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Association between big endothelin-1 and $CHADS_2$/CHA_2DS_2-VASc scores in non-valvular atrial fibrillation

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Abstract

Background Endothelial function, as measured by big endothelin-1 (ET-1), has been demonstrated to be useful in predicting adverse long-term events in patients with cardiovascular disease. Nevertheless, there are little data about the association between big ET-1 and thromboembolism risk in atrial fibrillation (AF). We aimed to investigate the relationship between big ET-1 and $CHADS_2$/CHA_2DS_2-VASc scores used for evaluating thromboembolic risk in patients with non-valvular AF. **Methods** The study population consisted of 238 consecutive AF patients (67.6% with paroxysmal AF and 32.4% with persistent AF). The patients were divided into two groups (high- or low-intermediate risk group) based on $CHADS_2$ and CHA_2DS_2-VASc scores (score ≥ 2 or < 2, respectively). Clinical, laboratory, and echocardiographic parameters were evaluated, and the $CHADS_2$/CHA_2DS_2-VASc scores were compared between groups. The association between big ET-1 levels and $CHADS_2$/CHA_2DS_2-VASc score was assessed. Multivariate logistic regression analysis was performed to identify independent predictors of $CHADS_2$/CHA_2DS_2-VASc scores. **Results** The high $CHADS_2$/CHA_2DS_2-VASc score group had older age, higher big ET-1 levels, and enlarged left atrial diameter than the low $CHADS_2$/CHA_2DS_2-VASc score group ($P < 0.05$). Multiple logistic regression analysis revealed that big ET-1 level was an independent determinant of high $CHADS_2$/CHA_2DS_2-VASc scores [odds ratio (OR) = 2.545 and OR = 3.816; both $P < 0.05$]. **Conclusions** Our study indicates that in non-valvular AF, big ET-1 was significantly correlated with $CHADS_2$/CHA_2DS_2-VASc scores and an independent predictor of high $CHADS_2$/CHA_2DS_2-VASc scores. Big ET-1 may serve as a useful marker for risk stratification in this setting.

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Keywords: Atrial fibrillation; Cardiac risk factors; Prevention; Stroke

1 Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is associated with thromboembolism, stroke, and death.[1–3] The $CHADS_2$ score has been the most commonly used for stroke risk stratification in patients with AF.[4] More recently, the CHA_2DS_2-VASc score has been recommended for thromboembolism risk stratification in patients with AF for better identification of low risk subjects.[1,5]

Endothelin-1 (ET-1) is a 21-amionocaid peptide present in mammalian endothelial cells, including humans.[6] ET-1 is produced by the vascular endothelium and atrial myocardial muscles[7] and participates in the pathophysiology of AF via the intracellular calcium overload of the atrial myocytes and atrial remodeling.[8,9] Big ET-1 is a 39-residue precursor of ET-1, has a long half-life and slower tissue clearance than ET-1, and is therefore deemed to be a better indicator of the ET-1 system.[10] Recently, several studies have shown that increased ET-1 levels predict adverse events in patients with stable coronary disease, heart failure and stroke.[11-14] Information about the association between thromboembolic risk and endothelial system in patients with AF is limited. This study aimed to explore the association between $CHADS_2$ and CHA_2DS_2-VASc scores and big ET-1 levels in patients with non-valvular AF.

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2 Methods

2.1 Study populations

Between June 2016 and December 2017, 238 consecutive patients with non-valvular AF were enrolled in the present study. AF was defined as an absence of P wave and irregular R-R interval in a 12-lead electrocardiogram (ECG) or 24-h Holter recording.[1] The definition of AF type was based on the ESC guidelines for the management of AF.[1]

Individuals with significant valvular disease, heart failure, congenital heart disease, cardiomyopathy, hepatic or renal dysfunction, acute or chronic pulmonary embolism, chronic obstructive pulmonary disease, thyroid dysfunction, or history of thalassemia were excluded. In addition, none of the participants had any history of inflammatory or infectious disease or recent (within the last four weeks) trauma or surgery; none were under treatment with nonsteroidal anti-inflammatory, statins, or corticosteroid drugs.

