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Plasma big endothelin-1 is an effective predictor for ventricular arrythmias and end-stage events in primary prevention implantable cardioverter-defibrillator indication patients

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Abstract

Objective To investigate whether plasma big endothelin-1 (ET-1) predicts ventricular arrythmias (VAs) and end-stage events in primary prevention implantable cardioverter-defibrillator (ICD) indication patigents. **Methods** In total, 207 patients fulfilling the inclusion criteria from Fuwai Hospital between January 2013 and December 2015 were retrospectively analyzed. The cohort was divided into three groups according to baseline plasma big ET-1 tertiles: tertile 1 (< 0.38 pmol/L, n = 68), tertile 2 (0.38–0.7 pmol/L, n = 69), and tertile 3 (> 0.7 pmol/L, n = 70). The primary endpoints were VAs. The secondary endpoints were end-stage events comprising all-cause mortality and heart transplantation. **Results** During a mean follow-up period of 25.6 ± 13.9 months, 38 (18.4%) VAs and 78 (37.7%) end-stage events occurred. Big ET-1 was positively correlated with NYHA class (r = 0.165, P = 0.018), serum creatinine concentration (Scr; r = 0.147, P = 0.034), high-sensitivity C-reactive protein (hs-CRP; r = 0.217, P = 0.002), Lg NT-pro BNP (r = 0.463, P < 0.001), left ventricular end diastolic diameter (LVEDD; r = 0.234, P = 0.039) and negatively correlated with left ventricular ejection fraction (LVEF; r = −0.181, P = 0.032). Kaplan-Meier analysis showed that elevated big ET-1 was associated with increased risk of VAs and end-stage events (P < 0.05). In multivariate Cox regression models, big ET-1 was an independent risk factor for VAs (hazard ratio (HR) = 3.477, 95% confidence interval (CI): 1.352–8.940, P = 0.010, tertile 2 *vs.* tertile 1; HR = 4.112, 95% CI: 1.604–10.540, P = 0.003, tertile 3 *vs.* tertile 1) and end-stage events (HR = 2.804, 95% CI: 1.354–5.806, P = 0.005, tertile 2 *vs.* tertile 1; HR = 4.652, 95% CI: 2.288–9.459, P < 0.001, tertile 3 *vs.* tertile 1). **Conclusions** In primary prevention ICD indication patients, plasma big ET-1 levels can predict VAs and end-stage events and may facilitate ICD-implantation risk stratification.

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Keywords: Big endothelin-1; End-stage events; Implantable cardioverter-defibrillator implantation; Primary prevention; Ventricular arrythmias

1 Introduction

Sudden cardiac death (SCD) is a serious public health problem worldwide, accounting for approximately 50% of all cardiovascular deaths.[1] An implantable cardioverter-defibrillator (ICD) can effectively terminate malignant tachyarrhythmia, prevent SCD and reduce all-cause mortality.[2–4] However, identification of primary prevention patients at high risk of SCD remains challenging.

According to current guidelines, left ventricular ejection fraction (LVEF) ≤ 35% is still recommended as the main criterion for implantation of an ICD for primary prevention of SCD.[1,5] However, recent studies have demonstrated that the application of LVEF alone lacks of both sensitivity and specificity for prediction of SCD.[6–8] Cardiac magnetic resonance imaging and electrical examination have also been explored for prediction of SCD,[9,10] but due to complexity of the operation, no factor has been widely used in clinical practice. The DANISH study revealed that the benefit of an ICD may be limited in patients with non-SCD risk and an evaluation in addition to LVEF might be needed before ICD implantation. In the era of optimal treatment of heart failure (HF) with drugs and devices, improving the

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efficiency and cost-effectiveness of ICD implantation for primary prevention of SCD is of great importance.[11]

The endothelial system is an important factor that regulates cardiovascular functions and contributes to neurohormonal activation, hemodynamic deterioration, and cardiovascular remodeling, and endothelin-1 (ET-1) has the strongest effect on this system. Big ET-1 is the precursor of ET-1 and has a longer half-life, which makes it a more suitable marker for the endothelial system. Previous studies have confirmed that big ET-1 is related to the pathophysiological progression of HF.[12,13] However, whether big ET-1 is related to SCD or ventricular arrythmias (VAs) is still unclear. The purpose of the present study was to investigate whether plasma big ET-1 could be a predictive factor for VAs and end-stage events in patients with indications for primary prevention ICD implantation.

