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Full Length Article

Plasma endothelin-1 level as a predictor for poor collaterals in patients with ≥95% coronary chronic occlusion

Ying Fan [a,b,1], Sha Li [a,1], Xiao-Lin Li [a], Xian-Liang Lin [a], Cheng-Gang Zhu [a], Rui-Xia Xu [a], Ping Qing [a], Na-Qiong Wu [a], Li-Xin Jiang [a], Bo Xu [a], Run-Lin Gao [a], Jian-Jun Li [a,*]

[a] Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fu Wai 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
[b] Department of Cardiology, The Fifth Hospital of Wuhan & Affiliated Guangci Hospital of Wuhan University, Wuhan 430050, China

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ABSTRACT

Background: Coronary collateral circulation (CCC) plays an important role in protecting myocardium from ischemic damage. The studies on factors which impact on CCC might be of great clinical interest. The aim of the present study was to evaluate endothelin-1 (ET-1) as a potential predictor for poor or good CCC in patients with angiography-proven ≥95% coronary occlusion.
Methods: We screened 1038 consecutive patients with ≥95% occlusion in at least one major epicardial coronary artery detected by coronary angiography. Of these, 663 patients were classified into the poor CCC group with Rentrop 0–2 grade collateral circulation and 375 patients into the good CCC group with Rentrop 3 grade. The association of plasma ET-1 levels with collateral status was assessed.
Results: We found that patients in the poor CCC group had a higher ET-1 level than those in the good CCC group (0.59 ± 0.48 vs. 0.39 ± 0.32 pmol/L, $p < 0.001$), and the ET-1 values increased with the descent of the Rentrop grades (p for trend < 0.001). Moreover, multivariate logistic regression analysis revealed an independent association between ET-1 and collateral status (odds ratio [95% CI] for poor CCC 2.27 [1.60–3.22], $p < 0.001$). Additionally, the association presented significance in both men (odds ratio [95% CI] for poor CCC 3.18 [2.20–4.74], $p < 0.001$) and women (odds ratio [95% CI] for poor CCC 3.10 [1.36–7.85], $p = 0.011$) when the sex-specific analysis was performed.
Conclusions: Plasma ET-1 level may be a useful, easily available marker for predicting the degree of CCC in patients with ≥95% coronary chronic occlusion.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. In the vast majority of patients, death is the consequence of artery occlusion with myocardial infarction (MI) in the context of atherosclerosis. Hence, the promotion of well-functioning coronary anastomoses (arteriogenesis) before a coronary event is an appealing therapeutic principle to reduce mortality [1,2]. Not surprisingly, collateral supply to the jeopardized region, which is a physiological adaption to severe coronary artery narrowing and/or occlusion for myocardium to circumvent ischemia, can also make sense [3–7]. The studies on factors which impact on coronary collateral circulation (CCC) may be worthy of investigation in clinical practice.

It has been demonstrated that even patients with the same degree of coronary artery obstruction may exhibit distinct patterns in collaterals, while the potential reasons for this difference is largely unknown. Several researches noted that the collateral development might be multifactorial [1]. The interaction between new blood vessel formation and inflammation might be one of the factors [8].

As a potent vasoconstrictor, endothelin-1 (ET-1) has been demonstrated to play a role in endothelia dysfunction and inflammation [9]. Elevated ET-1 level is shown to be associated with reperfusion injury and micro-vascular obstruction. Additionally, it might be actively involved in the pathophysiology of the onset and progression of coronary artery disease (CAD), from the formation of atherosclerotic plaque to the development of acute coronary syndrome (ACS) and heart failure (HF) [10–12]. Moreover, it had been reported that ET-1 levels were increased

Abbreviations: ACS, acute coronary syndrome; BMI, Body mass index; CABG, coronary artery bypass grafts; CAD, coronary artery disease; CCC, coronary collateral circulation; DM, diabetes mellitus; ET-1, endothelin-1; HDL-C, high density lipoprotein-cholesterol; HF, heart failure; LDL-C, low density lipoprotein-cholesterol; MI, myocardial infarction; PCI, percutaneous coronary interventional.

* Corresponding author at: Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, China.
E-mail address: lijianjun938@126.com (J.-J. Li).

[1] The first two authors contributed equally to the study.

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in the coronary arteries of infarcted heart at early stages following percutaneous coronary intervention (PCI) or coronary artery bypass grafts (CABG) [13–16].

However, there is no data available regarding the relationship between plasma ET-1 levels and CCC. Therefore, the aim of the present study was to evaluate ET-1 as a potential predictor for poor or good CCC in patients with angiography-proven ≥95% coronary occlusion.

2. Materials and methods

2.1. Study population

The study was approved by the Ethics Committee of the Fu Wai Hospital. From March 2010 to April 2014, we screened 1038 consecutive and eligible patients with ≥95% occlusion in at least one major epicardial coronary artery detected by coronary angiography at our institution. Exclusion criteria included patients with (1) any known inflammatory or infectious disease or confirmed or suspected cancer, (2) treatment by steroids, immune suppressive drugs or non-steroidal anti-inflammatory drugs except for low-dose aspirin, (3) ACS within the previous 6 months, (4) PCI within the previous 3 months, (5) history of CABG, (6) chronic HF (ejection fraction, EF < 50%), cardiomyopathy, and valvular heart disease, (7) pulmonary heart disease, (8) age > 75 years old, and (9) severe liver and kidney dysfunction.

