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Risk factors responsible for atrial fibrillation development between symptomatic patients with concealed or manifest atrioventricular accessory pathways ☆

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ABSTRACT

Background: Patients with manifest atrioventricular accessory pathways (mAPs) have a greater tendency to develop atrial fibrillation (AF) compared with patients with concealed atrioventricular accessory pathways (cAPs). However, the risk factors of developing AF in patients with various atrioventricular accessory pathways (APs) are not clear.
Methods: This retrospective study included 460 symptomatic patients with either cAPs (n = 246) or mAPs (n = 214) who underwent electrophysiological study and successful radiofrequency catheter ablation of APs. Clinical and electrophysiological characteristics were compared between cAPs and mAPs and between AF and non-AF groups with cAPs or mAPs. Independent risk factors of AF were analyzed using multivariate logistic regression.
Results: AF was more frequent in mAPs group than in cAPs group (23.4% vs 9.8%, p < 0.01). Clinical features were similar between cAPs and mAPs. Anterograde conduction properties served as the major electrophysiological feature of mAPs. Multivariate analysis indicated that mAPs, hypertension, post-ablation P wave dispersion (Pd), N-terminal proB-type natriuretic peptide (NT-proBNP) and creatinine were independent risk factors of AF in the complete cohort. Hypertension, post-ablation Pd and high-sensitivity C-reactive protein (hsCRP) were independent risk factors of AF in cAPs group. Post-ablation Pd, NT-proBNP, creatinine and shorter effective refractory period of anterograde accessory pathways (AAP ERP) were independent risk factors of AF in mAPs group.
Conclusions: Results from this study demonstrate that the risk factors of AF are not homogenous between concealed and manifest APs, which might suggest heterogeneous pathogenesis of AF in these two types of APs.

1. Introduction

Atrioventricular accessory pathways (APs) are the abnormal anatomical structures responsible for atrioventricular re-entrant tachycardia (AVRT) [1]. Besides AVRT, atrial fibrillation (AF) is another common arrhythmias related to APs [2]. Previous studies reported that patients with APs had a much higher tendency to develop AF than that in general population [3–6].

APs may exhibit anterograde and (or) retrograde conduction. There are two types of APs: manifest APs (mAPs) with atrioventricular or both atrioventricular and ventriculoatrial conduction properties, and concealed APs (cAPs) with only ventriculoatrial conduction properties. Previous studies showed that patients with mAPs were more prone to develop AF than those with cAPs [7,8].

Multiple factors are related to the development of AF in patients with APs. Previous studies demonstrated that AVRT could spontaneously degenerate into AF and surgical or catheter ablation of APs could often

reduce the recurrence of AF [9–12]. Thus, APs and AVRT might serve as one of the mechanisms responsible for the development of AF. On the other hand, AF might still persist after successful ablation of APs in some patients, suggesting the existence of AP-independent mechanisms responsible for the pathogenesis of AF [13–15]. Therefore, there were at least two pathogenesis of AF: AP-dependent and AP-independent atrial vulnerabilities [16].

This retrospective study was designed to compare the clinical and electrophysiological characteristics between cAPs and mAPs and between AF and Non-AF patients with either cAPs or mAPs. This study also aimed to identify and compare the risk factors responsible for AF development between patients of these two APs groups.

2. Methods

2.1. Patients

A total of 460 symptomatic patients [268 (58.3%) male, mean age: 42.7 ± 17.9 years old (range 5–91)] with documented AVRT, who underwent electrophysiological study (EPS) and radiofrequency catheter ablation (RFCA) from September 2004 to November 2013 in our department, were included in this study. The existence of APs was identified by EPS in all enrolled patients. There were 246 (53.5%) patients with cAPs and 214 (46.5%) with mAPs. Patients were also divided into AF group (n = 74, 16.1%) and non-AF group (n = 386, 83.9%) in the complete cohort and in patients with either cAPs or mAPs. Patients in AF group experienced at least one spontaneous episode of AF recognized on 12-lead standard electrocardiogram or 24-hour Holter monitoring.

2.2. Pre- and post-procedure management

All patients underwent standard examination procedures. A detailed medical history, physical examinations, laboratory tests and echocardiography examinations were performed before the EPS procedure. The laboratory tests included measurement of N-terminal-proB-type natriuretic peptide (NT-proBNP), cardiac troponin I (cTnI), creatinine, uric acid, high-sensitivity C-reactive protein (hsCRP), low density lipoprotein–cholesterol (LDL-c), D-dimer and thyrotropin.

After the EPS and AP ablation, a 12-leaded surface electrocardiogram was recorded immediately. Subsequently, the maximum P wave duration (Pmax) and minimum P wave duration (Pmin) were measured, and P wave dispersion (Pd) was calculated with the formula: Pmax − Pmin [17].

2.3. EPS and RFCA

All antiarrhythmic agents were discontinued for at least five half-lives prior to the EPS and RFCA. During the procedure, three electrode catheters were positioned at His bundle region, right ventricular apex and coronary sinus respectively.

The programmed stimulation protocol, including both atrial and ventricular incremental pacing and S1S2 extrastimulation, was performed before the RFCA to reveal the anatomical location and electrophysiological properties of the APs. In this study, the location of APs was classified into seven groups around the atrioventricular annulus, including the anteroseptum, the right free wall, the posteroseptum, the left posteral wall, the left lateral wall, middle septum and multiple APs located at different anatomical sites. Several electrophysiological data were measured, including anterograde and retrograde AP effective refractory period (AAP ERP and RAP ERP), anterograde and retrograde AP 1:1 conduction (AAP 1:1 conduction and RAP 1:1 conduction) and cycle lengths of the provoked AVRT (CL).

After completion of the electrophysiological study, the target site of ablation was identified. After successful ablation of the APs, another programmed stimulation protocol was performed to reveal the electrophysiological properties of atrioventricular node. The electrophysiological characteristics of atrioventricular node include both

anterograde and retrograde effective refractory period of atrioventricular node (AAVN ERP and RAVN ERP), anterograde and retrograde atrioventricular nodal 1:1 conduction (AAVN 1:1 conduction and RAVN 1:1) and dual atrioventricular nodal pathways (DAVNPs), etc.

2.4. Statistical analysis

The statistical computing was performed using the package of SPSS 18.0. Continuous variables with a normal distribution were expressed as mean ± standard deviation. The intergroup differences were tested using the t test and the χ^2 test. Data with a skewed distribution were expressed as median ± interquartile range and the intergroup differences were tested using the Mann–Whitney U test and the χ^2 test. When performing multiple comparisons, the one-way ANOVA with post hoc test (Scheffe method) was also applied in Tables 3 and 4. Statistical significance was defined as a two-sided p value < 0.05. To avoid variable selection caused by spurious correlations, only variables showing an association with AF at the p < 0.10 level in the univariate analysis were considered as potential risk factors, and then included into the multivariate regression model. Multivariate logistic regression analysis was performed in search of independent risk factors of AF. This analysis was based on a stepwise algorithm, with the p value set at 0.05 for entering and 0.1 for exclusion. Odds ratio (OR) and 95% confidence intervals (CI) of each independent risk factor for AF in concealed or manifest APs were reported in Table 5.

3. Results

3.1. Clinical and electrophysiological characteristics of patients with concealed or manifest APs

AP ablation was successful in all patients. Incidence of AF was significantly higher in mAPs group than in cAP group. All clinical features

Table 1
Clinical characteristics in patients with concealed or manifest APs.

Clinical characteristics	Concealed APs (n = 246)	Manifest APs (n = 214)	p value
AF	24 (9.8)	50 (23.4)	<0.001
Male	150 (61.0)	118 (55.1)	0.206
Age, years	42.7 ± 17.6	42.6 ± 18.2	0.333
Duration of tachycardia, years	7.8 ± 9.2	7.6 ± 10.0	0.860
Presyncope	15 (6.1)	12 (5.6)	0.823
Syncope	6 (2.4)	3 (1.4)	0.643
Hypertension	51 (20.7)	34 (15.9)	0.182
Coronary artery disease	12 (4.9)	19 (8.9)	0.088
Valvular heart disease	1 (0.4)	4 (1.9)	0.189
Diabetes mellitus	15 (6.1)	6 (2.8)	0.091
Chronic kidney disease	176 (71.5)	151 (70.6)	0.816
CHADS2 score	0.4 ± 0.7	0.3 ± 0.6	0.065
CHA2DS2-VASc score	1.1 ± 1.0	1.0 ± 1.0	0.716
Left atrial diameter, mm	31.7 ± 4.3	32.4 ± 4.6	0.052
Left ventricular end-diastolic diameter, mm	47.3 ± 4.5	47.4 ± 4.0	0.661
Left ventricular ejection fraction, %	66.2 ± 5.6	65.6 ± 5.5	0.413
Pmax, ms	112.6 ± 11.4	113.3 ± 10.2	0.333
Pmin, ms	75.9 ± 9.3	75.8 ± 8.9	0.841
Pd, ms	36.7 ± 9.1	37.5 ± 9.7	0.445
NT-proBNP, pg/mL	49.8 ± 69.0	56.0 ± 76.0	0.229
cTnI, ng/mL	0.033 ± 0.118	0.043 ± 0.172	0.172
Creatinine, μmol/L	63.5 ± 16.9	69.9 ± 64.8	0.092
Uric acid, μmol/L	327.2 ± 84.8	311.9 ± 87.1	0.767
hsCRP, mg/L	3.22 ± 2.03	3.04 ± 2.43	0.459
LDL-c, mmol/L	2.51 ± 0.62	2.53 ± 0.61	0.991
D-dimer, ng/mL	0.16 ± 0.14	0.15 ± 0.14	0.992
Thyrotropin, mIU/L	2.45 ± 1.61	2.36 ± 1.75	0.605