All patients provided written informed consent, and this study was approved by the Ethics Committee of our hospital (Number: 2015-ZX51; Date：December 16th, 2015). All study procedures were conducted according to the principles expressed in the Declaration of Helsinki.

2.2 Clinical characteristics

To stratify subjects, comorbid conditions and other risk factors such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, history of stroke or transient ischemic attack, vascular disease, age 65–74, and sex were taken into account according to $CHADS_2$/CHA_2DS_2-VASc scores to assess the long-term thromboembolic risk associated with AF. In both $CHADS_2$ and CHA_2DS_2-VASc scores, a score of 0 was categorized as low risk, 1 as intermediate risk, and ≥ 2 as high risk.[1,4,5] In the present study, we divided patients into high- and low-intermediate risk groups.

Patients were interviewed, and records were reviewed to determine medical history, medications, echocardiography findings, and plasma big ET-1 levels. All patients with AF had at least one documented ECG or 24-h Holter. Serum creatinine, sodium, and potassium levels were measured. White blood cell (WBC) count and hemoglobin levels were also assessed.

Transthoracic echocardiography was performed in all patients to exclude the presence of valvular heart disease. The left atrial diameter (LAD), left ventricular end diastolic diameter, left ventricular posterior wall thickness, and interventricular septal thickness were determined. The left ventricular ejection fraction was evaluated by the Simpson method.

2.3 Big ET-1 measurement

For the big ET-1 measurement, 5 mL of whole blood was collected into tubes containing potassium EDTA (1 mg/mL blood) as an anticoagulant to produce plasma. Specimens were centrifuged at 3000 r/min within 2 h of collection. All testing and device operating procedures were in accordance with manufacturer's recommendations. The serum specimen was used for big ET-1 measurement using commercially available assay kits (BIOMEDICA Medizinprodukte GmbH & Co KG, Wein, Austria). The measurement range of this test was 0–13.5 fmol/mL. Inter- and intra-assay coefficients of variation for big ET-1 were < 6% and < 3%, respectively.

2.4 Statistical analysis

Continuous variables with normal distribution are presented as means ± SD. The Kolmogorov-Smirnov test was used to determine normality of data distribution and variables with non-normally distributed scores are presented as median plus interquartile range. Due to skewed distribution, big ET-1 values were transformed logarithmically and the normal distribution of the transformed scores of the variables was confirmed before further analyses. Categorical variables are presented with absolute values and relative frequencies and continuous variables were compared using the 2-sample *t*-test for independent samples when dealing with approximately normally distributed variables and the Wilcoxon rank-sum test otherwise. Categorical variables were compared using the Pearson's χ^2 test.

Correlations between two continuous variables were evaluated with Pearson's or Spearman's test. Multivariate logistic regression analysis was performed to identify independent predictors of high $CHADS_2$/CHA_2DS_2-VASc scores. Receiver-operating characteristics (ROC) analyses were used to detect the cutoff value of big ET-1 levels which predicted $CHADS_2$/CHA_2DS_2-VASc scores. The best cutoff value of big ET-1 was the point on the curve with the largest difference between sensitivity and (1-specificity) in each horizontal ordinate point. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software version 19.0 (SPSS, Inc., Chicago, Illinois, USA).

3 Results

This study included 238 consecutive patients (mean age: 58 ± 10 years; 69.7% male) with non-valvular AF, 67.6% of whom had paroxysmal AF. Among them, 34.0% of patients according to the $CHADS_2$ score and 55.9% according to the

CHA_2DS_2-VASc score were considered to have high thromboembolic risk (≥ 2).