2.2. Coronary angiography and collateral scoring

Coronary angiography was routinely performed by the Judkin's method without the use of nitroglycerin. Percentage stenosis diameter was measured using computerized quantitative angiography in a biplane-mode (Philips DCI, Eindhoven, the Netherlands). Two experienced interventional cardiologists, who were blinded to patient characteristics, reviewed the angiograms and graded the coronary collaterals according to the Rentrop classification [17] (the Rentrop scoring system 0, 1, 2, 3; 0 = no visible filling of any collateral channels; 1 = filling of the small side branches; 2 = partial collateral filling of the epicardial artery; and 3 = complete collateral filling of the epicardial artery). Collateral grading was classified as poor collateral development when the collateral grades were 0 to 2 and as good collateral development when the grade was 3. In subjects with >1 collateral supplying the distal aspect of the diseased artery, the higher collateral grade was used. In subjects with >1 qualifying severely diseased vessel, the vessel with the higher collateral grade was chosen for analysis. Intra- and inter-observer agreements of coronary collateral grades were determined from a random sample of 50 coronary angiograms, while disagreements were resolved by a further joint reading. As a result, 663 patients were classified into the poor CCC group and 375 patients were in the good CCC group.

2.3. Risk factor assessment

Information including smoking, alcohol consumption and physical activity status was collected through direct interview with the patients. A current smoker was defined by smoking at least one cigarette per day. Alcohol consumption was defined as having at least one drink per day. Regular physical activity was defined as experiencing at least 30 min of brisk walking three or more times per week. Medical records were reviewed for reports of previous MI and PCI. Body mass index (BMI) was calculated as weight (kg) divided by height^2 (m^2), and hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, or treatment with anti-hypertensive medication in the previous 2 weeks. Diabetes was defined according to current guidelines from the American Diabetes Association [18].

2.4. Laboratory measurement

Venous blood samples were collected after a 12-hour overnight fast prior to coronary angiography. Plasma ET-1 levels were measured using a highly sensitive and specific commercial sandwich enzyme immunoassay (BI-20082H, Biomedica, Wien, Austria). Plasma was added to wells containing solid-phase mouse anti-human endothelin-1 polyclonal antibody. The cross-reactivity with other endothelin peptides is <1%. The kit has a detection limit of 0.02 pmol/L (0.00005 ng/mL).

2.5. Statistical analysis

Statistical analysis was performed using the SPSS for Windows (version 19.0; SPSS Inc., Chicago, Illinois). Continuous variables were expressed as mean ± standard deviation; categorical variables were defined as percentages. A Student's *t*-test was used to compare normally distributed continuous variables, and a Mann–Whitney *U* test was used for non-normally distributed continuous variables. Categorical data among the groups were compared using a Chi-square test. Potential predictors for poor CCC were identified using univariate and multivariate logistic regression analyses (poor CCC is "Yes" as 1, and good CCC is "No" as 0, with the poor CCC as the dependent variable). A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Baseline characteristics according to the collateral status were listed in Table 1. As mentioned above, there were 663 patients with poor CCC and 375 with good CCC. The mean age of the patients with poor CCC was 56.2 ± 9.9 years, and good CCC was 55.4 ± 9.3 years (p = 0.180). No

Table 1
Baseline characteristics of the patients.

Variables	Rentrop collateral classification		
	Poor CCC (n = 663)	Good CCC (n = 375)	*P*-values
Clinical characteristics			
Age (years)	56.2 ± 9.9	55.4 ± 9.3	0.180
Male (n, %)	540 (81.5%)	306 (81.6%)	0.753
BMI (kg/m^2)	26.12 ± 3.23	26.16 ± 3.01	0.851
Current smokers (n, %)	407 (61.4%)	230 (61.3%)	0.986
Daily alcohol consumption (n, %)	226 (34.1%)	114 (30.4%)	0.224
Regular physical activity (n, %)	345 (52.0%)	201 (53.6%)	0.628
Hypertension (n, %)	417 (62.9%)	236 (62.9%)	0.990
Diabetes mellitus (n, %)	212 (32.0%)	88 (23.5%)	**0.004**
Previous MI (n, %)	153 (23.1%)	95 (25.3%)	0.449
Previous PCI (n, %)	139 (21.0%)	69 (18.4%)	0.334
Laboratory findings			
Total cholesterol (mg/dl)	161.62 ± 44.70	160.73 ± 45.72	0.356
HDL-C (mg/dl)	38.43 ± 9.89	38.68 ± 9.90	0.697
LDL-C (mg/dl)	101.34 ± 39.96	98.31 ± 38.12	0.237
Triglycerides (mg/dl)	176.05 ± 145.23	169.68 ± 100.20	0.409
Serum creatinine (mg/dl)	0.88 ± 0.17	0.87 ± 0.17	0.124
Fasting glucose (mg/dL)	104.39 ± 30.71	102.95 ± 29.01	0.802
ET-1 (pmol/L)	0.59 ± 0.48	0.39 ± 0.32	<**0.001**
Cardiovascular medication (n, %)			
Aspirin	542 (81.8%)	301 (80.2%)	0.557
Beta-blockers	294 (44.3%)	165 (44.0%)	0.915
ACE-Is or ARBs	183 (27.6%)	89 (23.7%)	0.173
Calcium channel blockers	167 (25.2%)	108 (28.8%)	0.205
Nitrates	247 (37.3%)	130 (34.7%)	0.405
Statins	440 (66.4%)	270 (72.0%)	0.061

Data were expressed as mean ± SD or the number (%) of patients. The bold values indicate statistical significance. CCC, coronary collateral circulation; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ET-1, endothelin-1; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers