

Apelin

A novel prognostic predictor for atrial fibrillation recurrence after pulmonary vein isolation

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Abstract

Apelin, the ligand for the APJ receptor, is involved in the pathogenesis of atrial fibrillation (AF). However, whether serum apelin can predict the recurrence of AF after pulmonary vein isolation (PVI) has not been determined.

A prospective cohort study was performed in patients with AF (but without structural heart disease) who were undergoing first-time PVI. Serum apelin-12 was measured by enzyme-linked immunosorbent assay. Echocardiographic examination was performed at baseline, 3 months, and 6 months after PVI. Patients were followed up for 6 months after PVI, and the association between baseline apelin-12 and AF recurrence (early recurrence: within 3 months after ablation; late recurrence: 3–6 months after ablation) was analyzed.

A total of 61 patients were included in the study. Baseline serum level of apelin-12 was significantly lower in patients with early (median [interquartile range]: 1844 [1607–2061] vs 2197 [1895–2455] ng/L, $P=.01$) and late (1639 [1524–1853] vs 1923 [1741–2303] ng/L, $P=.02$) AF recurrence compared with patients without these events. Results of Cox stepwise multivariate analysis demonstrated that lower baseline apelin-12 (<2265 ng/L) was independently associated with increased AF recurrence within 6 months after PVI ($P<.05$). The specificity and positive predictive value of apelin-12 for AF recurrence were significantly higher than those of baseline N-terminal brain proBNP (60.4% vs 28.6%, $P<.001$; 58.8% vs 34.4%, $P=.01$), although the sensitivity and negative predictive value were similar.

Reduced baseline serum apelin-12 may be an independent risk factor for the recurrence of AF after PVI in patients without structural heart disease.

Abbreviations: AF = atrial fibrillation, PVI = pulmonary vein isolation, PV = pulmonary veins.

Keywords: apelin, atrial fibrillation, pulmonary vein isolation, recurrence

1. Introduction

Atrial fibrillation (AF) has become one of the most common cardiac arrhythmias seen in clinics. Comorbidities of AF may increase the risks of thromboembolic events, such as stroke, and lead to deterioration of cardiac function and incidence of heart failure, thereby contributing to morbidity and mortality.^[1] Electrophysiologically, many potential mechanisms are thought to be involved in the pathogenesis and progression of AF, including simultaneous re-entrant circuits and variability in wavelength initiated by rapidly firing foci. The latter originates from the pulmonary veins (PV),^[2] and targeted myocardial ablation by PV isolation (PVI) has become one of the most

effective treatments for AF. However, previous evidence suggests considerable recurrence of AF after the PVI procedure, varying from 14% to 35% in paroxysmal AF and up to 70% in persistent AF.^[3–7] Therefore, developing biomarkers for predicting AF recurrence after ablation is clinically important in identifying AF patients who respond well to PVI treatment.

Many factors, mostly involved in the pathogenesis of AF, can potentially predict recurrence of AF after PVI, such as preexistent left atrial scarring, reduced cardiac systolic function, comorbidities of renal dysfunction, and increased serum markers, including high-sensitive C-reactive protein (CRP), endothelin-1, N-terminal pro-brain natriuretic peptide (NT-proBNP), and platelet-derived growth factor (PDGF).^[8–15]

Apelin, an endogenous peptide ligand of the previously orphaned G-protein-coupled receptor APJ, is synthesized as a preproprotein, which is cleaved through N-terminal proteolysis to generate several mature biologically active forms including apelin-36, apelin-17, apelin-16, apelin-13, and apelin-12.^[16–18]

Recent studies have suggested apelin plays an important role in the pathogenesis of cardiovascular diseases. For instance, mice deficient in apelin exhibited a reduced response to cardiac pressure overload^[19] and the levels of serum apelin-12 were decreased in patients with essential hypertension.^[20] These findings suggest a potential role of apelin in the maintaining of cardiovascular homeostasis. Consistent with the above findings, a more recent prospective clinical study proposed a predictive value of apelin-12 in patients with ST elevation myocardial infarction.^[21]

Previous studies also showed an implication of apelin in AF. For example, decreased circulating levels of apelin were observed in lone AF patients and in patients with persistent AF.^[22,23] The

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latter study also showed that AF patients with low levels of serum apelin are associated with worse outcomes, suggesting a prognostic value of plasma apelin for patients with arrhythmia recurrence. However, to the best of our knowledge, few studies have evaluated the predictive effect of serum apelin on AF recurrence after PVI. In this prospective cohort study, we aimed to evaluate the levels of serum apelin-12 as a predictor for AF recurrence after PVI in AF patients without structural heart disease.

2. Methods

2.1. Patient characteristics

This study included 61 consecutive patients who underwent circumferential PVI for symptomatic and drug-refractory paroxysmal AF or persistent AF between May 2010 and April 2011 in our center. Patients having one of the following conditions were excluded from this study: mitral valvular heart disease, pulmonary disease, a recent infection, surgery, acute coronary syndrome during the past 2 months prior to enrollment, and/or previous catheter ablation for AF. All selected patients signed informed consent and this study was approved by the ethics committee of Chongqing Medical University.

2.2. Study protocol

All included patients had transthoracic echocardiograms (Philips iE33 ultrasound PHILIPS (USA) Investment Co., Ltd. Bothell. www.medical.philips.com) before as well as at 3 and 6 months after PVI. Left atrium diameter, valvular abnormality, left ventricular (LV) wall motion, and LV ejection fraction (LVEF) were assessed. The blood samples were obtained from the antecubital vein of each participant, and stored in ethylenediaminetetra-acetic acid-containing and aprotinin (2 µg/mL) tubes after a resting period of 12 hours before PVI, and at 1, 3, and 6 months after PVI. Blood was centrifuged at 4°C, and plasma aliquots were stored at -80°C until the biochemical analyses were performed. The plasma levels of apelin-12, NT-proBNP, and PDGF-AA were measured by the enzyme-linked immunosorbent assay with commercially available kits according to the manufacturer's instructions (RayBio Human ELISA Kit, Norcross, GA).

2.3. PVI procedure

PVI was performed according to the procedure described by O'Carroll et al.^[17] Briefly, a multipolar mapping catheter was placed into the coronary sinus via the left subclavian vein to record coronary sinus electrograms. The ablation catheter and circular mapping catheter were placed via the right femoral vein to the left atrium using a double trans-septal puncture technique.

PVI was performed by applying radiofrequency energy at ostial sites which showed the earliest bipolar pulmonary vein (PV) potentials during sinus rhythm or paced rhythm. Radiofrequency energy was delivered with a target temperature of 45°C and a maximum power output of 30 to 40 W for 30 seconds (Stockert, Biosense-Webster Inc., South Diamond Bar, CA) using a 4-mm irrigated tip with saline cooling of the ablation electrode (Navistar, Biosense-Webster) under the guidance of the CARTO system and fluoroscopy. Successful PVI was defined as having either the abolition or dissociation of the distal PV potentials from the left atrial electrograms.

2.4. Follow-up

All patients were examined at 1, 3, and 6 months after PVI. A 12-lead ECG and 12-lead 24-hour Holter or 1-week long-term Holter were performed at every visit, or whenever patients reported symptoms of palpitations. During the follow-up period, antiarrhythmic agents were discontinued for all patients, unless continuous medication was considered necessary for patients with persistent arrhythmia.

2.5. Definition of AF recurrence

The existence of AF was defined as atrial tachyarrhythmia (including AF, AFL, AT) continuing for ≥ 30 seconds as determined by 12-lead ECG and 12-lead 24-hour Holter or 1-week long-term Holter during follow-up. We classified the patients into 2 different groups according to clinical outcomes as follows: early recurrence of AF (ERAF), that is, recurrence within 3 months post-ablation; and late recurrence of AF (LRAF), that is, recurrence between 3 and 6 months, that is, the end of the follow-up period.

2.6. Statistical analysis

Statistical analysis was performed with SPSS v17.0 statistical software (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. The normally distributed variables were expressed as mean \pm standard deviation (SD) and compared with Student *t* test, while the non-normally distributed variables were reported as median (first and third quartiles) and compared with the Mann-Whitney *U* test. A Chi-squared test was used for statistical analysis of categorical variables. Receiver-operator characteristic (ROC) curves were established to calculate areas under the curve (AUC) to evaluate the predictive values of apelin-12 and other factors for the recurrence of AF. The best cut-off values of the above mentioned markers for the prediction of AF recurrence were also derived from the ROC curves. Univariate Cox regression analysis was performed to determine the association between the serum markers and the recurrent AF at follow-up. Adjusted odds ratios and 95% confidence interval (CI) were applied for estimation of the associations. All statistical tests were two-sided probability tests, and a *P*-value $< .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics and outcomes of participants

Baseline characteristics of these 61 patients are presented in Table 1. The mean age of the patients was 55.8 years and 59.0% were men. During follow-up, ERAF occurred in 36.1% (22/61) of the patients, and the incidence of overall LRAF was 18.0% (11/61).

3.2. Clinical characteristics of patients with ERAF

In the present study, a total of 22 ERAF patients were enrolled. Among these 22 ERAF patients, 12 were treated with amiodarone for arrhythmia (but 6 did not resume sinus rhythm after 1 month treatment and then changed to beta-blocker to control ventricular rate), 2 underwent secondary ablation (1 successfully restored sinus rhythm, and the other one was treated with beta-blocker to control ventricular rate), 5 received DC cardioversion (3 successfully recovered sinus rhythm, and 2 received beta-blocker controlled ventricular rate), and 3 were

Table 1**Baseline characteristics of patients with and without early recurrence of atrial fibrillation (ERAF).**

Parameters	Baseline	No ERAF (n=39)	ERAF (n=22)	P-value
Age, y	55.80 ± 13.42	53.81 ± 15.84	58.50 ± 7.56	.137
Male sex, n (%)	36 (59.02%)	23 (58.97%)	13 (59.09%)	.993
Weight, kg	62.36 ± 9.78	63.67 ± 10.07	60.43 ± 8.97	.318
High, m	1.64 ± 0.07	1.65 ± 0.08	1.62 ± 0.06	.127
Smoking, n (%)	15 (24.59%)	10 (25.64%)	5 (22.73%)	.800
Body mass index, kg/m ²	23.11 ± 2.92	23.23 ± 2.88	23.10 ± 2.77	.887
Duration of AF history, y	4.41 ± 3.83	4.94 ± 4.36	3.72 ± 3.08	.248
Non-paroxysmal AF, n (%)	17 (27.87%)	8 (20.51%)	9 (40.91%)	.088
Hypertension, n (%)	22 (36.07%)	15 (38.46%)	7 (31.82%)	.604
Diabetes mellitus, n (%)	6 (9.84%)	4 (10.26%)	2 (9.09%)	.883
Coronary artery disease, n (%)	10 (16.39%)	6 (15.38%)	4 (18.18%)	.777
Systolic blood pressure, mmHg	125.77 ± 20.74	126.97 ± 23.28	123.10 ± 16.08	.511
Diastolic blood pressure, mmHg	77.18 ± 11.85	78.46 ± 12.98	74.90 ± 9.91	.290
Heart rate, beats/min	76.20 ± 15.31	74.08 ± 14.53	80.70 ± 16.59	.127
T3, pmol/L	4.81 ± 0.77	4.68 ± 0.91	4.42 ± 1.21	.444
T4, pmol/L	39.67 ± 25.47	20.58 ± 14.93	21.31 ± 12.93	.876
TSH, μ U/mL	5.07 ± 2.74	3.79 ± 2.69	3.13 ± 1.71	.410
Creatinine, μ mol/L	77.54 ± 14.97	77.63 ± 17.41	78.74 ± 12.36	.872
High-sensitivity C-reactive protein, mg/L	3.18 ± 6.98	3.63 ± 7.87	3.53 ± 6.91	.979
Beta-blocker, n (%)	30 (49.18%)	18 (46.15%)	12 (54.55%)	.529
Calcium-channel blocker, n (%)	7 (11.48%)	4 (10.26%)	3 (13.64%)	.691
Angiotensin-converting enzyme inhibitor, n (%)	25 (40.98%)	15 (38.46%)	10 (45.45%)	.594
Angiotensin receptor blocker, n (%)	13 (21.31%)	8 (20.51%)	5 (22.73%)	.839
Statin, n (%)	7 (11.48%)	5 (12.82%)	2 (9.09%)	.661

AF = atrial fibrillation, T = thyroxine, TSH = thyroid-stimulating hormone.

directly treated with beta-blocker to control ventricular rate. By the end of the study follow-up period, a total of 12 patients in ERAF had not recovered sinus rhythm, and these 12 ERAF patients were considered clinical failure.

For patients with or without ERAF, the baseline characteristics were generally matched in demographic features, comorbidities of coronary artery disease (CAD) and diabetes mellitus (DM), baseline thyroid functions, and concurrent medications (Table 1). However, the baseline level of serum apelin-12 was significantly lower in patients with ERAF (median [interquartile range]: 1844 [1607–2061] vs 2197 [1895–2455] ng/L, $P = .01$) compared with

that of those patients without ERAF (Table 2). Moreover, a significantly higher level of NT-proBNP was also noticed in patients with ERAF compared with that of those without ERAF ($P = .03$, Table 2). However, the levels of serum apelin-12 and NT-proBNP were not significantly different at 1, 3, and 6 months after PVI in patients with and without ERAF. The echocardiographic study showed that patients with ERAF had significantly larger left atrial diameter and lower LVEF at baseline compared with those without ERAF (Table 3), although the echocardiographic parameters were not significantly different between these 2 groups at 3 and 6 months post-PVI.

Table 2**Biomarker levels following pulmonary vein isolation (PVI) in patients with and without early recurrence of atrial fibrillation (ERAF).**

Parameters	No ERAF (n=39)	ERAF (n=22)	P-value
Before PVI			
NT-proBNP, pg/mL	317 (284–491)	455 (404–509)	.036
PDGF-AA, pg/mL	2043 (1141–2141)	1878 (1077–2039)	.139
Apelin-12, ng/L	2197 (1895–2455)	1844 (1607–2061)	.011
1 month after PVI			
NT-proBNP, pg/mL	289 (226–377)	272 (199–384)	.778
PDGF-AA, pg/mL	1869 (1714–1981)	1781 (1325–1943)	.394
Apelin-12, ng/L	2810 (1848–3800)	2279 (2082–3130)	.868
3 months after PVI			
NT-proBNP, pg/mL	232 (173–384)	214 (200–280)	.925
PDGF-AA, pg/mL	2028 (1964–2127)	2074 (1999–2109)	.967
Apelin-12, ng/L	2893 (2050–3126)	2251 (1525–3516)	.813
6 months after PVI			
NT-proBNP, pg/mL	186 (145–253)	222 (206–301)	.206
PDGF-AA, pg/mL	1858 (965–2172)	1432 (867–2068)	.865
Apelin-12, ng/L	2013 (2086–2370)	2251 (1417–3965)	.673

Median and 25th and 75th percentiles are presented.

AF = atrial fibrillation, ERAF = early recurrence of AF, NT-proBNP = N-terminal pro-brain natriuretic peptide, PDGF = platelet-derived growth factor, PVI = pulmonary vein isolation.

Table 3

Transthoracic echocardiographic parameters following pulmonary vein isolation (PVI) in patients with and without atrial fibrillation recurrence.

Parameters	No ERAF (n=39)	ERAF (n=22)	P-value	No LRAF (n=50)	LRAF (n=11)	P-value
Before PVI						
LAD, mm	36.51±5.01	40.08±4.76	<.001	37.02±5.30	38.29±4.39	.550
LVDD, mm	46.62±4.06	49.42±7.84	.058	47.45±6.04	47.14±3.30	.857
LVSD, mm	29.47±4.67	33.32±7.65	.012	30.73±6.38	29.71±3.58	.570
IVST, mm	10.76±1.50	10.37±1.65	.292	10.67±1.49	10.29±1.82	.417
LVEF (%)	67.30±8.47	62.34±8.08	<.001	65.71±8.86	66.43±7.25	.586
3 months after PVI						
LAD, mm	35.75±5.44	37.83±5.76	.227	36.11±5.76	38.80±4.92	.194
LVDD, mm	45.84±3.25	47.91±4.06	.083	47.30±6.94	47.40±2.72	.964
LVSD, mm	28.95±3.93	31.75±11.80	.284	30.26±8.54	28.60±3.24	.556
IVST, mm	10.25±1.52	9.83±1.55	.375	10.15±1.61	9.80±1.03	.530
LVEF (%)	66.90±6.32	65.00±15.40	.585	65.52±11.23	69.80±5.87	.261
6 months after PVI						
LAD, mm	35.40±4.35	36.25±3.15	.650	35.30±4.24	36.50±3.42	.516
LVDD, mm	45.20±4.37	43.25±5.9	.433	44.50±4.70	45.00±5.50	.838
LVSD, mm	26.30±3.30	26.25±3.49	.976	20.60±3.86	25.00±4.07	.032
IVST, mm	9.50±1.51	9.83±1.85	.653	9.40±1.35	10.33±2.06	.234
LVEF (%)	69.80±5.09	69.00±3.30	.706	70.20±5.14	68.00±2.51	.255

ERAF=early recurrence of AF, IVST=intra-ventricular septum dimension, LAD=left atrial dimension, LRAF=late recurrence of AF, LVDD=left ventricular diastolic dimension, LVEF=left ventricular ejection fraction, LVSD=left ventricular systolic dimension.

3.3. Clinical characteristics of patients with LRAF

Patients with LRAF were older and had higher diastolic blood pressure (DBP), but were matched for other baseline characteristics such as demographic features, comorbidities of CAD and DM, baseline thyroid functions, as well as the concurrent medications with those without LRAF (Table 4). Compared with No ERAF patients, LRAF patients had higher NT-proBNP at baseline and 3 months after PVI, and had significantly lower apelin-12 at baseline and 3 and 6 months after PVI (Table 5). Echocardiographic

parameters in both groups were generally similar except that LRAF patients had significantly enlarged LVSD at 6 months after PVI compared with non-ERAF patients (Table 3).

3.4. Predictive value of baseline serum apelin-12 for AF recurrence

We next used multivariate Cox regression analysis to determine the correlation of factors with the AF recurrence. As shown in

Table 4

Baseline characteristics of patients with and without late recurrence of atrial fibrillation (LRAF).

Parameters	No LRAF (n=50)	LRAF (n=11)	P-value
Age, y	58.35±13.98	65.69±12.11	<.001
Male sex, n (%)	23 (46.00%)	6 (54.55%)	.607
Weight, kg	63.08±6.98	63.05±4.53	.928
High, m	1.66±0.08	1.66±0.05	.253
Smoking, n (%)	12 (24.00%)	3 (27.27%)	.819
Body mass index, kg/m ²	23.19±2.36	23.30±1.24	.461
Duration of AF history, y	4.26±3.00	4.76±1.58	.472
Nonparoxysmal AF, n (%)	11 (22.00%)	6 (54.55%)	.029
Hypertension, n (%)	18 (36.00%)	4 (36.36%)	.982
Diabetes mellitus, n (%)	5 (10.00%)	1 (9.09%)	.927
Coronary artery disease, n (%)	8 (16.00%)	2 (18.18%)	.860
Systolic blood pressure, mmHg	131.12±24.51	131.64±11.35	.265
Diastolic blood pressure, mmHg	80.55±13.17	84.78±12.40	<.001
Heart rate, beats/min	72.32±8.23	72.39±5.90	.805
T3, pmol/L	4.85±0.70	4.86±1.05	.946
T4, pmol/L	18.00±2.12	17.73±1.90	.129
TSH, μ U/mL	5.62±3.07	6.06±2.09	.314
Creatinine, μ mol/L	74.58±11.07	74.08±15.17	.399
High-sensitivity C-reactive protein, mg/L	3.13±6.36	3.57±6.86	.865
Beta-blocker, n (%)	25 (50.00%)	5 (45.45%)	.785
Calcium-channel blocker, n (%)	5 (10.00%)	2 (18.18%)	.441
Angiotensin-converting enzyme inhibitor, n (%)	21 (42.00%)	4 (36.36%)	.731
Angiotensin receptor blocker, n (%)	11 (22.00%)	2 (18.18%)	.780
Statin, n (%)	6 (12.00%)	1 (9.09%)	.784

AF=atrial fibrillation, T=thyroxine, TSH=thyroid-stimulating hormone.

Table 5

Biomarker levels following pulmonary vein isolation (PVI) in patients with and without late recurrence of atrial fibrillation (LRAF).

Parameters	No LRAF (n=50)	LRAF (n=11)	P-value
Before PVI			
NT-proBNP, pg/mL	339 (278–404)	477 (401–488)	.001
PDGF-AA, pg/mL	2015 (1220–2117)	1974 (1298–2232)	.171
Apelin-12, ng/L	1922 (1741–2303)	1639 (1524–1853)	.023
1 month after PVI			
NT-proBNP, pg/mL	291 (253–369)	262 (206–347)	.501
PDGF-AA, pg/mL	1869 (1693–1984)	1732 (1474–1906)	.179
Apelin-12, ng/L	2746 (1967–3782)	2058 (2004–3644)	.974
3 months after PVI			
NT-proBNP, pg/mL	217 (197–393)	404 (340–466)	.029
PDGF-AA, pg/mL	2043 (1974–2127)	2105 (2009–2194)	.322
Apelin-12, ng/L	2966 (2251–3488)	2170 (1771–2325)	.027
6 months after PVI			
NT-proBNP, pg/mL	218 (164–292)	268 (246–288)	.111
PDGF-AA, pg/mL	1432 (867–1998)	1853 (1299–2085)	.385
Apelin-12, ng/L	2288 (2242–3589)	1609 (1435–2273)	.015

AF=atrial fibrillation, Median and 25th and 75th percentiles are presented, NT-proBNP=N-terminal pro-brain natriuretic peptide, PDGF=platelet-derived growth factor.