2 Methods

2.1 Population selection

The present study retrospectively analysed the data of patients with symptomatic HF and left ventricular systolic dysfunction (LVEF ≤ 35%) at Fuwai Hospital (National Center of Cardiovascular Diseases, Beijing, China) between January 2013 and December 2015. Additional inclusion criteria were as follows: (1) age greater than 18 years; (2) available baseline big ET-1 results; and (3) indication for primary prevention ICD implantation. The exclusion criteria were as follows: (1) indication for the secondary prevention of SCD; (2) severe valvular disease was the main cause of HF; (3) a scheduled heart transplant within one year; and (4) participation in another clinical therapeutic trial that required the consent of the patient at the same time. In total, 218 patients qualified according to the inclusion criteria. However, eight candidates were excluded due to indications for the secondary prevention of SCD, and three patients were lost during follow-up. The ethics committee of the Fuwai Hospital approved the present study (No. 2012–427), and all patients signed informed consent forms before enrollment.

2.2 Data collection

The baseline data for all admitted patients in this study were obtained from their inpatient medical records during hospitalization. Demographic and clinical characteristics, including age, sex, body mass index (BMI), New York Heart Association (NYHA) class, etiology (ischemic cardiomyopathy or nonischemic cardiomyopathy), comorbidities (hypertension, diabetes, atrial fibrillation, and stroke), baseline laboratory data [routine blood examinations, biochemistry, and N-terminal pro brain natriuretic peptide (NT-pro BNP)], and medications (renin-angiotensin system blockers, β-blockers, spironolactone, loop diuretics, amiodarone, and digoxin) were reviewed and analyzed by two separate physicians who were blinded to the other results. Biochemistry assessments included alanine aminotransferase (ALT), high-sensitivity C-reactive protein (hs- CRP), and serum creatinine concentration (Scr). Echocardiography parameters, LVEF and left ventricular end-diastolic diameter (LVEDD) were evaluated by two physicians with experience in echocardiography. The LVEF was calculated using the modified Simpson's biplane rule.

2.3 Big ET-1 and patient groups

Venous blood samples were collected from all patients after 12 h of fasting on the next morning of admission. All blood samples were tested in the medical examination center of Fuwai Hospital according to the standard procedure. The plasma big ET-1 level was measured with a highly sensitive and specific commercial sandwich enzyme immunoassay (BI-20082H, Biomedica, Wien, Austria). The normal range was less than 0.25 pmol/L, and the detection sensitivity was 0.02 pmol/L. Then, the patients were divided into three tertiles according to the baseline level of plasma big ET-1: tertile 1 (< 0.38 pmol/L, n = 68), tertile 2 (0.38–0.7 pmol/L, n = 69), and tertile 3 (> 0.7 pmol/L, n = 70).

2.4 Follow-up and endpoints

All patients were followed up regularly through outpatient or telephone calls at 3, 6, 12, 24 and 36 months. The primary endpoint events were VAs including SCD, appropriate ICD therapy and documented sustained ventricular tachycardia or nonfatal ventricular fibrillation. SCD was defined as sudden and unpredictable death following cardiovascular symptoms within 1 h. ICD appropriate therapy refers to appropriate anti-tachycardia pacing (ATP) and shock for sustained ventricular tachycardia.[14] The secondary endpoint events were a composite of end-stage events consisting of all-cause mortality and heart transplantation.

2.5 Statistical analysis

Continuous variables are presented as the mean ± SD, and nominal data are presented as numbers and percentages. Baseline characteristics were compared among the groups using one-way analysis of variance for continuous variables and chi-square tests for categorical variables. Kaplan-Meier curves were generated to compare the endpoints between groups. The Log-rank test was used to evaluate significant differences. Cox proportional hazard models were used to evaluate differences in endpoint events between groups. All variables with a statistically significant effect were intro-

duced into a multivariate Cox proportional hazards model (forced-entry method). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to show the effects of variables. SPSS 23.0 (IBM Corp., Armonk, New York) and GraphPad Prism 7.0 (GraphPad Software, La Jolla, California) were used to perform all statistical analyses. A *P*-value < 0.05 was considered significant in all conditions.