As demonstrated in Table 1, high $CHADS_2$/CHA_2DS_2-VASc score groups had older age, higher prevalence of hypertension, diabetes, history of congestive heart failure/ left ventricular dysfunction, and stroke and more use of aspirin and angiotensin converting enzyme inhibitors/angiotensin receptor blocker compared to the low $CHADS_2$/ CHA_2DS_2-VASc score groups ($P < 0.05$). Furthermore, high $CHADS_2$/CHA_2DS_2-VASc score groups had higher LAD and big ET-1 levels compared to the low-intermediate risk group.

Regression analysis showed that Ln(big ET-1) levels correlated with $CHADS_2$ ($r = 0.208$, $P = 0.001$) and CHA_2DS_2-VASc ($r = 0.199$, $P = 0.001$) scores in all subjects. Nevertheless, no relationship between Ln(big ET-1) and WBC count ($r = 0.018$, $P = 0.787$), or serum creatinine levels ($r = 0.083$, $P = 0.202$) was detected.

Table 1. Characteristics of the study populations with $CHADS_2$ score/CHA_2DS_2-VASc score.

	CHA_2DS_2 Score			CHA_2DS_2-VASc Score		
	High risk (*n* = 81)	**Low-intermediate risk (*n* = 157)**	***P* value**	**High risk (*n* = 133)**	**Low-intermediate risk (*n* = 105)**	***P* value**
Age, yrs	60 ± 11	57 ± 10	0.035	61 ± 10	54 ± 10	< 0.001
Male	54 (66.7%)	112 (71.3%)	0.457	71 (53.4%)	95 (90.5%)	< 0.001
Persitent AF	27 (33.3%)	50 (31.8%)	0.816	41 (30.8%)	36 (34.3%)	0.109
BMI, kg/m^2	24.5 ± 3.0	24.9 ± 2.1	0.325	24.5 ± 2.7	25.0 ± 2.1	0.165
Hypertension	64 (79.0%)	69 (43.9%)	< 0.001	95 (71.4%)	38 (36.2%)	< 0.001
Diabetes mellitus	58 (71.6%)	13 (8.3%)	< 0.001	65 (48.9%)	6 (5.7%)	< 0.001
Previous stroke	30 (37.0%)	0	< 0.001	30 (22.6%)	0	< 0.001
History of CHF/LV dysfunction	12 (14.8%)	3 (1.9%)	0.003	14 (10.5%)	1 (1.0%)	0.003
Previous history of PAD/MI	50 (61.7%)	6 (3.8%)	< 0.001	51 (38.3%)	5 (4.8%)	< 0.001
Smoking	24 (29.6%)	58 (36.9%)	0.261	43 (32.3%)	39 (37.1%)	0.438
WBC, $\times 10^9$/L	6.3 ± 1.9	6.0 ± 1.7	0.301	6.2 ± 1.9	6.1 ± 1.6	0.301
Na^+, mmol/L	140.8 ± 2.7	141.3 ± 2.4	0.093	141.1 ± 2.6	141.2 ± 2.4	0.093
K^+, mmol/L	4.0 ± 0.4	4.0 ± 0.3	0.864	4.0 ± 0.3	4.0 ± 0.3	0.864
Hb, g/L	143 ± 17	144 ± 7	0.685	141 ± 16	148 ± 17	0.002
Serum creatinine, μmol/L	81.9 ± 16.9	79.5 ± 17.0	0.300	81.9 ± 16.9	79.5 ± 17.0	0.04
Blood urea nitrogen, mmol/L	5.5 ± 1.7	5.4 ± 1.4	0.592	5.3 ± 1.5	5.5 ± 1.4	0.289
Echocardiogram						
LAD, mm	42 ± 7	40 ± 5	0.005	41 ± 7	40 ± 5	0.464
LVEDD, mm	51 ± 4	49 ± 4	0.776	47 ± 5	48 ± 5	0.030
LVEF	61% ± 6%	62% ± 5%	0.825	61% ± 5%	62% ± 5%	0.706
LVPWT, mm	9.5 ± 1.4	9.4 ± 1.2	0.325	9.3 ± 1.2	9.6 ± 1.4	0.064
IVST, mm	9.8 ± 1.9	9.6 ± 1.6	0.291	9.7 ± 1.7	9.6 ± 1.6	0.814
Previous medications						
Warfarin	7 (8.1%)	11 (7.0%)	0.651	11 (8.3%)	7 (6.7%)	0.642
Aspirin	57 (70.3%)	63 (40.1%)	< 0.001	75 (56.4%)	45 (42.9%)	0.050
ACEI/ARB	53 (65.4%)	55 (35.0%)	< 0.001	70 (52.6%)	38 (36.2%)	0.011
β-blocker	31 (38.3%)	43 (27.4%)	0.086	47 (35.3%)	27 (25.7%)	0.111
CCB	15 (18.5%)	20 (12.7%)	0.233	21 (15.8%)	14 (13.3%)	0.595
Statins	31 (38.8%)	49 (31.2%)	0.246	45 (34.1%)	35 (33.3%)	0.902
Big ET-1 level, fmol/mL	0.31 (0.27–0.37)	0.26 (0.20–0.36)	0.001	0.30 (0.25–0.38)	0.26 (0.20–0.35)	< 0.001
Ln (big ET-1), fmol/mL	−1.13 ± 0.24	−1.29 ± 0.44	0.002	−1.17 ± 0.34	−1.34 ± 0.43	0.001

