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Plasma big endothelin-1 levels at admission and future cardiovascular outcomes: A cohort study in patients with stable coronary artery disease☆

Bing-Yang Zhou, Yuan-Lin Guo, Na-Qiong Wu, Cheng-Gang Zhu, Ying Gao, Ping Qing, Xiao-Lin Li, Yao Wang, Qian Dong, Geng Liu, Rui Xia Xu, Chuan-Jue Cui, Jing Sun, Jian-Jun Li *

Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No 167 Bei Li Shi Road, Xi Cheng District, Beijing 100037, China

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ABSTRACT

Background: Big endothelin-1 (ET-1) has been proposed as a novel prognostic indicator of acute coronary syndrome, while its predicting role of cardiovascular outcomes in patients with stable coronary artery disease (CAD) is unclear.

Methods and results: A total of 3154 consecutive patients with stable CAD were enrolled and followed up for 24 months. The outcomes included all-cause death, non-fatal myocardial infarction, stroke and unplanned revascularization (percutaneous coronary intervention and coronary artery bypass grafting). Baseline big ET-1 was measured using sandwich enzyme immunoassay method. Cox proportional hazard regression analysis and Kaplan–Meier analysis were used to evaluate the prognostic value of big ET-1 on cardiovascular outcomes. One hundred and eighty-nine (5.99%) events occurred during follow-up. Patients were divided into two groups: events group ($n = 189$) and non-events group ($n = 2965$). The results indicated that the events group had higher levels of big ET-1 compared to non-events group. Multivariable Cox proportional hazard regression analysis showed that big ET-1 was positively and statistically correlated with clinical outcomes (Hazard Ratio: 1.656, 95% confidence interval: 1.099–2.496, $p = 0.016$). Additionally, the Kaplan–Meier analysis revealed that patients with higher big ET-1 presented lower event-free survival ($p = 0.016$).

Conclusions: The present study firstly suggests that big ET-1 is an independent risk marker of cardiovascular outcomes in patients with stable CAD. And more studies are needed to confirm our findings.

1. Introduction

It has been well recognized that coronary artery disease (CAD) is an inflammatory driven disease and a large number of previous studies have suggested a close correlation of inflammatory markers with cardiovascular outcomes [1–3]. Notably, it has been demonstrated that endothelin-1 (ET-1) can increase the expression of inflammatory factors including C-reactive protein, tumor necrosis factor-α and interleukins which are related to atherosclerosis [4–6]. Meanwhile, ET-1, derived from endothelial cells, has been suggested to be associated with endothelial dysfunction [7]. Interestingly, endothelial dysfunction is also reported to be an atherosclerotic risk factor and correlated with future cardiovascular events [8]. Therefore, ET-1 has been regarded as a pro-inflammatory factor. Additionally, its role on inflammation and damaged endothelial function in clinical outcomes has been gradually attractive in cardiovascular field. In fact, previous studies have revealed that ET-1 plays an important role on the presence as well as the severity of CAD [9–12]. However, among the researches, many focused on the impact of ET-1 on acute myocardial infarction (AMI) and there is limited data with regard to the effects of ET-1 on clinical outcomes in patients with stable CAD.

Consequently, the aim of the present study was to investigate the prognostic role of big ET-1 on future cardiovascular outcomes in patients with stable CAD.

2. Methods

2.1. Study population

From March 2011 to February 2014, 3422 consecutive patients with stable CAD (typical chest pain existing for at least three months) were enrolled in the present study. Among these patients, 268 (7.83%) patients were excluded because they did not complete the 24-month follow-up. Therefore, 3154 patients with stable CAD were eligible in this study. The present study was in accordance with the principles of the 1975 Declaration of Helsinki and informed consent was obtained from every patient.

☆ Statement of authorship: All authors above take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author.
E-mail address: lijianjun938@126.com (J.-J. Li).

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Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or currently taking *anti*-hypertensive medications. Diabetes mellitus was defined as fasting serum glucose ≥7.0 mmol/L or random serum glucose ≥11.0 mmol/L or the 2-h serum glucose of the oral glucose tolerance test ≥11.0 mmol/L or using hypoglycaemic medications currently. Dyslipidemia was defined as total cholesterol ≥5.1 mmol/L or triglyceride ≥1.7 mmol/L or using lipid-lowering medications at admission. BMI was calculated by square of weight divided by height.

