary vascular access, significantly higher than that (7.7%) of patients without VAT events. The cumulative VAT-free survival is shown in **Fig. 1**. AF patients had a worse VAT-free survival than patients without AF by Kaplan-Meier analysis ($p<0.001$, log rank test).

Possible VAT risk factors, including age, AF, DM, HTN, CVD history, PreHD SBP, PreHD DBP,

Table 1. Demographic data of entire study population

	AF (−) $n=513$	AF (+) $n=55$	p
Age (years)	55.6 ± 13.9	69.5 ± 11.2	< 0.001
Male gender	238 (46.4)	22 (40)	0.37
Co-morbidity			
Hypertension	237 (46.2)	36 (65.5)	0.007
Diabetes	188 (36.6)	24 (43.6)	0.31
CVD history	86 (16.8)	17 (30.9)	0.01
Underlying disease			
CGN	199 (38.8)	16 (29.1)	
Diabetes	165 (32.2)	20 (36.4)	0.095
Hypertension	29 (25.9)	2 (11.1)	
Type of vascular access			
nAVF	458 (89.3)	41 (74.5)	0.001
AVG	55 (10.7)	14 (25.5)	
PreHD SBP (mmHg)	142 ± 16	138 ± 14	0.065
PreHD DBP (mmHg)	81 ± 8	77 ± 8	0.001
PostHD SBP (mmHg)	135 ± 17	133 ± 16	0.26
PostHD DBP (mmHg)	78 ± 8	75 ± 9	0.002
ΔSBP (mmHg)	−7 ± 14	−5 ± 13	0.45
ΔDBP (mmHg)	−3 ± 8	−2 ± 9	0.79
C-reactive protein (mg/dL)	0.6 ± 1.1	1.4 ± 1.8	0.002
Hemoglobin (g/dL)	11.2 ± 1.9	10.8 ± 2.1	0.11
Albumin (g/dL)	3.5 ± 0.6	3.2 ± 0.7	0.005
Creatinine (mg/dL)	10.8 ± 3.3	10.3 ± 7.5	0.38
Potassium (mEq/L)	4.4 ± 1.2	4.4 ± 1.3	0.95
Calcium (mg/dL)	9.5 ± 3.7	9.2 ± 1.0	0.48
Phosphate (mg/dL)	5.0 ± 1.8	5.0 ± 1.7	0.88
Cholesterol (mg/dL)	172 ± 39	164 ± 47	0.16
Triglyceride (mg/dL)	156 ± 135	167 ± 150	0.56

AF: atrial fibrillation, CVD: cardiovascular disease, CGN: chronic glomerulonephritis, nAVF: native arteriovenous fistula, AVG: arterio-venous graft, PreHD: before hemodialysis sessions, SBP: systolic blood pressure, DBP: diastolic blood pressure, PostHD: end of hemodialysis sessions, Δ: changes of blood pressure during hemodialysis sessions.

Table 2. Patients' clinical characteristics according to the development of vascular access thrombosis (VAT) events