Data are presented as mean ± SD or *n* (%). ACEI: angiotensin converting enzyme inhibitors; AF: atrial fibrillation; ARB: angiotensin receptor blocker; BMI: body mass index; CCB: calcium channel blocker; CHF: congestive heart failure; ET-1: big endothelin-1; Hb: hemoglobin; IVST: interventricular septal thickness; K: potassium; LAD: left atrial diameter; LV: left ventricle; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVPWT: left ventricular posterior wall thickness; MI: myocardial infarction; Na: sodium; PAD: peripheral artery disease; WBC: white blood cell.

Multivariate analysis showed that Ln(big ET-1) and LAD levels were associated with high $CHADS_2$ score (OR = 2.545 and 1.058; $P < 0.05$, respectively), while age, gender, and Ln (big ET-1) were independent predictors of CHA_2DS_2-VASc score (OR = 1.075, 13.080 and 3.816; $P < 0.05$, respectively, Tables 2 & 3).

ROC curve analysis showed that the area under the curve (AUC) for Ln(big ET-1) was 0.640 (95% CI: 0.572–0.708, $P < 0.001$) to predict a high $CHADS_2$ score. The best cut-off value of Ln (big ET-1) to predict a high $CHADS_2$ score was –1.37 (big ET-1 level of 0.25 fmol/mL) with a sensitivity of 85.2% and a specificity of 52.2% (Figure 1A). ROC curve analysis demonstrated that the AUC for big ET-1 was 0.623 (95% CI: 0.549–0.697, $P < 0.001$) to predict a high CHA_2DS_2-VASc score. The best cut-off value of Ln (big ET-1) to predict high CHA_2DS_2-VASc score was -1.46 (big ET-1 level of 0.23 fmol/mL) with a sensitivity of 84.2% and a specificity of 55.2% (Figure 1B).

Table 2. Multivariate logistic regression results for detecting independent factors of high $CHADS_2$ score in AF patients.

Variables	Univariate OR, 95% CI	Univariate *P* value	Multivariate OR, 95% CI	Multivariate *P* value
Ln (big ET-1), fmol/mL	3.029 (1.471–6.238)	0.003	2.545 (1.155–5.610)	0.021
Age, yrs	1.030 (1.002–1.058)	0.037	1.024 (0.994–1.055)	0.118
Gender	1.244 (0.699–2.216)	0.458	1.528 (0.643–3.361)	0.337
Serum creatinine, μmol/L	1.009 (0.992–1.025)	0.300	1.005 (0.986–1.024)	0.589
LAD, mm	1.067 (1.018–1.118)	0.007	1.058 (1.000–1.114)	0.049
LVEDD, mm	1.008 (0.995–1.064)	0.775	1.000 (0.935–1.069)	0.989
LVEF, %	0.994 (0.943–1.048)	0.050	1.017 (0.956–1.082)	0.590

AF: atrial fibrillation; ET-1: endothelin-1; LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; OR: odds ratio.