3 Results

3.1 Baseline characteristics and groups

Data from 207 patients, composed of 111 patients with ischemic cardiomyopathy (53.6%) and 96 patients with non-ischemic cardiomyopathy (46.4%), were ultimately analyzed. Males were predominant in the study population (79.7%), and the mean age was 56.38 ± 14.00 years old.

The baseline characteristics of patients are shown in Table 1. Participants in tertile 2 and tertile 3 had worse NYHA classes, lower LVEF, more manifestations of atrial fibrillation, and more use of amiodarone and digoxin. Patients with an elevated big ET-1 level also had higher levels of Scr, hs-CRP, Lg NT-pro BNP, and LVEDD. Moreover, the tertile 3 group had a lower rate of renin-angiotensin system blocker use.

Table 1. Baseline characteristics according to big ET-1 tertiles.

	Total (*n* = 207)	Tertile 1 (*n* = 68)	Tertile 2 (*n* = 69)	Tertile 3 (*n* = 70)	*P*-value
Demographics					
Age, yrs	56.38 ± 14.00	56.13 ± 13.73	57.89 ± 13.63	55.15 ± 14.67	0.506
Male	165 (79.7%)	53 (77.9%)	53 (76.8%)	59 (84.3%)	0.498
BMI, kg/m^2	23.93 ± 4.08	23.72 ± 3.60	24.48 ± 4.24	23.61 ± 4.36	0.399
NYHA III/IV	170 (82.1%)	50 (73.5%)	57 (82.6%)	63 (90.0%)	0.041
Comorbidities					
ICM	111 (53.6%)	40 (58.8%)	36 (52.2%)	35 (50.0%)	0.558
HTN	90 (43.5%)	30 (44.1%)	34 (49.3%)	26 (37.1%)	0.350
DM	56 (27.1%)	19 (27.9%)	22 (31.9%)	15 (21.4%)	0.374
Stroke	3 (1.4%)	1 (1.5%)	1 (1.4%)	1 (1.4%)	1.000
AF	53 (25.6%)	8 (11.8%)	16 (23.2%)	29 (41.4%)	< 0.001
Laboratory examination					
WBC, 10^9/L	7.41 ± 2.00	7.55 ± 1.83	7.63 ± 2.19	7.07 ± 1.92	0.199
Hb, g/L	142.15 ± 26.18	144.15 ± 20.47	141.88 ± 20.14	140.48 ± 35.10	0.394
ALT, U/L	41.78 ± 43.90	48.66 ± 55.34	35.49 ± 35.90	41.29 ± 37.74	0.213
Scr, μmol/L	97.99 ± 28.58	91.77 ± 24.57	98.32 ± 28.54	103.70 ± 31.29	0.049
hs-CRP, mg/L	6.20 ± 4.96	4.52 ± 4.62	6.81 ± 5.05	7.24 ± 4.82	0.002
Lg NT-pro BNP, pg/mL	3.29 ± 0.50	3.10 ± 0.44	3.27 ± 0.40	3.49 ± 0.56	< 0.001
Echocardiography					
LVEF, %	28.62 ± 5.35	30.02 ± 5.03	28.89 ± 5.13	27.00 ± 5.49	0.003
LVEDD, mm	67.41 ± 9.62	64.94 ± 8.82	67.45 ± 9.49	69.76 ± 10.02	0.013
Medications and devices					
ACEI/ARB	126 (60.9%)	46 (67.6%)	46 (66.7%)	34 (48.6%)	0.035
β-blocker	201 (97.1%)	66 (97.1%)	68 (98.6%)	67 (95.7%)	0.608
Amiodarone	28 (13.5%)	7 (10.3%)	7 (10.1%)	14 (20.0%)	0.150
Spirolactone	167 (80.7%)	56 (82.4%)	52 (75.4%)	59 (84.3%)	0.376
Digoxin	134 (64.7%)	36 (52.9%)	44 (63.8%)	54 (77.1%)	0.012
Loop diuretic	200 (96.6%)	64 (94.1%)	69 (100.0%)	67 (95.7%)	0.143
CRT-P	17 (8.2%)	5 (7.4%)	4 (5.8%)	8 (11.4%)	0.458
ICD/CRT-D	33 (15.9%)	13 (19.1%)	6 (8.7%)	14 (20.0%)	0.130

Data are presented as mean ± SD or *n* (%). ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ALT: alanine aminotransferase; ARB: angiotensin receptor blocker; BMI: body mass index; CRT-P: cardiac resynchronization therapy-pacemaker; CRT-D: cardiac resynchronization therapy and implantable cardioverter-defibrillator; DM: diabetes mellitus; Hb: hemoglobin; hs-CRP: high-sensitivity C-reactive protein; HTN: hypertension; ICD: implantable cardioverter-defibrillator; ICM: ischemic cardiomyopathy; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class; NT-pro BNP: N-terminal pro brain natriuretic peptide; Scr: serum creatinine; WBC: white blood cell.