Table 6

Univariate regression analyses for the predictors of late recurrence of atrial fibrillation (LRAF).

Parameters	Univariate analysis		
	Relative risk	95%CI	P-value
Age, y	0.983	0.957–1.010	.226
BMI, kg/m ²	1.064	0.914–1.239	.421
Hypertension	0.802	0.336–1.913	.619
DM	0.278	0.037–2.072	.212
CAD	0.839	0.284–2.480	.751
Diastolic blood pressure at baseline, mmHg	1.055	1.011–1.101	.015
LAD at baseline, mm	1.019	0.942–1.102	.638
LVEF at baseline (%)	1.037	0.991–1.085	.121
NT-proBNP at baseline, pg/mL	1.011	1.007–1.014	<.001
PDGF-AA at baseline, pg/mL	1.000	0.999–1.000	.343
Apelin-12 at baseline, ng/L	0.997	0.995–0.998	<.001

BMI=body mass index, CAD=coronary artery disease, CI=confidence interval, DM=diabetes mellitus, LAD=left atrial dimension, LVEF=left ventricular ejection fraction, NT-proBNP=N-terminal pro-brain natriuretic peptide, PDGF=platelet-derived growth factor.

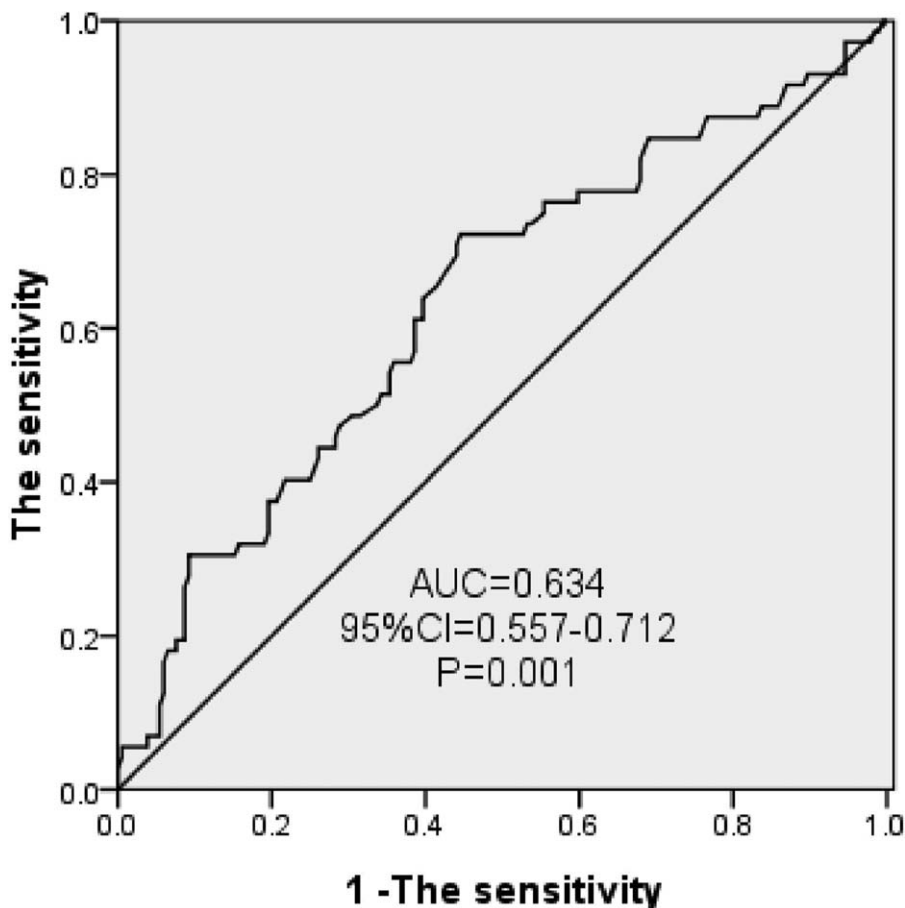


Figure 1. Determination of the predictive value of baseline serum apelin-12 within 6 months after PVI. Receiver-operator characteristic curves were established as detailed in statistical analysis section. AUC=area under the curve, CI=confidence interval, PVI=pulmonary vein isolation.

Table 6, among all factors tested, the higher mean diastolic BP, higher plasma NT-proBNP, and lower plasma apelin-12 at baseline were independent predictors of AF recurrence at 6 months after PVI ($P = .015$, $P < .001$, and $P < .001$, respectively). We also generated ROC curves to determine the 95% CI and the optimal cutoff value of serum apelin-12 and NT-proBNP, respectively, for the prediction of AF recurrence within 6 months after PVI. As shown in Figs. 1 and 2, respectively, serum apelin-12 had an AUC of 0.63 (95% CI: 0.56–0.71) with a cutoff value of 2265.14 ng/L, while serum NT-proBNP had an AUC of 0.60 (95% CI: 0.53–0.78) with a cutoff value of 392.41 pg/mL.