Table 3. Multivariate logistic regression results for detecting independent factors of high CHA_2DS_2-VASc score in AF patients.

Variables	Univariate OR, 95% CI	Univariate *P* value	Multivariate OR, 95% CI	Multivariate *P* value
Ln (big ET-1), fmol/mL	3.028 (1.577–6.527)	0.001	3.816 (1.544–9.428)	0.004
Age, yrs	1.075 (1.044–1.107)	< 0.001	1.075 (1.039–1.113)	< 0.001
Gender	8.296 (3.977–17.308)	< 0.001	13.080 (4.533–37.737)	< 0.001
Serum creatinine, μmol/L	0.984 (0.968–0.999)	0.043	1.001 (0.978–1.024)	0.965
LAD, mm	1.016 (0.974–1.061)	0.462	1.015 (0.958–1.075)	0.620
LVEDD, mm	0.943 (0.894–0.995)	0.033	1.004 (0.930–1.084)	0.916
LVEF, %	0.990 (0.940–1.042)	0.704	0.993 (0.932–1.059)	0.842

AF: atrial fibrillation; ET-1: endothelin-1; LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction.

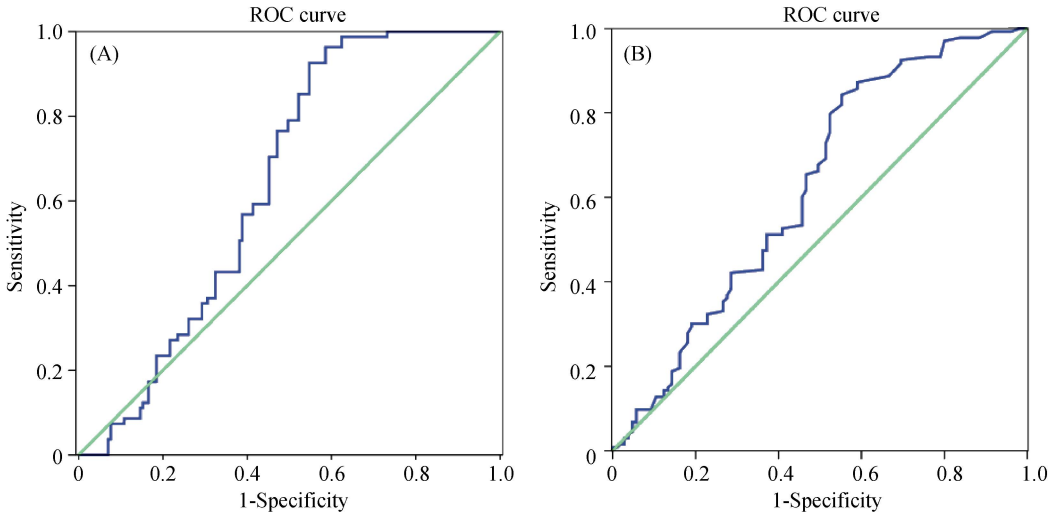

Figure 1. ROC curves for Ln (big endotheline-1) values in prediction of high $CHADS_2$ (Panel A) and CHA_2DS_2-VASc (Panel B) scores. ROC: receiver operating characteristics.

4 Discussion

4.1 Major findings

This study demonstrated that: (1) the high thromboembolic risk group as evaluated by the $CHADS_2$/CHA_2DS_2-VASc scores had higher big ET-1 levels compared to the low-intermediate risk group; (2) baseline big ET-1 levels were independently associated with $CHADS_2$/CHA_2DS_2-VASc scores; and (3) big ET-1 was an independent predictor of both high $CHADS_2$ and CHA_2DS_2-VASc scores.