Table 2. Correlation analysis between big ET-1 and baseline variables.

Baseline variables	*r*	*P*-value
NYHA III/IV	0.165	0.018
WBC	–0.123	0.076
Scr	0.147	0.034
hs-CRP	0.217	0.002
Lg NT-pro BNP	0.463	< 0.001
LVEF	–0.256	< 0.001
LVEDD	0.234	0.001

hs-CRP: high-sensitivity C-reactive protein; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class; NT-pro BNP:N-terminal pro brain natriuretic peptide; Scr: serum creatinine; WBC: white blood cell.

3.2 Relationship between big ET-1 and baseline variables

In the correlation analysis, big ET-1 was positively correlated with NYHA class (r = 0.165, P = 0.018), Scr (r = 0.147, P = 0.034), hs-CRP (r = 0.217, P = 0.002), Lg NT-pro BNP (r = 0.463, P < 0.001), and LVEDD (r = 0.234, P = 0.039) and negatively correlated with LVEF (r = −0.181, P = 0.032) (Table 2).

3.3 Clinical outcomes and Kaplan-Meier survival analysis

The average follow-up period was 25.6 ± 13.9 months, VAs occurred in 38 primary prevention patients (18.4%), of whom 30 suffered SCD, six received an appropriate ICD therapy and two survived documented sustained ventricular tachycardia or nonfatal ventricular fibrillation. Patients in tertile 2 and tertile 3 had higher rates of VAs than those in tertile 1 (8.8% *vs.* 23.2% *vs.* 22.9%, tertile 1–3, P = 0.026).

Seventy-eight (37.7%) end-stage events occurred including seven heart transplantations. The risk of end-stage events increased according to big ET-1 level (14.7% *vs.* 40.6% *vs.* 57.1%, tertiles 1–3, P < 0.001). As shown in Figure 1, in the Kaplan-Meier survival analysis, big ET-1 was associated with increased risk of VAs and end-stage events (P < 0.05).

3.4 Plasma big ET-1 as a predictor for VAs and end-stage events

In the univariate Cox regression models, in tertile 2 and tertile 3, big ET-1 along with ICD implantation, Scr, spironolactone and amiodarone were significantly related to VAs (P < 0.05). The multivariate Cox regression modeling results showed that a high plasma big ET-1 level was an independent risk factor for VAs (HR = 3.477, 95% CI: 1.352–8.940, P = 0.010, tertile 2 *vs.* tertile 1; HR = 4.112, 95% CI: 1.604–10.540, P = 0.003, tertile 3 *vs.* tertile 1) (Table 3).

Additionally, in tertile 2 and tertile 3, big ET-1 as well as BMI, atrial fibrillation (AF), ALT, Lg NT-pro BNP, LVEF, LVEDD and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) use were positively associated with end-stage events (P < 0.05). Multivariate Cox regression modeling results showed that a high plasma big ET-1 level was an independent risk factor for end-stage events (HR = 2.804, 95% CI: 1.354–5.806, P = 0.005, tertile 2 *vs.* tertile 1; HR = 4.652, 95% CI: 2.288–9.459, P < 0.001, tertile 3 *vs.* tertile 1) (Table 4).