Kaplan–Meier curves (for probability of AF recurrence by median levels of serum apelin-12) were generated for the 180 days of follow-up (Fig. 3; log-rank test, $P = .001$). Similar trends were also found for NT-proBNP (Fig. 4; log-rank test, $P < .001$), whereas no differences were observed for PDGF-AA. The specificity and positive predictive value of serum apelin-12 for AF recurrence were significantly higher than those of baseline N-terminal brain proBNP (60.4% vs 28.6%, $P < .001$; 58.8% vs 34.4%, $P = .01$), although the sensitivity and negative predictive value were similar (90.91% vs 84.00%, $P = .424$; 91.43% vs 80.00%, $P = .221$).

4. Discussion

Our study of patients with recurring AF (but without structural heart disease) revealed that reduced baseline serum apelin-12 may be an independent risk factor for the recurrence of AF after PVI in these patients. Moreover, our results expanded previous observations showing that changes in plasma apelin level occurred in lone AF subjects^[22] and that apelin had a predictive value for AF recurrence after electric cardioversion.^[23] Our findings also indicated that measuring baseline serum apelin-12 may be important for identifying AF patients with a higher risk of AF recurrence after PVI, and that the predictive value of baseline serum apelin-12 for AF recurrence may be similar to NT-proBNP.

Apelin is highly expressed in cardiomyocytes, endothelial cells, and vascular smooth muscle cells (VSMC), suggesting that apelin may play an important role in physiology and pathophysiology of cardiovascular system.^[24,25] Meanwhile, the heart atrium also has high expression of apelin.^[26] A previous study by Szokodi et al^[27] indicated that administration with apelin-16, an active form of apelin,^[16] increased mean arterial filling pressure and cardiac contractility in the isolated perfused rat heart through stimulation of Ca^{2+} influx and activation of phospholipase C systems. In addition, it has been suggested that apelin also reduced preload and afterload in the heart, leading to a significant

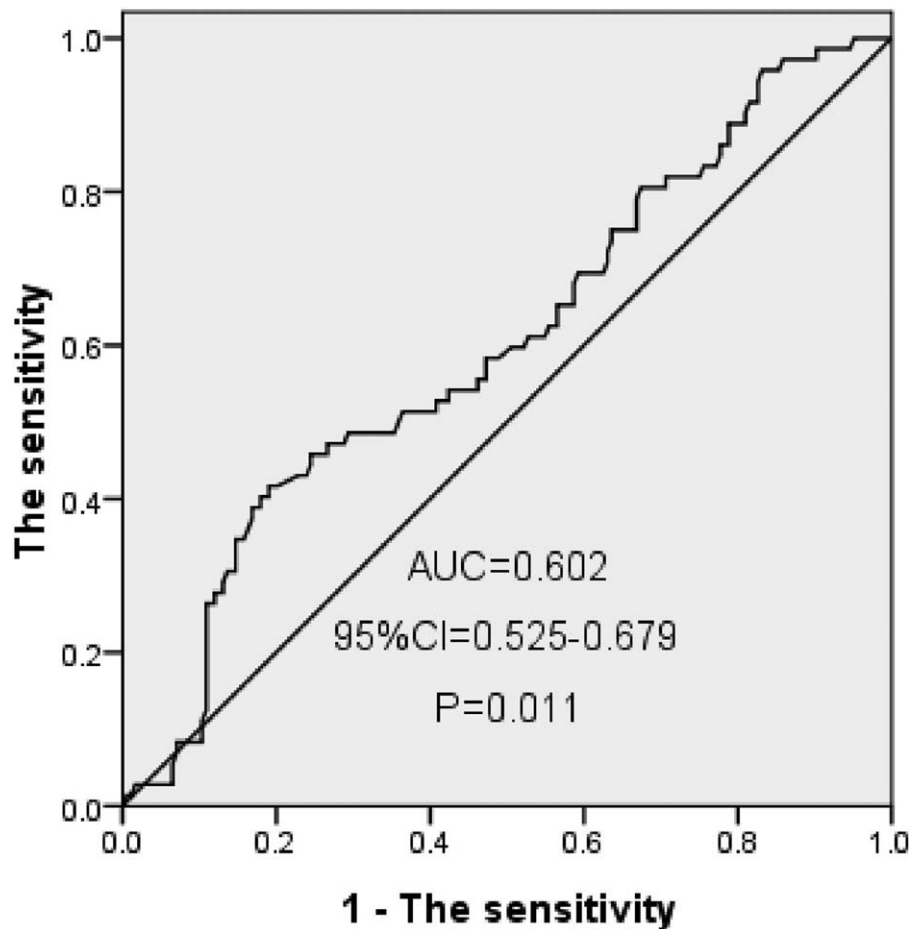


Figure 2. Determination of the predictive value of serum NT-proBNP within 6 months after PVI. Receiver-operator characteristic curves were established as detailed in statistical analysis section. AUC = area under the curve, CI = confidence interval, NT-proBNP = N-terminal pro-brain natriuretic peptide, PVI = pulmonary vein isolation.