All data in this table were presented as mean ± SD, median ± IQR, or n (%). Pmax, maximum P wave duration; Pmin, minimum P wave duration; Pd, P wave dispersion; NT-proBNP, N-terminal-proB-type natriuretic peptide; cTnI, cardiac troponin I; hsCRP, high-sensitivity C-reactive protein; LDL-c, low density lipoprotein cholesterol.

were similar between patients with cAPs and mAPs before ablation (Table 1). As for electrophysiological characteristics, the AAP ERP failed to be measured in 9 cases of mAPs due to either the longer effective refractory period of the atria or the easily provoked AF. The RAP ERP failed to be measured in 13 cases (6 in cAP group and 7 in mAP group) due to either the longer effective refractory period of the ventricles or the easily provoked AF. Besides the anterograde conduction capabilities of the mAPs, shorter AVN 1:1 conduction was also more often in mAP group than in cAP group. Moreover, right free wall APs were more common while left lateral APs were less frequent in mAP group compared to cAPs group (Table 2).

3.2. Clinical and electrophysiological characteristics in concealed or manifest AP patients with or without AF

As shown in Table 3, AF patients in cAP group (group B) were older, had higher incidence of hypertension, coronary artery disease, diabetes mellitus and chronic kidney disease, had larger left atrial diameter and longer post-ablation Pmax and Pd, and also had higher values of hsCRP and D-dimer compared with non-AF patients in cAP group (group A).

Compared with non-AF patients in mAP group (group C), AF patients in mAP group (group D) were older, more frequently male, hypertensive, tended to have a higher incidence of history of coronary artery disease and chronic kidney disease, had larger left atrial diameter and left ventricular end-diastolic diameter, had longer Pmax and Pd after ablation and had elevated levels of NT-proBNP, creatinine and D-dimer.

For patients without AF history, the clinical characteristics were similar between cAP and mAP groups (group A vs. group C). For individuals with AF history, patients in cAP group (group B) had higher incidence of hypertension and diabetes mellitus and larger CHADS2 score than those in mAP group (group D).

As shown in Table 4, the electrophysiological data, including AAVN 1:1 conduction, AAVN ERP, RAVN 1:1 conduction, RAVN ERP, RAP 1:1 conduction and RAP ERP, were similar between AF and non-AF patients in cAP group (group B vs. group A). There was also no significant difference in the anatomical sites of the APs, the occurrence of multiple APs and DAVNPs between the two groups.

Compared with non-AF patients in mAP group (group C), AAP ERP of AF patients in mAP group (group D) were significantly shorter.

Table 2
Electrophysiological characteristics in patients with concealed or manifest APs.

Electrophysiological characteristics	Concealed APs (n = 246)	Manifest APs (n = 214)	p value
AAVN 1:1 conduction, ms	352 ± 22	344 ± 21	0.001
AAVN ERP, ms	265 ± 22	266 ± 17	0.401
RAVN 1:1 conduction, ms	385 ± 42	381 ± 38	0.228
RAVN ERP, ms	318 ± 25	322 ± 26	0.074
AAP 1:1 conduction, ms	–	364 ± 20	–
AAP ERP, ms	–	308 ± 23	–
RAP 1:1 conduction, ms	298 ± 19	300 ± 20	0.261
RAP ERP, ms	272 ± 18	275 ± 17	0.095
CL, ms	341 ± 41	345 ± 43	0.294
AP numbers, n	1.1 ± 0.3	1.2 ± 0.6	0.278
Location of APs, n (%)			
Anteroseptal	4 (1.6)	15 (7.0)	0.004
Right free wall	17 (6.9)	38 (17.8)	<0.001
Posteroseptal	29 (11.8)	40 (18.7)	0.039
Left posteral	21 (8.5)	19 (8.9)	0.897
Left lateral	164 (66.7)	85 (39.70)	<0.001
Midseptal	1 (0.4)	6 (2.8)	0.087
Multiple	10 (4.1)	11 (5.1)	0.582
DAVNPs, n (%)	12 (4.9)	7 (3.3)	0.388

All data in this table were presented as mean ± S.D. or n (%). AAVN, anterograde atrioventricular node; ERP, effective refractory period; RAVN, retrograde atrioventricular node; AAP, anterograde accessory pathway; RAP, retrograde accessory pathway; CL, cycle length of the provoked atrioventricular reentrant tachycardia; DAVNPs, dual atrioventricular nodal pathways.

Moreover, the location distributions of APs were also statistically different. Left lateral APs were prone to be found in group D. Other electrophysiological parameters (AAVN 1:1 conduction, AAVN ERP, RAVN 1:1 conduction, RAVN ERP, AAP 1:1 conduction, RAP 1:1 conduction, RAP ERP) were similar between the two groups. There was also no significant difference in the occurrence of multiple APs and DAVNPs between these two groups.

3.3. Risk factors for AF in patients with APs

Variables showing association with AF at the level of p < 0.10 in univariate analysis were included into the multivariate logistic regression model. For the complete cohort, stepwise regression analysis indicated that mAPs, hypertension, post-ablation Pd, NT-proBNP and creatinine were independent risk factors of AF in patients with APs (Table 5).

For patients in cAP group, hypertension, post-ablation Pd and hsCRP were independent risk factors of AF, while post-ablation Pd, NT-proBNP, creatinine and shorter AAP ERP were independent markers for the development of AF in mAPs group (Table 5).

4. Discussion

4.1. Main findings

This study observed that manifest APs had a considerably higher incidence of AF than concealed APs. Anterograde conduction capability served as the major electrophysiological feature of mAPs. Post-ablation Pd, NT-proBNP, creatinine and shorter AAP ERP were independent risk factors of AF in mAP group while hypertension, Pd and hsCRP were independent risk factors in cAP group. These different clinical and electrophysiological properties and risk factors suggested heterogeneous pathogenesis of AF between these two types of APs.

4.2. Manifest APs had a higher tendency to develop AF

In line with previous studies [7,18,19], we also observed significantly higher AF incidence in patients with manifest APs compared to concealed APs (23.4% vs 9.8%, p < 0.01). Multivariate analysis also showed that manifest APs was an independent risk factor of AF in the complete cohort. However, the clinical characteristics, including gender, age, comorbidities, echocardiographic measurements, electrocardiogram measurements and AF-associated biomarkers, were similar between concealed and manifest APs. Besides, the electrophysiological characteristics of atrioventricular node and retrospective conduction properties of APs were similar between the two types of APs as well. These results suggested that the anterograde conduction capability of APs rather than the retrograde conduction property was the critical determinant of AF.

The reason that manifest APs were associated with increased incidence of AF is not fully understood. Previous literature claimed that anatomical structural differences in and near the APs apparently affected refractoriness and conduction properties of the APs [20]. Branching of the manifest APs might be the anatomical substrate responsible for micro-reentry and reflection [18]. It is known that the wavetail of the retrograde impulse propagation to the atrium through manifest APs could interact with the subsequent anterograde wavefront, initiating wavebreak and functional reentry in the branching frameworks, which could then facilitate the initiation and maintenance of AF [21]. Other theory claimed that the manifest APs were associated with increased hemodynamic changes and stretches in atria. The accelerated atrial remodeling induced by elevated atrial pressure and hypoxia might be another explanation of the greater tendency of AF in manifest APs [22]. Further investigations are still needed to clarify the underlying mechanisms.

Table 3
Clinical characteristics in AF or non-AF patients with concealed or manifest APs.

Clinical characteristics	A: non-AF and concealed APs (n = 222)	B: AF and concealed APs (n = 24)	C: non-AF and manifest APs (n = 164)	D: AF and manifest APs (n = 50)	ANOVA F	p value
Male	134 (60.4)	16 (66.7)	81 (49.4)	37 (74.0) ‡		
Age, y	41.2 ± 16.8	57.0 ± 18.2*	38.6 ± 17.4	55.9 ± 14.1‡	19.835	<0.001
Duration of tachycardia, y	7.4 ± 8.9	10.8 ± 11.2	7.2 ± 9.1	9.2 ± 12.5	1.493	0.216
Presyncope	12 (5.4)	3 (12.5)	7 (4.3)	5 (12.0)		
Syncope	5 (2.3)	1 (4.2)	2 (1.2)	1 (2.0)		
Hypertension	36 (16.2)	15 (62.5)*	20 (12.2)	14 (28.0) †‡		
Coronary artery disease	6 (2.7)	6 (25.0)*	7 (4.3)	12 (24.0) ‡		
Valvular heart disease	1 (0.5)	0 (0.0)	3 (1.8)	1 (2.0)		
Diabetes mellitus	10 (4.5)	5 (20.8)*	5 (3.0)	1 (2.0) †		
Chronic kidney disease	153 (68.9)	23 (95.8)*	104 (63.4)	47 (94.0)‡		
CHADS2 score	0.3 ± 0.6	1.1 ± 1.1*	0.2 ± 0.5	0.6 ± 0.9†‡	17.393	<0.001
CHA2DS2-VASc score	0.9 ± 0.8	2.3 ± 1.4*	0.8 ± 0.8	1.7 ± 1.3‡	29.796	<0.001
Left atrial diameter, mm	31.6 ± 4.4	34.1 ± 5.1*	31.8 ± 4.0	36.4 ± 5.1‡	15.292	<0.001
Left ventricular end-diastolic diameter, mm	47.2 ± 4.2	49.4 ± 6.2	47.3 ± 3.9	49.1 ± 4.0‡	3.309	0.020
Left ventricular ejection fraction, %	66.2 ± 5.4	65.8 ± 7.2	65.8 ± 5.4	64.7 ± 7.1	1.615	0.185
Pmax, ms	111.5 ± 10.8	122.1 ± 11.8*	111.2 ± 9.7	120.4 ± 8.1‡	18.227	<0.001
Pmin, ms	75.8 ± 9.2	76.7 ± 10.1	75.7 ± 9.1	76.0 ± 8.3	0.079	0.972
Pd, ms	35.7 ± 8.4	45.4 ± 11.0*	35.4 ± 8.7	44.4 ± 9.7‡	22.267	<0.001
NT-proBNP, pg/ml	46.5 ± 56.0	132.8 ± 311.0	51.2 ± 51.0	124.5 ± 678.0‡	10.386	<0.001
cTnI, ng/ml	0.031 ± 0.119	0.055 ± 0.114	0.032 ± 0.182	0.082 ± 0.128	1.894	0.130
Creatinine, μmol/L	63.0 ± 17.1	69.0 ± 14.7	62.2 ± 18.5	95.2 ± 127.6‡	7.760	<0.001
Uric acid, μmol/L	324.0 ± 83.5	356.8 ± 92.7	309.8 ± 86.2	318.8 ± 90.7	2.407	0.067
hsCRP, mg/ L	3.32 ± 1.96	5.06 ± 2.80*	3.36 ± 2.46	4.39 ± 4.29	5.627	0.001
LDL-c, mmol/ L	2.52 ± 0.64	2.42 ± 0.42	2.54 ± 0.62	2.50 ± 0.58	0.249	0.862
D-dimer, ng/ml	0.15 ± 0.12	0.24 ± 0.22*	0.13 ± 0.11	0.22 ± 0.19‡	9.405	<0.001
Thyrotropin, mIU/L	2.49 ± 1.65	2.02 ± 1.14	2.38 ± 1.89	2.31 ± 1.19	0.692	0.557

All data in this table were presented as mean ± SD, median ± IQR, or n (%). p < 0.05, * vs A, † vs B, ‡ vs C. ANOVA, analysis of variance; Pmax, maximum P wave duration; Pmin, minimum P wave duration; Pd, P wave dispersion; NT-proBNP, N-terminal-proB-type natriuretic peptide; cTnI, cardiac troponin I; hsCRP, high-sensitivity C-reactive protein; LDL-c, low density lipoprotein cholesterol.