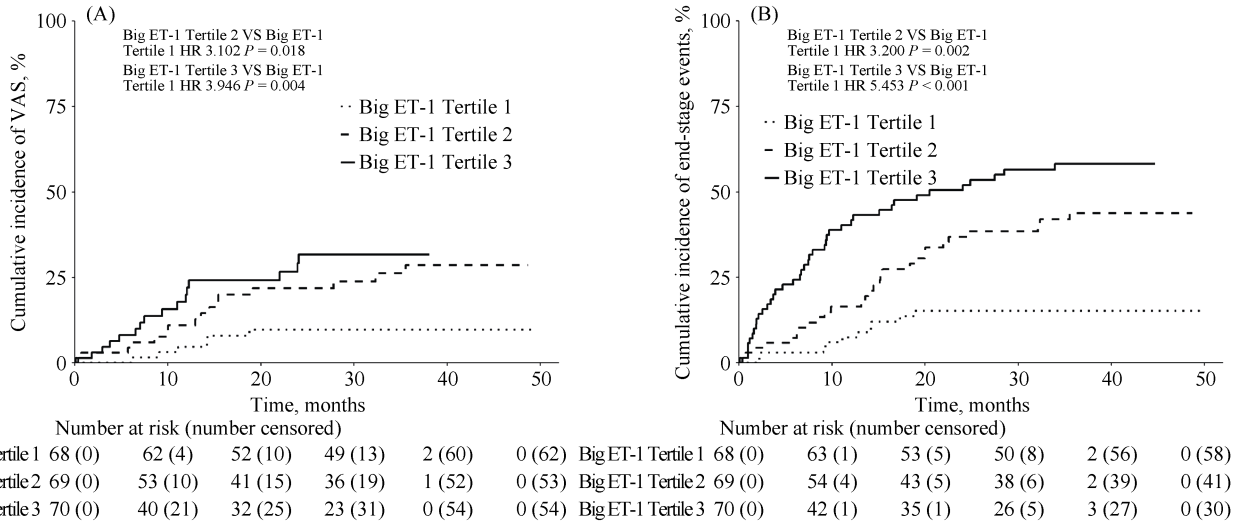

Figure 1 Kaplan-Meier estimates of the cumulative incidence of VAs (A) and end-stage events (B) in the three groups. VAs: ventricular arrhythmias

Table 3. Predictors of VAs risk, uni- and multivariate Cox proportional hazards models.

Variables	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, yrs	1.013 (0.989–1.037)	0.305		
NYHA III/IV = 1	0.713 (0.337–1.506)	0.375		
ICM = 1	1.052 (0.555–1.944)	0.877		
AF=1	1.512 (0.763–2.999)	0.236		
Scr, umol/L	1.011 (1.002–1.021)	0.022		
Lg (NT-pro BNP) pg/ml	1.576 (0.729–3.407)	0.247		
Big ET-1		0.015		0.011
Big ET-1 Tertile2	3.102 (1.21–7.931)	0.018	3.477 (1.352–8.940)	0.010
Big ET-1 Tertile3	3.946 (1.541–10.104)	0.004	4.112 (1.604–10.540)	0.003
LVEF, %	0.978 (0.922–1.037)	0.457		
LVEDD, mm	1.033 (0.999–1.069)	0.056		
Amiodarone = 1	2.284 (1.109–4.703)	0.025		
Spirolactone=1	0.480 (0.246–0.939)	0.032		
CRT-P = 1	0.259 (0.036–1.890)	0.183		
ICD /CRT-D = 1	2.461 (1.221–4.962)	0.012	2.741 (1.352–5.558)	0.005

AF: atrial fibrillation; CRT-D: cardiac resynchronization therapy and implantable cardioverter-defibrillator; CRT-P: cardiac resynchronization therapy-pacemaker; ICD: implantable cardioverter-defibrillator; ICM: ischemic cardiomyopathy; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; NT-pro BNP: N-terminal pro brain natriuretic peptide; NYHA: New York Heart Association class; Scr: serum creatinine.

Table 4. Predictors of end-stage events risk, uni- and multi-variate Cox proportional hazards models.

Variables	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.008 (0.992–1.025)	0.319		
BMI	0.938 (0.887–0.992)	0.025	0.920 (0.868–0.976)	0.006
NYHA III/IV = 1	1.256 (0.679–2.323)	0.468		
ICM = 1	1.173 (0.748–1.838)	0.487		
AF = 1	1.962 (1.239–3.106)	0.004		
ALT	0.989 (0.981–0.998)	0.012	0.991 (0.983–0.999)	0.023
Lg (NT-pro BNP)	3.193 (1.770–5.759)	< 0.001		
Big ET-1		< 0.001		< 0.001
Big ET-1 Tertile2	3.198 (1.553–6.586)	0.002	2.804 (1.354–5.806)	0.005
Big ET-1 Tertile3	5.449 (2.722–10.907)	< 0.001	4.652 (2.288–9.459)	< 0.001
LVEF	0.938 (0.902–0.976)	< 0.001		
LVEDD	1.053 (1.028–1.077)	< 0.001	1.035 (1.012–1.060)	0.003
ACEI/ARB = 1	0.588 (0.377–0.917)	0.019		
β-blocker = 1	1.205 (0.296–4.908)	0.794		
CRT-P = 1	0.398 (0.126–1.264)	0.398		
ICD/CRT-D = 1	0.686 (0.343–1.375)	0.288		

ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ALT: alanine aminotransferase; ARB: angiotensin receptor blocker; BMI: body mass index; CRT-P: cardiac resynchronization therapy-pacemaker; CRT-D: cardiac resynchronization therapy and implantable cardioverter-defibrillator; ICD: implantable cardioverter-defibrillator; ICM: ischemic cardiomyopathy; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class; NT-pro BNP: N-terminal pro brain natriuretic peptide.

4 Discussion

The results of the present study demonstrated that plasma big ET-1, as a simple and practicable blood marker, is significantly and independently related to SCD risk in the primary prevention ICD indication population and thus may aid in selecting appropriate patients, especially for primary prevention ICD implantation.

Plasma big ET-1 has been studied as a predictor and prognostic marker in coronary artery disease, myocardial infarction, and HF.[15,16] Moreover, big ET-1 can predict the responsiveness and prognosis of patients undergoing cardiac resynchronization therapy.[17] However, the relationship between big ET-1 and VAs has been less investigated. Shah, *et al*.[18] found that the level of big ET-1 was significantly increased during ventricular fibrillation in pigs with acute myocardial infarction. Szûcs and colleagues demonstrated that the big ET-1 level was significantly increased in eleven patients with persistent ventricular tachycardia or ventricular fibrillation.[19] However, the above studies did not explore the predictive value of big ET-1 for VAs in patients at a high risk for SCD in clinical settings. The patients included in our study were at high risk for SCD, with decreased LVEF and indications for primary prevention ICD implantation.

In our study, the risk of VAs in patients with primary prevention ICD indications was compared according to tertiles of the baseline level of plasma big ET-1. The results showed that the risk of SCD was increased in patients with high plasma big ET-1 levels. Compared to tertile 2, the risk for patients in tertile 3 was higher, but it did not reach statistical significance, which may be related to the high mortality rate of tertile 3 and the small number of patients included in this study. Furthermore, the predictive value of plasma big ET-1 for the combined endpoint of heart transplantation and all-cause mortality was also excellent. A higher level of plasma big ET-1 resulted in a higher risk of end-stage events.

Big ET-1 is mainly secreted by the vascular endothelium. It exerts its bioactivity, including vasoconstriction, myocardial fibrosis and inflammation, in the development of cardiovascular diseases via two G protein-coupled receptors.[20] The effective prognostic value of big ET-1 in predicting VAs seems to be explained by its potential physiological mechanism. First, an increase in big ET-1 can activate the sympathetic nervous system and renin-angiotensin aldosterone system, promote the proliferation of cardiomyocytes and increase the extracellular matrix, which may lead to the formation of the pathological substrate of arrhythmia.[21] In addition, big ET-1 can act with ion channels. Liu, *et al*.[22] found that an exogenous increase in big ET-1 levels accelerated the depolarization of cardiomyocytes, prolonged the duration of the action potential, and thus increased heart rate variability (HRV). Moreover, big ET-1 can promote ventricular remodeling. Liu, *et al*.[23] found that myocardial fibrosis and ventricular remodeling were mediated by the TGF-β1-endothelin-1 signaling pathway in patients with HF.

4.1 Limitations

The sample size of the study was rather small. Additionally, the changes in plasma big ET-1 levels were not monitored dynamically during the follow-up period. Therefore, further large, prospective randomized controlled trials are needed to confirm the accuracy of the conclusions.

4.2 Conclusions

In primary prevention ICD indication patients, plasma big ET-1 levels are predictive of VAs and end-stage events and thus may aid in ICD implantation risk stratification.

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References

1 Al-Khatib SM, Stevenson WG, Ackerman MJ, *et al*. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2018; 72: 1677–1749.

