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Journal of Clinical and Experimental Cardiology

Research Article

The Biomark of Atrial Fibrillation in Patients with Essential Hypertension: Aldosterone

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ABSTRACT

Atrial fibrillation (AF) is a common arrhythmia associated with increased mortality and morbidity.

Keywords: Atria; Fibrillation; Arrhythmia; Mortality

INTRODUCTION

Several clinical studies have proved that angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) had a beneficial effect on either new-onset AF or recurrent AF with structural heart disease, including heart failure with reduced ejection fraction [1,2],hypertension with left ventricular hypertrophy [3,4]. postoperative AF and post-myocardial infarction AF [5,6]. Of interest, GISSI-AF trial [7],J-RHYTHM II trial and ANTIPAF trial showed noeffect of RAAS antagonism therapy on reducing the incidence of recurrent AF in hypertensive patients without concomitant structural heart disease. Murray KT's analysisprovided the evidence that ACEIs or ARBs were beneficial only in some AF subgroups with congestive heart failure or left ventricular dysfunction, which underscored the role of angiotensin II inhibition in AF patients [8-10]. These results raise substantial questions about whether previous studies suggesting lower new-onset AF or recurrent AF rates with ACEIs or ARBs are generalizable. We should highlight the need for additional prospective studies defining more fully the role of ACEIs or ARBs therapy in treating AF patients without structural heart disease. Hypertension has been shown to be the most prevalent and independent risk factor for AF. Hypertensive patients have up to a 42% increased risk of developing AFand up to 70% of patients with AF have a history of hypertension [11-14] ACEIs or ARBs are major drug classes for the treatment of hypertension. Some clinical trials did not support the opinion that the use of ARBs or ACEIs can reduce the incidence of new-onset AF or recurrent AF in hypertensive patients without concomitant structural heart disease. The activation of RAAS is one of many mechanisms of hypertension and AF. We speculate that if RAAS is activated in hypertensive patients, pharmacological interruption of this signaling pathway may play an important role in an antiarrhythmic effect in hypertensive patients even though these hypertensive patients have not structural heart disease. That is, different pathophysiological types of AF should be differentiated in patients using clinical characteristics supplemented by blood biomarkers, potentially opening the way towards a more personalized therapy of AF. Some studies showed aldosterone level was decreased significantly within 24 hours in AF patients who maintained sinus rhythm after cardioversion [15-17]. Patients with primary aldosteronism had a 12-fold higher risk of developing AF when compared to blood pressure-matched controls [18]. suggesting that aldosterone plays an important role in AF development. Aldosterone is the end product of RAAS. The activity of RAAS stimulates secretion of aldosterone. We hypothesize that plasma aldosterone level serve as a biomarker for the activation of RAAS in hypertensive patients, which guides RAAS antagonism treatment to prevent new-onset AF and recurrent AF in hypertensive patients without concomitant structural heart disease.

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Received: May 26, 2020; Accepted: June10, 2020; Published: June17, 2020

Citation: Xu J, Wang R, Fu M, Kuang D, Shen l, Wei Y, et al. (2020). The Biomark of Atrial Fibrillation in Patients with Essential Hypertension: Aldosterone. J ClinExpCardiolog11:670. DOI: 10.35248/2155-9800.20.11.670.

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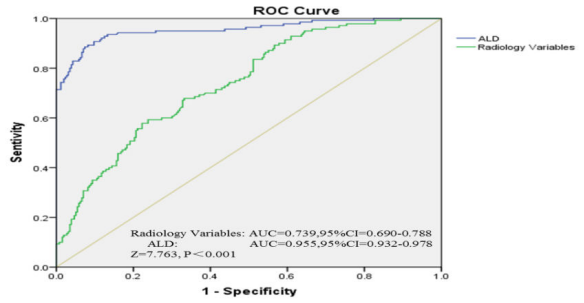

Figure 1: ROC analysis of plasma aldosterone for predicting the occurrence of AF in hypertensive patients.