	VAT (−) $n=414$	VAT (+) $n=154$	p
Age	56 ± 14.2	58.7 ± 13.2	0.04
Male gender	181 (43.7)	79 (51.3)	0.11
Smoking	52 (12.6)	25 (16.2)	0.26
AF	14 (3.4)	41 (26.6)	< 0.001
PAF	11 (78.6)	29 (70.7)	0.57
CAF	3 (21.4)	12 (29.3)	
Co-morbidity			
Diabetes	140 (33.8)	72 (46.8)	0.005
Hypertension	188 (45.4)	85 (55.2)	0.038
CVD	69 (16.7)	34 (22.1)	0.14
Underlying disease			
CGN	165 (39.9)	50 (32.5)	
Diabetes	120 (29)	65 (42.2)	0.02
Hypertension	81 (19.6)	27 (17.5)	
Type of vascular access			
nAVF	382 (92.3)	117 (76)	< 0.001
AVG	32 (7.7)	37 (24)	
Medication			
Aspirin	76 (18.4)	36 (23.4)	0.18
Warfarin	30 (7.2)	11 (7.1)	0.97
Statins	103 (24.9)	29 (18.8)	0.13
PreHD SBP (mmHg)	140 ± 16	145 ± 16	0.002
PreHD DBP (mmHg)	80 ± 8	80 ± 8	0.76
PostHD SBP (mmHg)	134 ± 17	139 ± 17	< 0.001
PostHD DBP (mmHg)	77 ± 8	78 ± 8	0.12
ΔSBP (mmHg)	−7 ± 14	−6 ± 14	0.38
ΔDBP (mmHg)	−3 ± 7	−2 ± 8	0.19
C-reactive protein (mg/dL)	0.5 ± 1.1	1.2 ± 1.4	< 0.001
Hemoglobin (gm/dL)	11.2 ± 2.0	11.2 ± 1.7	0.96
Creatinine (mg/dL)	10.8 ± 4.1	10.6 ± 3.3	0.54
Potassium (mg/dL)	4.4 ± 1.2	4.5 ± 1.1	0.79
Albumin (mg/dL)	3.5 ± 0.6	3.5 ± 0.7	0.82
Calcium (mg/dL)	9.6 ± 1.1	9.2 ± 1.0	0.18
Phosphate (mg/dL)	5.0 ± 1.8	5.2 ± 1.8	0.22
Cholesterol (mg/dL)	174 ± 40	164 ± 39	0.012
Triglyceride (mg/dL)	160 ± 146	149 ± 109	0.38

PAF: paroxysmal atrial fibrillation, CAF: chronic atrial fibrillation, including permanent and persistent atrial fibrillation, CGN: chronic glomerulonephritis, CVD: cardiovascular disease, nAVF: native arteriovenous fistula, AVG: arteriovenous graft, statins include levostatin, fluvastatin and simvastatin, PreHD: before hemodialysis sessions, SBP: systolic blood pressure, DBP: diastolic blood pressure, PostHD: end of hemodialysis sessions, Δ: changes of blood pressure during hemodialysis sessions.

PostHD SBP, Post HD DBP, ΔSBP, ΔDBP, types of vascular access, albumin and CRP were analyzed using univariate Cox regression. Parameters including AF, type of vascular access, DM, HTN, age and CRP had $p<0.05$ and were further analyzed using multivariate Cox regression. The results are shown in **Table 3**. AF ($p<0.001$), AVG ($p<0.001$), DM ($p=0.001$), HTN ($p=0.028$), age ($p=0.049$) and CRP ($p=0.045$) were independently linked to the development of VAT events in chronic HD patients with a HR of 2.47 (95% CI: 1.66 to 3.69), 2.1 (95% CI: 1.43 to 3.09), 1.72 (95% CI: 1.25 to 2.39), 1.45 (95% CI: 1.04 to 2.02), 1.01 (95% CI:1.00 to 1.03 for every 1 year older) and 1.09 (95% CI: 1.00 to 1.18 for every 1 mg/dL increase of CRP), respectively.

Discussion

We found that atrial fibrillation is an important risk factor for vascular access thrombosis in chronic HD patients with 9.7% AF prevalence rate[6, 13]. This finding was supported by a worse vascular access thrombosis event-free survival curve (**Fig. 1**) and a two times higher VAT risk in AF patients (**Table 3**). The association between AF and VAT was independent of the types of vascular access and traditional VAT risk factors, such as DM, HTN and age. The association between AF and VAT may be explained by the common underlying chronic inflammation in AF patients[14-15] and patients who developed VAT[2-3, 5]. Mounting evidence links the pathogenesis of AF to chronic inflammation[14-16]. In addition, we also found higher serum CRP in AF patients[17]; however, the association between AF and VAT events is independent of serum CRP levels. Consistent with our previous findings[2], patients with VAT had a higher CRP (1.2 ± 1.4) than patients without VAT (0.5 ± 1.1, $p < 0.001$, *t*-test). The independent association between VAT and serum CRP levels can be explained by the limitation of CRP[18] in HD patients. It is possible that AF is linked to VAT through different mechanisms, such as worsening of the local blood flow of vascular access[19-20] or increase of the D-dimer[21], therefore increasing the risk for VAT.