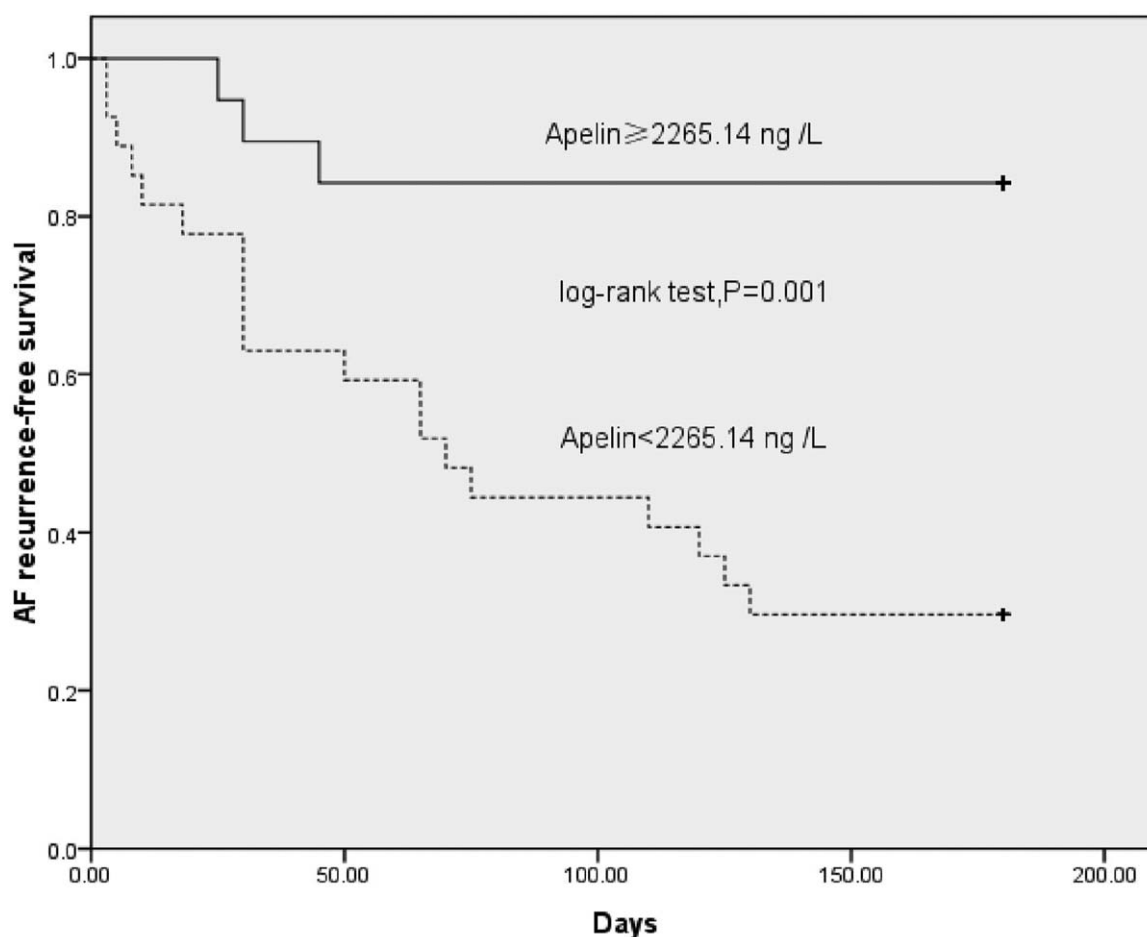


Figure 3. Estimation of the proportion of patients free from AF recurrence after PVI based on the cut-off baseline serum apelin-12. Kaplan–Meier curves were generated for this estimation. AF=atrial fibrillation, PVI=pulmonary vein isolation.

reduction of left atrial pressure.^[28] This is particularly important since reduction of intra-atrial pressure may improve the physical characteristics of atria and decrease pulmonary vein ectopic electrical activity, thereby exerting potent vasodilator and positive inotropic activities leading to an increase in the conduction velocity and a decrease in the field potential duration in in vitro neonatal cardiomyocytes—all of which have been proved to be important mechanisms underlying the pathogenesis and progression of AF. These protective effects of apelin may be the mechanisms involved in increased serum apelin at baseline, which may be used to predict favorable outcomes after PVI procedures.

The pathophysiological mechanisms underlying the pathogenesis of AF are complicated. For instance, inflammation and oxidative stress contribute significantly to the pathogenesis of AF.^[29,30] An increased activity of apelin may also exert beneficial effects on cardiac function, which contributes to the reduced risk of AF recurrence post-PVI in patients with relatively higher serum apelin. Indeed, a previous study of ischemic cardiomyopathy using a rat model indicated that one of the active forms, apelin-13, improved cardiac function,^[31] which was further confirmed by subsequent observations showing that expression of apelin was upregulated in an early compensated phase of heart failure and was reversely correlated with the disease progression and severity.^[32] Moreover, Siddiquee et al^[33] reported that apelin protected against angiotensin II-induced cardiovascular fibrosis. Since an upstream therapy including ACEI or ARB likely prevents AF recurrence via

regulation of atrial remodeling,^[34] we hypothesized that the increased apelin levels may also benefit patients with AF with the same mechanisms. Indeed, our findings together with those from other groups suggested that the increased activity of apelin may have a beneficial effect on AF patients, and that higher serum apelin predicts a lower risk of AF recurrence after PVI.