2 Moss AJ, Zareba W, Hall WJ, *et al*. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346: 877–883.

3 Bardy GH, Lee KL, Mark DB, *et al*. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; 352: 225–237.

4 Zhang S, Ching CK, Huang D, *et al*. Utilization of implantable cardioverter-defibrillators for the prevention of sudden cardiac death in emerging countries: Improve SCA clinical trial. *Heart Rhythm* 2020: 17: 468–475.

5 Priori SG, Blomstrom-Lundqvist C, Mazzanti A, *et al*. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015; 36: 2793–2867.

6 de Haan S, de Boer K, Commandeur J, *et al*. Assessment of left ventricular ejection fraction in patients eligible for ICD therapy: Discrepancy between cardiac magnetic resonance imaging and 2D echocardiography. *Neth Heart J* 2014; 22: 449–455.

7 Køber L, Thune JJ, Nielsen JC, *et al*. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *N Engl J Med* 2016; 375: 1221–1230.

8 Vaduganathan M, Patel RB, Michel A, *et al*. Mode of death in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2017: 69: 556–569.
9 Wu KC. Sudden cardiac death substrate imaged by magnetic resonance imaging. *Circ Cardiovasc Imaging* 2017; 10: e005461.
10 Tse G, Yan BP. Traditional and novel electrocardiographic conduction and repolarization markers of sudden cardiac death. *Europace* 2017; 19: 712–721.
11 Boriani G, Cimaglia P, Biffi M, *et al*. Cost-effectiveness of implantable cardioverter-defibrillator in today's world. *Indian Heart J* 2014; 66: S101–S104.
12 Gaggin HK, Truong QA, Gandhi PU, *et al*. Systematic evaluation of endothelin 1 measurement relative to traditional and modern biomarkers for clinical assessment and prognosis in patients with chronic systolic heart failure. *Am J Clin Pathol* 2017; 147: 461–472.
13 Chowdhury Mohammed A, Moukarbel George V, Gupta R, *et al*. Endothelin 1 is associated with heart failure hospitalization and long-term mortality in patients with heart failure with preserved ejection fraction and pulmonary hypertension. *Cardiology* 2019; 143: 124–133.
14 Pedersen CT, Kay GN, Kalman J, *et al*. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. *Heart Rhythm* 2014; 11: e166–e196.
15 Perez AL, Grodin JL, Wu Y, *et al*. Increased mortality with elevated plasma endothelin-1 in acute heart failure: an ASCEND-HF biomarker substudy. *Eur J Heart Fail* 2016; 18: 290–297.
16 Díez J. Chronic heart failure as a state of reduced effectiveness of the natriuretic peptide system: implications for therapy. *Eur J Heart Fail* 2017; 19: 167–176.
17 Yang S, Liu Z, Liu S, *et al*. Association of baseline big endothelin-1 level with long-term prognosis among cardiac resynchronization therapy recipients. *Clin Biochem* 2018; 59: 25–30.
18 Shah AP, Youngquist ST, McClung CD, *et al*. Endothelin-1 attenuates the hemodynamic response to exogenous epinephrine in a porcine ischemic ventricular fibrillation cardiac arrest model. *J Interferon Cytokine Res* 2011; 31: 679–684.
19 Szûcs A RA, Soós P, Szilágyi S *et al*. Effect of incessant ventricular tachyarrhythmias on serum endothel in and big-endothelin levels. *J Cardiovasc Pharmacol* 2004; 44 (Suppl 1): S402–406.
20 Jankowich M, Choudhary G. Endothelin-1 levels and cardiovascular events. *Trends Cardiovasc Med* 2020; 30: 1–8.
21 Iglarz M, Clozel M. At the heart of tissue: endothelin system and end-organ damage. *Clinical Science (London, England: 1979)* 2010; 119: 453–463.
22 Liu T, Qin M, Shi SB, *et al*. Effects of endothelin-1 chronic stimulation on electrical restitution, beat-to-beat variability of repolarization, and ventricular arrhythmogenesis. *J Cardiovasc Pharmacol* 2013; 62: 549–558.
23 Liu J, Zhuang T, Pi J, *et al*. Endothelial Foxp1 Regulates Pathological Cardiac Remodeling Through TGF-β1-Endothelin-1 Signal Pathway. *Circulation* 2019; 140: 665–680.