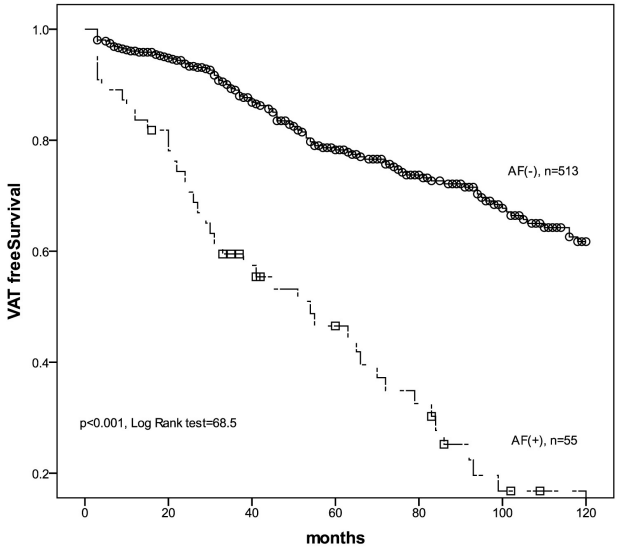

Fig. 1. Vascular access thrombosis event-free survival among patients with and without atrial fibrillation (AF), n = patient number.

The type of vascular access is one of the most important prognostic factors in vascular access patency: an nAVF is better than an AVG and forearm is better than upper-arm vascular access[22-24]. The percentage of AVG was significantly higher among AF patients (**Table 1**), suggesting a poor vascular reserve for vascular access surgery. In our HD program, 87.9% (499/568) of patients had an nAVF as the primary vascular access. Of 41 AF patients with nAVF, 32 (78%) patients had a forearm nAVF and 9 patients had an upper-arm nAVF as the primary vascular access. The percentage of forearm nAVF was significantly lower than that (90.6%) of patients without AF ($p = 0.012$, χ^2 test). Seventeen (30.9%) of AF patients took aspirin and 10 (7.6%) patients took statins regularly. Five (9.1%) patients took warfarin 67% of the time within the therapeutic range. The use of aspirin, warfarin or statins was not significantly associated with a decrease of VAT risk in univariate Cox regression. Because this is a retrospective observational study, more studies are needed to determine if prophylactic medications reduce VAT risks in chronic HD patients.

The $CHADS_2$ score (congestive heart failure, hypertension, age older than 75 years, diabetes, and previous stroke or transient ischemic stroke)[25-26] is a classification scheme for patients with AF to evaluated the need for antithrombotic therapy based on the patient-specific risk of stroke. We found that the $CHADS_2$ score was significantly associated with thromboembol-

Table 3. Hazard ratio of possible risk factors for vascular access thrombosis in multivariate Cox regression

	HR	95% CI		*p*
Atrial fibrillation	2.47	1.66	3.69	< 0.001
Vascular access AVG v.s. nAVF	2.10	1.43	3.09	< 0.001
Diabetes	1.72	1.25	2.39	0.001
Hypertension	1.45	1.04	2.02	0.028
Age	1.01	1.00	1.03	0.049
CRP (every 1 mg/dL increase)	1.09	1.00	1.18	0.045

AVG: arteriovenous graft, nAVF: native arteriovenous fistula, CRP: C-reactive protein

ic events in end-stage renal disease patients in the previous study[17]; however, no correlation was found between the $CHADS_2$ score and the development of VAT. The average $CHADS_2$ score was 1.6 ± 1 for AF patients who developed VAT and 2.0 ± 1.2 for AF patients without VAT events ($p = 0.28$). In addition, the $CHADS_2$ score was not correlated to serum CRP levels in our study ($p = 0.23$, Pearson's correlation analysis), which can be explained by the different nature of thromboembolic events and VAT[26-28]. Neointimal hyperplasia may play a key role in the development of VAT, but not in thromboembolic events among AF patients.

In conclusion, atrial fibrillation is associated with the development of vascular access thrombosis among chronic HD patients with primary functional vascular access. The association between atrial fibrillation and VAT is independent of the vascular access type, chronic inflammation markers and traditional VAT risk factors.

Competing Interests

There are no conflicts of interest in this study.

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