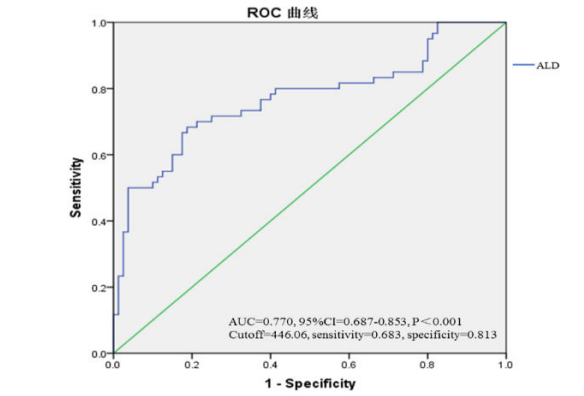

Figure 2: ROC analysis of plasma aldosterone for predicting the recurrence of AF in hypertensive patients after catheter ablation.

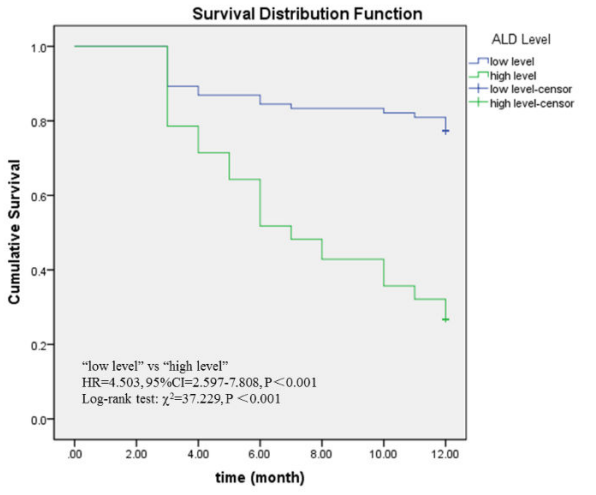

Figure 3: Kaplan-Meier survival curves illustrating recurrence-free rates of AF in hypertensive patients with high plasma aldosterone level and low plasma aldosterone level followed up for 12 months after catheter ablation.

Green line-hypertensive patients with high plasma aldosterone level (ALD ≥ 446.06)

Blue line-hypertensive patients with low plasma aldosterone level (ALD<446.06).

Method

Our research consisted of two stages: 1) the case-control study elucidated that plasma aldosterone level acted as a diagnostic biomarker of AF in hypertensive patients; 2) the cohort study depicted that plasma aldosterone level was related to recurrence of AF after catheter ablation. We evaluated 396 hypertensive patients, 140 with AF and 256 with sinus rhythm.

RESULTS

Nonparametric Mann-Whitney U test showed that there was significant difference between hypertensive patients without concomitant structural heart disease with AF and with sinus rhythm in plasma aldosterone level (411.20 (IQR+258.28) pg/ml vs. 83.11 (IQR+67.68) pg/ml, p<0.001). (Table 1). Multivariable regression analysis indicated that plasma aldosterone level showed significant predictive value for AF in hypertensive patients (OR+1.029, 95%CI1.022-1.036p<0.001) after adjustment for age, LAD, LVEDD and LVEF (Table 2). ROC curves of plasma aldosterone to predict AF events in hypertensive patients without concomitant structural heart disease showed that the sensitivity and specificity for AF diagnosis were respectively 86.4% and 93.4%, when cut-off value of plasma aldosterone was at 173.9 pg/ml in hypertensive patients without concomitant structural heart disease. AUC was 0.955 in differentiating AF patients from non-AF patients in hypertensive patients without concomitant structural heart disease (Figure 1). 140 AF patients were followed up for 12 months after catheter ablation. In multivariable regression analysis, plasma aldosterone showed significant predictors for recurrence in AF patients (OR+1.006, 95% CI+1.004-1.009, p<0.001). When the cut-off value of plasma aldosterone was 446.06 pg/ml, the sensitivity and specificity for predicting recurrence of AF after catheter ablation were 68.3% and 81.3%, respectively (AUC+0.770, 95% CI+0.687-0.853, p<0.001) (Figure 2). 12-month recurrence-free rates were significantly higher in AF patients with low plasma aldosterone level (<446.06 pg/ml) compared to those with high plasma aldosterone level (>446.06 pg/ml) (77.4% vs. 26.8%, p<0.001). Cox proportional hazards regression model was used to test for potential confounding factors that could affect prognostic value of recurrence of AF after catheter ablation in hypertensive patients. Plasma aldosterone level remained independently associated with 12 months recurrence rate (HR=4.50, 95% CI +2.60-7.81, p<0.001) after adjusting for age, gender, BP, LAD, LVESD, LVEDD and LVEF, AF course, the type of AF and the method of catheter ablation (Table 3 and Figure 3).