NT-proBNP is a natriuretic hormone which, in the absence of heart failure, is secreted from the atrium in response to atrial distension and overload.^[35–37] Consistent with the previous findings,^[38–40] we showed that an increased plasma NT-proBNP level predicted a higher risk for AF recurrence post-PVI. Previous studies have demonstrated that BNP inhibited the resting sympathetic activity of the heart, thereby potentiating vagal activity through activating the cGMP pathway and inciting atrial overload and atrial remodeling, which results in sustaining atrial fibrillatory rotors and potentially initiating and sustaining AF.^[41–44] Therefore, NT-proBNP was suggested to predict AF recurrence early in AF patients who underwent PVI. By comparing AUC under ROC curves of apelin-12 and NT-proBNP, our study showed that the predictive value of baseline serum apelin-12 for AF recurrence seemed to be similar to that of NT-proBNP. These results should be confirmed in further studies.

The strengths of our study include our study was a prospective study and we examined the potential for the baseline serum apelin-12 as a predictor for the occurrence of AF recurrence after ablation. However, we also note that our study had some limitations. First,

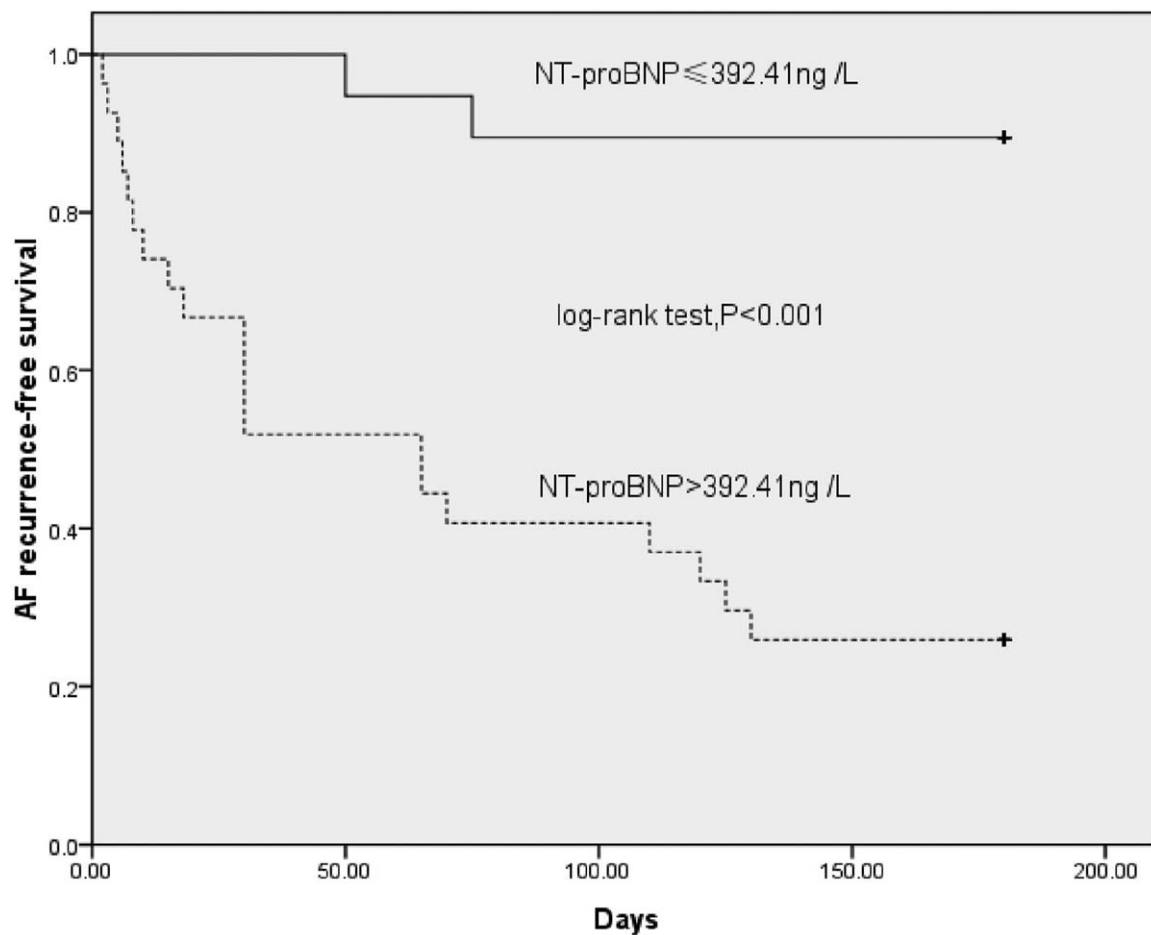


Figure 4. Estimation of the proportion of patients free from AF recurrence after PVI based on the cut-off value of serum NT-proBNP. Kaplan–Meier curves were generated for this estimation. AF=atrial fibrillation, NT-proBNP=N-terminal pro-brain natriuretic peptide, PVI=pulmonary vein isolation.

the sample size (61 patients) was relatively small. Therefore, the findings of the present study should be validated in the future studies with a large cohort with more statistical power. Also, our observational study could not indicate a causative relationship between increased serum apelin-12 and reduced risk of AF recurrence. Hence, the therapeutic value of the treatment targeting the apelin-APJ system deserves further investigation. Finally, our study only had a follow-up duration of 6 months, and the predictive significance of serum apelin-12 in patients with AF warrants further evaluation.

In summary, reduced baseline serum apelin-12 may be an independent risk factor for recurrence of AF after PVI. Therefore, measuring the baseline serum apelin-12 may be useful for identifying AF patients at a higher risk of AF recurrence after PVI. Moreover, the predictive value of baseline apelin-12 for AF recurrence may be similar to the commonly used biomarker, NT-proBNP.

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