2.2. Laboratory analysis

Blood samples were collected into EDTA-containing tubes after at least 12-h fasting in the morning. Erythrocyte sedimentation rate was measured using Westergren method. Concentration of high sensitivity C-reactive protein (hs-CRP) was measured by immunoturbidimetry (BeckmannAssay360, Bera, Calif., USA). Concentration of fibrinogen was determined by the method of Clauss and a Stagoauto analyzer with STA Fibrinogen kit (Diagnostica Stago, Taverny, France). Big ET-1 was measured using a highly sensitive and specific commercial sandwich enzyme immunoassay (BI-20082H, Biomedica, Wien, Austria). Concentrations of total cholesterol, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and lipoprotein (a) were measured using automatic biochemistry analyzer (Hitachi 7150, Japan). Information of other disease and therapy of every patient was collected from self-reported medical history.

2.3. Follow-up

Patients were prospectively followed up at 6, 12, and 24 months by clinic or interviewing (directly or using telephone) conducted by trained nurses or doctors. The endpoints included all cause death, non-fatal myocardial infarction, stroke and unplanned revascularization. All-cause death was defined as death mainly caused by AMI, congestive heart failure, stroke, malignant arrhythmia and other structural or functional cardiac diseases. Non-fatal myocardial infarction was defined as elevated myocardial enzyme along with typical chest pain or typical electrocardiogram changes or new dysfunction of ventricular wall motion. Stroke was defined as acute cerebral infarction diagnosed by the imaging or typical symptoms. Unplanned revascularization was defined as unexpected percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). For died patients, data were obtained from their families or hospitals.

2.4. Statistical analysis

Continuous variables were expressed as mean ± SD or median with 25th and 75th percentile when appropriate. Student *t* test or Mann–Whitney *U* test was used for continuous variables to compare the statistical differences between groups. Categorical variables were presented as number (percentage) and analyzed by χ^2 statistic test. Univariate and multivariate Cox proportional regression analyses were performed to examine the risk of big ET-1 for clinical outcomes. Variable with a *p*-value <0.1 in the univariate Cox proportional hazard model was examined in the multivariate Cox proportional hazard model. The event-free survival rates among median of big ET-1 were estimated by the Kaplan–Meier method and compared by the log rank test. SPSS version 22.0 program (SPSS Inc., IL, USA) was used in the analysis of statistical data and two-tailed *p* values <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Patients enrolled in the present study were divided into two groups: events group ($n = 189$) and non-events group ($n = 2965$). As is shown in Table 1, patients in events group were older (60.39 ± 10.67 vs. 58.38 ± 9.95 years, $p = 0.008$) and had higher percentage of hypertension (75.66% vs. 62.80%, $p < 0.001$). In addition, concentration of erythrocyte sedimentation rate (ESR) was relatively higher ($p = 0.055$) and big ET-1 was statistically higher ($p = 0.004$) in events group.

3.2. Big ET-1 and cardiovascular risk factors

As is well-known, big ET-1, the biological precursor of ET-1, has a longer half-life time in the peripheral circulation [13] and may be a more accurate plasma indicator of endothelial dysfunction. Therefore, we used plasma big ET-1 instead of ET-1 in the present study. Data indicated that the median of big ET-1 was 0.30 pmol/L. Low big ET-1 was defined as <0.3 pmol/L and high big ET-1 was defined as ≥0.3 pmol/L. As is presented in Table 2, high big ET-1 group had significantly higher occurrence of hypertension (66.03% vs. 61.15%, $p = 0.004$), diabetes mellitus (30.72% vs. 25.88%, $p = 0.003$), dyslipidemia (78.80% vs. 75.25%, $p = 0.018$), and current smoking (35.50% vs. 31.80%, $p = 0.028$). Meanwhile, the inflammatory indicators including ESR and high sensitive C-reactive protein (hsCRP) were statistically higher in high big ET-1 group ($p < 0.05$). Events in high big ET-1 group were significantly higher (7.02% vs. 4.97%, $p = 0.015$).

3.3. Cardiovascular outcomes during follow-up

During 24-month follow-up, 189 cardiovascular events occurred. Among them, 29 (15.34%) died, 43 (22.75%) had stroke, 30 (15.87%) developed non-fatal myocardial infarction and 87 (46.03%) underwent PCI or CABG.