4.3. Shortened AAP ERP increased the AP-dependent atrial vulnerability in manifest APs

Although with some inconsistencies, the majority of previous studies observed that AAP ERP appeared shorter in AF group than in the control group for patients with manifest APs [8,23–25]. Soylu et al. [23] reported that, both AAP ERP and RAP ERP were shorter in AF group. Fujimura et al. [24] reported that AAP ERP was shorter in AF group while RAP ERP remained similar between AF group and the control. Our study came up with the similar result as Fujimura's report.

Moreover, according to multivariate regression analysis, shorter AAP ERP served as an independent risk factor of AF in manifest APs.

It still remains uncertain how the shortened AAP ERP enhances the propensity of AF in manifest APs. One mechanism is that shorter AAP ERP allows faster ventricular responses during atrial tachycardia or other types of supraventricular tachycardia. Another possible mechanism is that shorter AAP ERP could facilitate micro-reentry within the branching frameworks of the manifest APs. In addition, shortened AAP ERP might be correlated with severe cardiac sympathetic dysfunction, which is associated with the occurrence of AF in patients with

Table 4
Electrophysiological characteristics in AF or non-AF patients with concealed or manifest APs.

Electrophysiological characteristics	A: non-AF and concealed APs (n = 222)	B: AF and concealed APs (n = 24)	C: non-AF and manifest APs (n = 164)	D: AF and manifest APs (n = 50)	ANOVA F	p value
AAVN 1:1 conduction, ms	351 ± 21	357 ± 30	345 ± 21	342 ± 21	4.846	0.002
AAVN ERP, ms	264 ± 21	269 ± 26	267 ± 17	264 ± 16	0.947	0.418
RAVN 1:1 conduction, ms	383 ± 39	404 ± 61	382 ± 38	378 ± 39	2.440	0.064
RAVN ERP, ms	318 ± 25	322 ± 27	322 ± 26	323 ± 29	1.248	0.292
AAP 1:1 conduction, ms	–	–	365 ± 21	360 ± 17		
AAP ERP, ms	–	–	314 ± 19	286 ± 18‡		
RAP 1:1 conduction, ms	298 ± 19	300 ± 25	300 ± 20	299 ± 21	0.524	0.666
RAP ERP, ms	272 ± 18	276 ± 23	275 ± 17	275 ± 17	1.351	0.257
CL, ms	342 ± 40	328 ± 40	344 ± 43	347 ± 40	1.247	0.292
AP numbers, n	1.0 ± 0.0	1.0 ± 0.0	1.1 ± 0.3	1.2 ± 0.6	2.117	0.097
Location of APs, n (%)						
Anteroseptal	4 (1.8)	0 (0.0)	13 (7.9) *	2 (4.0)		
Right free-wall	16 (7.2)	1 (4.2)	34 (20.7)*	4 (8.0)‡		
Posteroseptal	26 (11.7)	3 (12.5)	31 (18.9)*	9 (18.0)		
Left posteral	19 (8.6)	2 (8.3)	16 (9.8)	3 (6.0)		
Left lateral	147 (66.2)	17 (70.8)	56 (34.1)*	29 (58.0)‡		
Midseptal	0 (0.0)	1 (4.2)	6 (3.7)*	0 (0.0)		
Multiple	10 (4.5)	0 (0.0)	8 (4.9)	3 (6.0)		
DAVNPs, n (%)	12 (5.4)	0 (0.0)	3 (1.8)	4 (8.0)		

All data in this table were presented as mean ± S.D. or n (%). p < 0.05, * vs A, † vs B, ‡ vs C. ANOVA, analysis of variance; AAVN, anterograde atrioventricular node; ERP, effective refractory period; RAVN, retrograde atrioventricular node; AAP, anterograde accessory pathway; RAP, retrograde accessory pathway; CL, cycle length of the provoked atrioventricular reentrant tachycardia; DAVNPs, dual atrioventricular nodal pathways.

Table 5
Independent risk factors of AF in patients with APs, concealed APs and manifest APs.

Clinical/electrophysiological parameters	OR	95% CI	p value
APs (complete cohort)			
mAPs	3.340	1.781–6.264	<0.001
Hypertension	3.006	1.546–5.845	0.001
Post-ablation Pd	1.097	1.062–1.132	<0.001
NT-proBNP	1.001	1.000–1.001	0.018
Creatinine	1.026	1.010–1.043	0.001
Concealed APs			
Hypertension	7.478	2.798–19.983	<0.001
Post-ablation Pd	1.090	1.034–1.149	0.001
hsCRP	1.233	1.017–1.496	0.033
Manifest APs			
Post-ablation Pd	1.088	1.026–1.153	0.005
NT-proBNP	1.003	1.000–1.006	0.020
Creatinine	1.057	1.022–1.093	0.001
AAP ERP	0.970	0.947–0.994	0.015

OR, odds ratio; CI: confidence interval; AAP ERP: effective refractory period of anterograde accessory pathways.

WPW syndrome [26]. All above-mentioned mechanisms can lead to inappropriate atrial stretch and hypoxia, therefore, increase the AP-dependent atrial vulnerability and contribute to the genesis and sustaining of AF.

In both concealed and manifest APs, the RAP ERP showed no difference between AF and Non-AF groups in our study. Thus, the anterograde rather than the retrograde conduction properties of APs took a crucial role in pathogenesis of AF. These results suggested that the AP-dependent atrial vulnerability contributed more in manifest APs than in concealed APs.

4.4. Hypertension increased the AP-independent atrial vulnerability

Although most patients with APs were relatively young and did not have structural heart diseases, some individuals do developed comorbidities with aging, such as hypertension, coronary artery disease, valvular heart disease and diabetes mellitus. These comorbidities, which were proved to be risk factors of AF in general population, might also increase intrinsic atrial vulnerability in patients with APs [27]. In the present study, the incidence of hypertension, coronary artery disease, valvular heart disease and diabetes mellitus in APs were 18.5%, 6.7%, 1.1% and 4.6%, respectively. For both concealed and manifest APs, the incidences of hypertension and coronary artery disease were higher in AF group. AF patients with concealed APs tended to have higher incidence of diabetes mellitus as well. Previous literatures demonstrated that hypertension was an independent risk predictor for AF in general population without APs [28,29]. In our study, multivariate analysis showed that hypertension was an independent risk factor for AF in the complete cohort (OR = 3.006) and in concealed AP group (OR = 7.478). These results suggested that hypertension, as well as coronary artery disease and diabetes mellitus, might increase the intrinsic and AP-independent atrial vulnerability in patients with APs, especially in concealed APs. Hypertension served as the major risk factor of AF in patients with concealed APs.

4.5. P wave dispersion reflected the intrinsic atrial muscle vulnerability

Atrial electrophysiological abnormalities, especially atrial conduction delays were observed in patients with APs, even if they had no previous history of AF [30]. These abnormalities were thought to be critically associated with the vulnerability to AF. Atrial conduction delays and dispersion can be evaluated by not only the invasive EPS but also the noninvasive, 12-lead surface ECG. P-wave dispersion (Pd) is defined as the difference between the maximum P wave duration (Pmax) and the minimum P wave duration (Pmin) recorded from multiple different ECG leads [17]. Significant correlations have been shown between Pmax and the longest duration of the right atrial electrograms,

the maximal number of their fragmented deflections and the repetitive atrial firing zone [31]. Pd could also be attributed to an underlying heterogeneity of atrial conduction [32,33].

For manifest APs, measuring the P wave duration is a difficult job due to the ventricular preexcitation and the existence of delta wave. Besides, the impulse could propagate retrogradely from ventricle to atrium through either concealed or manifest APs, resulting in slower conduction velocity of the next sinus impulse. Therefore, P wave duration should be measured after the ablation of APs. Previous study reported that Pmax and Pd became significantly longer in patients with AF history even when left atrial diameter and left ventricular ejection fraction were similar between AF and the control groups [23]. It suggested that Pmax and Pd might be more sensitive than left atrial diameter in reflecting atrial remodeling during AF genesis. In our study, Pmax and Pd were significantly larger in AF group than in non-AF group. And multivariate analysis also showed that Pd was an independent risk factor of AF in both concealed and manifest APs. These results indicated that the atrial conducting delays, inhomogeneous and discontinuous propagation of sinus impulses and increased atrial muscle intrinsic vulnerability played a critical role in the pathogenesis of AF.