4.2 Thromboembolic risk in AF and $CHADS_2$ and CHA_2DS_2-VASc score

Several risk factors have been used to evaluate the thromboembolic risk in AF, including clinical, biochemical, and echocardiographic indices.[15–17] The $CHADS_2$ score is the most commonly recommended scoring system for the assessing the thromboembolic risk.[4] The more recent CHA_2DS_2-VASc score contains more risk factors and better stratifies low-risk patients.[1,5] In fact, the CHA_2DS_2-VASc score provides further information for evaluation of stroke risk in patients with AF and a $CHADS_2$ score of 0 or 1. Such a score is used to determine whether or not treatment is required with anticoagulation or antiplatelet therapy.

4.3 Big ET-1 and $CHADS_2$ and CHA_2DS_2-VASc score in AF

Elevated ET-1 levels are associated with adverse long-term events in patients with various diseases, including stable coronary disease, heart failure, and acute myocardial infarction.[11,12,18] Furthermore, ET-1 levels are elevated in patients with a history of stroke compared to those in controls.[13,14] ET-1 is a good predictor of cerebrovascular events in patients with a history of stroke.[19] This effect may be a result of the potent and long-acting vasoconstrictor effect of ET-1. Until now, several studies have explored the potential association between ET-1 and AF.[20–25] In patients with AF, the plasma ET-1 concentration is elevated independently of the underlying structural heart disease.[20] Furthermore, a decrease in the expression of endothelin A-receptors can predict new-onset AF post-bypass surgery.[21] ET-1 shortens the atrial action potential duration and effective refractory period by inhibiting the L-type calcium current.[22] Also, ET-1 may modulate the rennin-angiotensin-aldosterone system, increase the myocardial inotropic function, and stimulate cardiac hypertrophy.[23] ET-1 can stimulate the production of proinflammatory cytokines such as interleukin-6, leading to an inflammatory state.[24] Our previous study has shown that in paroxysmal AF patients, serum big ET-1 levels are elevated and are associated with inflammatory activation.[25] All of these effects derived from ET-1 facilitate electrical or structural remodeling in AF and cause AF chronicity.

With regard to the thromboembolic risk, to our knowledge, there are very few studies evaluating the association between ET-1 levels and stroke risk in patients with non-valvular AF. The present study demonstrated that increased big ET-1 levels are associated with increased $CHADS_2$ and CHA_2DS_2-VASc scores in patients with non-valvular AF. Furthermore, multivariate analyses showed that baseline big ET-1 levels were independently related with $CHADS_2$/CHA_2DS_2-VASc scores.

The possible underlying mechanisms for the relationship between big ET-1 and thromboembolic risk scores could be as follows. First, the endothelin system has been implicated in facilitating electrical or structural remodeling in AF and causing AF chronicity; big ET-1 may be a valuable endothelial marker in this sense. Second, several thromboembolic risk factors that are components of the $CHADS_2$/CHA_2DS_2-VASc scores such as heart failure, hypertension, diabetes, and stroke have been associated with increased ET-1 concentrations.[13,14,26–29]

4.4 Study limitations

The present study has several limitations. First, the sample size of this study was relatively small. Second, big ET-1 might be a marker associated with aging and may not be specific for AF but just a disease-related marker in the general population. Third, no follow-up data regarding thromboembolic events are available. Further large sample prospective studies are required to explore the actual role of big ET-1 in predicting the thromboembolic events in patients with non-valvular AF.

4.5 Conclusions

In non-valvular AF patients, big ET-1 levels are associated with the thromboembolic risk determined by the well-established risk measures such as $CHADS_2$ and CHA_2DS_2-VASc scores. Considering that big ET-1 is a simple and easily available laboratory parameter, it may serve as a useful marker for risk stratification in this setting. Its relative value, adding to existing scores, in predicting future thromboembolic events requires further investigation in prospective studies.

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