3.4. Predictive role of big ET-1 on cardiovascular outcomes

Univariate Cox proportional hazard regression analysis indicated that big ET-1 was associated with cardiovascular outcomes (hazard ratio (HR): 1.810, 95% confidence interval (CI): 1.255–2.609, $p = 0.001$, Table 3). We also found that age, hypertension, and ESR were risk factors of cardiovascular outcomes ($p < 0.05$). Therefore, we next carried out multivariate Cox proportional hazard regression analysis in order to examine the independent risk value of big ET-1 on cardiovascular outcomes (Table 3). After adjustment of age, left ventricular ejection fraction (LVEF), hypertension, creatinine, ESR, and fibrinogen, big ET-1 was found to be independently associated with cardiovascular outcomes (HR: 1.656, 95%CI 1.099–2.496, $p = 0.016$).

In addition, the Kaplan–Meier analysis revealed that higher big ET-1 presented lower event-free survival ($p = 0.016$, Fig. 1).

Table 1
Baseline clinical and biochemical characteristics of patients.

Variable	Events ($n = 189$)	Non-events ($n = 2965$)	*P* value
Clinical factors	–	–	–
Age, y	60.39 ± 10.67	58.38 ± 9.95	**0.008**
Male, *n* (%)	132 (69.84)	2178 (73.46)	0.276
BMI (kg/m^2)	25.72 ± 3.26	25.73 ± 3.18	0.955
LVEF (%)	63.72 ± 6.88	62.25 ± 7.14	**0.005**
Hypertension, *n* (%)	143 (75.66)	1862 (62.80)	<**0.001**
Diabetes mellitus, *n* (%)	62 (32.80)	830 (27.99)	0.154
Dyslipidemia, *n* (%)	151 (79.89)	2278 (76.83)	0.332
Current smoking, *n* (%)	59 (31.22)	1002 (33.79)	0.467
Previous PCI or CABG, *n* (%)	51 (26.98)	820 (27.65)	0.841
Previous MI	63 (33.33)	834 (28.13)	0.124
Laboratory factors	–	–	–
ESR (mm/h)	8.00 (3.25–15.00)	7.00 (3.00–14.00)	**0.055**
HsCRP (mg/L)	1.83 (0.87–3.40)	1.51 (0.80–2.99)	0.149
FIB (μg/mL)	3.31 ± 0.79	3.21 ± 0.76	0.064
Big ET-1 (pmol/L)	0.33 (0.25–0.49)	0.30 (0.22–0.45)	**0.004**
Creatinine (μmol/L)	74.20 ± 14.17	77.41 ± 16.87	**0.011**
Uric Acid (μmol/L)	349.99 (293.37–417.52)	342.40 (291.80–401.86)	0.148
TC (mmol/L)	4.22 ± 1.12	4.14 ± 1.12	0.354
TG (mmol/L)	1.52 (1.11–2.11)	1.52 (1.13–2.09)	0.861
LDL-C (mmol/L)	2.49 ± 0.94	2.47 ± 0.90	0.819
HDL-C (mmol/L)	1.00 (0.84–1.27)	1.02 (0.87–1.22)	0.833
Lp (a) (mmol/L)	173.16 (75.05–416.95)	164.81 (73.13–367.50)	0.462
Medications	–	–	–
ACE inhibitors, *n* (%)	9 (4.76)	160 (5.40)	0.707
ARBs, *n* (%)	9 (4.76)	159 (5.36)	0.721
β-blockers, *n* (%)	47 (24.87)	692 (23.34)	0.630
Statins, *n* (%)	98 (51.85)	1522 (51.33)	0.832

Data were expressed as mean ± SD, median with 25th and 75th percentile or *n* (%). BMI, body mass index; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; MI: myocardial infarction; ESR: erythrocyte sedimentation rate; hsCRP: high sensitive C-reactive protein; FIB: fibrinogen; ET-1: endothelin-1; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL—-C, high density lipoprotein cholesterol; Lp(a), lipoprotein (a); ACEIs, angiotensin-converting enzymes; ARBs, angiotensin receptor blocker. The bold data indicated statistical significance.

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