4.6. AF-associated biomarkers in patients with APs

Growing evidences show that inflammation might be associated with the pathogenesis of AF [34]. CRP, an acute phase protein produced by the liver, is one of inflammatory biomarkers associated with AF genesis [35]. The continuous development of more sensitive CRP methods (high-sensitivity CRP, hsCRP) has made it possible to detect and measure CRP level in almost all individuals. Although some inconsistencies exist, the majority of studies reported elevated CRP levels to be an independent risk factors for AF in general population [36,37]. In our study, the level of hsCRP was significant higher in AF group and hsCRP was an independent risk factor of AF in concealed APs. These results suggested that the increased inflammatory state and AP-independent atrial vulnerability might play important roles in the development of AF in patients with APs.

Creatinine is accepted as a useful index of renal function. The prevalence of AF was higher in patients of chronic kidney disease compared with general population [38–40]. In general population, the AF prevalence increased with increasing creatinine and decreasing GFR values [41,42]. In the present study, the creatinine value was elevated in AF group of patients with manifest APs. Multivariate regression also indicated that creatinine was an independent risk factor of AF in manifest APs. Thus, renal dysfunction, acting as one part of AP-independent atrial vulnerability, plays an important role in the pathogenesis of AF in patients with manifest APs.

N-terminal pro-B-type natriuretic peptide (NT-proBNP), largely produced by the ventricles, is considered as a biomarker of cardiac failure. However, physiological studies also observed increased BNP production in the atria of individuals with AF [43,44]. It was reported that NT-proBNP level was significantly higher in patients with AF compared with controls in sinus rhythm [45]. Previous studies demonstrated that the higher NT-proBNP value could predict an increased risk of development of AF in community-based population, even after adjustment for other known risk factors of AF [46,47]. However, there was limited information on the role of NT-proBNP in APs population. In our study, the level of NT-proBNP was significantly higher in AF group than in non-AF group for manifest APs patients. Moreover, NT-proBNP was an independent risk factor of AF in the complete cohort and in manifest AP patients. The elevated NT-proBNP values might be attributed to alteration in ventricular and atrial filling patterns. Atrial vulnerability would increase with the electrical conduction through the APs, the loss of mechanical atrial synchrony, the calcium overload and myocardial ischemia, leading to the appearance and maintenance of AF in patients with APs.

4.7. Different pathogenesis of AF between concealed and manifest APs

As mentioned above, the AP-independent and AP-dependent atrial vulnerabilities were hypothesized as two possible mechanisms of AF [16]. Results from this study suggested heterogeneous mechanisms of AF for concealed and manifest APs.

For concealed APs, plenty of clinical differences but no electrophysiological difference were found between AF and non-AF groups, suggesting that the intrinsic, atrium-inherent and AP-independent atrial vulnerability played a critical role in AF genesis.

For manifest APs, however, both clinical and electrophysiological differences were reported between AF and non-AF groups, indicating that not only AP-independent atrial vulnerability but also AP-dependent atrial vulnerability played important roles in the development of AF. Moreover, the incidences of hypertension and diabetes mellitus, which were considered as important contributors of intrinsic and AP-independent atrial vulnerability, were even lower in AF patients with manifest APs compared to AF patients with concealed APs. Considering the higher AF incidence in patients with manifest APs, above results suggested that the AP-dependent atrial vulnerability might contribute more for the AF genesis in patients with manifest APs.

5. Limitations

Limitations of this study need to be addressed. First, the nature of the design of this retrospective study can only demonstrate an association rather than a causal relationship between all these clinical and electrophysiological factors and AF development in AP patients. A prospective study as well as a follow-up study to estimate the risk factors of AF after AP ablation is still required. Second, Svendsen et al. [48] reported a survey of a large number of AP patients who were either symptomatic or asymptomatic and who had ablation as well as those who did not have ablation. In the present study, however, the patients were all symptomatic and selected to have an electrophysiological study and ablation. Therefore, it is difficult to identify risk factors of AF in those who were asymptomatic and who were symptomatic but did not have an electrophysiological study and ablation. Further studies on this issue are required. Third, the electrophysiological data of atrioventricular nodes were measured after the ablation of APs. We are not sure whether the ablation of APs would change the conduction properties of atrioventricular nodes. It is worth noting that the electrophysiological data of atrioventricular nodes were difficult to acquire before AP ablation in a part of patients due to the provocation of AVRT or AF.

6. Conclusions

This study evaluated the different clinical and electrophysiological characteristics between concealed and manifest APs and between AF and non-AF groups in each type of APs. Results from this study demonstrate that the risk factors of AF are not homogenous between concealed and manifest APs, which might suggest heterogeneous pathogenesis of AF in these two types of APs.

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Conflict of interest

None declared.

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