Table 1: Baseline clinical characteristics of hypertensive patients with AF and sinus rhythm.

		SR (n=256)	AF (n=140)	p
Ageyears), (IQR)	M	63.00 (13.75)	60.00 (11.00)	0.015*

Gender M/F	148/108	85/55	0.575
SBP mmHg	136.23 18.86	133.4715.36	0.337
DBP mmHg	81.24	79.7813.96	0.483
LAD mm, M (IQR)	37.00 (6.00)	41.00 (8.00)	0.001*
LVESD mm, M (IQR)	31.00 (5.00)	32.00 (4.00)	0.094
LVEDD mm, M (IQR)	48.00 (6.00)	49.00 (5.00)	0.001*
LVEF%	66.00 (7.00)	64.84 (8.00)	0.001*
ALD pg/ml, M (IQR)	83.11 (67.68)	411.20 (258.28)	0.001*
ALD Level, n (%)			0.001*
173.9	238 (93.0)	19 (13.6)	
173.9	18 (7.0)	121 (86.4)	

SR: Sinus Rhythm; AF: Atrial Fibrillation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; LAD: Left Atrial Diameter; LVESD: Left Ventricular End Systolic Diameter; LVEDD: Left Ventricularend Diastolic Diameter; LVEF: Left Ventricular Ejection Fraction; ALD: Plasma Aldosterone Level.

Table 2: Multivariable regression for predicting atrial fibrillation in hypertensive patients.

Variable	OR	95%CI	p value
Age	0.949	0.906-0.995	0.03
LAD	1.181	1.093-1.277	0.001
LVEF	0.868	0.800-0.943	0.001
ALD	1.029	1.022-1.036	0.001

LAD: Left Atrial Diameter; LVEF: Left Ventricular Ejection Fraction; ALD: Aldosterone;OR :Odds Ratio; CI: Confidence Interval.

AF: Atrial Fibrillation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; LAD: Left Atrial Diameter; LVESD: Left Ventricular End Systolic Diameter; LVEDD; Left Ventricularend Diastolic Diameter; LVEF: Left Ventricular Ejection Fraction; CPVA: Circumferential Pulmonary Vein Ablation; ALD : Aldosterone.

Table 3: Baseline clinical characteristics of hypertensive patients with non-recurrence AF and recurrence AF.

	AF sample (n+140)		p
	Non-recurrence AF	Recurrence AF	
	n+80	n+60	
Gender, n (%)			0.842
Man	48 (60.0)	37 (61.7)	
Female	32 (40.0)	23 (38.3)	
Disease Course, n (%)			0.998
≤1year	32 (40.0)	24 (40.0)	
1~5year	23 (28.7)	17 (28.3)	
5year	25 (31.3)	19 (31.7)	
Age, M (IQR)	61.00 (9.75)	59.50 (13.75)	0.452
AF Type, n (%)			0.877
Paroxysmal AF, n (%)	53 (66.3)	39 (65.0)	
Persistent AF, n (%)	27 (33.7)	21 (35.0)	
SBP mmHg	134.95 18.65	135.36 15.32	0.857
DBP mmHg	81.11 10.50	80.82 12.38	0.85
LAD, ⅈx S	41.37 6.75	41.31 4.88	0.948
LVESD, M (IQR)	32.00 (5.00)	32.00 (4.00)	0.991
LVEDD, M (IQR)	49.00 (5.00)	49.00 (5.00)	0.796
LVEF, M (IQR)	64.00 (9.00)	65.00 (7.25)	0.514
CPVA, n (%)	79 (98.8)	58 (96.7)	0.8
Linear ablation, n (%)	50 (62.5)	41 (68.3)	0.474
CFAE ablation, n (%)	18 (22.5)	7 (11.7)	0.098
Cardioversion, n (%)	2 (2.5)	7 (11.7)	0.066
Intraoperative transfer, n (%)	10 (12.5)	12 (20.0)	0.228
Cardioversion during ablation, n (%)	18 (22.5)	12 (20.0)	0.721
ALD, M (IQR)	345.76 (220.97)	495.75 (181.80)	0.001*

CONCLUSION

The results of our study showed that hypertensive patients without concomitant structural heart disease with higher plasma aldosterone were more prone to the occurrence of AF and the recurrence of AF after catheter ablation, which indicated that plasma aldosterone level could potentially be a biomarkerof upstream treatments using RAAS blockers in hypertensive patients without concomitant structural heart disease.

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