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Full Length Article

Relationship between metabolites of arachidonic acid and prognosis in patients with acute coronary syndrome

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ABSTRACT

Objective: To investigate the correlation of arachidonic acid (ARA) metabolites and prognosis in ACS patients.
Methods and results: This is a mono-center retrospective nested case-control study. We followed up 470 ACS patients, of whom 39 patients had MACE in a mean follow up time of 1037 days (identified as MACE group). Another 39 clinically matched patients without MACE were selected from the 470 ACS patients (Non-MACE group). Thirty-nine subjects without Coronary Heart Disease were enrolled as Control group. Metabolites of ARA were determined by LC-MS/MS. We found that plasma levels of LTB_4, 8-HETE, 11-HETE, 12-HETE, and 15-HETE were significantly increased in MACE and Non-MACE groups, 5-HETE and 9-HETE were significantly increased in MACE group comparing with Control group ($P < 0.05$). Importantly, plasma level of 19-HETE in MACE group was significantly lower than Non-MACE and Control groups. 19-HETE significantly correlated with the prognosis of ACS after adjustment for clinical characteristics (HR = 0.103, 95% C.I.: 0.014–0.766). The AUC for ROC curve of 19-HETE in predicting MACE was 0.637 ($P < 0.05$). Survival analysis showed that ACS patients with 19-HETE levels higher than 0.13 ng/ml tend to have better prognosis than those lower than 0.13 ng/ml ($P < 0.05$). GRACE score and serum Fib levels were also significantly correlated with MACE. 20-HETE level was found significantly higher in STEMI group comparing with NSTE-ACS group ($P < 0.05$).
Conclusion: Plasma arachidonic acid metabolites may act as prognostic markers for ACS patients.

1. Introduction

Acute Coronary Syndrome (ACS) as acute event of Coronary Heart Disease (CHD) continues to be the leading cause of death worldwide [1,2]. Despite development in medication therapy as well as Percutaneous Coronary Intervention (PCI), the mechanism of recurrence of Major Adverse Cardiovascular Event (MACE) in ACS patients has not been fully elucidated. Arachidonic acid (ARA) plays crucial part in the pathophysiological process of ACS, especially in plaque rupture, inflammatory cell adhesion and platelet aggregation [3].

ARA is an n-6 essential fatty acid that is a major constituent of biomembranes. It has been reported that supplementation with ARA among the elderly improves coronary flow velocity reserve as examined by transthoracic Doppler echocardiography [4]. However, ARA supplementation did not increase ARA metabolites or induce cardiovascular, inflammatory or allergic diseases in Japanese elderly individuals [5]. These results shed lights on its potential therapeutic value, emphasizing the importance of in-depth understanding of ARA metabolites in ACS patients. ARA could be metabolized through three different pathways: cyclooxygenase (COX) pathway, lipoxygenase (LOX) pathway and cytochrome P450 (CYP) pathway. COX pathway metabolites such as prostaglandin E2 (PGE2) and thromboxane A_2(TXA_2), LOX pathway metabolites such as Leukotreines B_4 (LTB_4), 5-hydroperoxy-eicotetraenoic acid (5-HPETE) and 15-hydroxyeicosatetraenoic acid (15-HETE), CYP pathway metabolites such as epoxyeicosatrienoic acids (EETs) and 20-HETE have shown indispensable roles in atherosclerosis and ACS [6–11]. Existing results on the function of ARA metabolites in cardiovascular disease mainly focus on cellular and animal research, clinical evidences especially their relationships with clinical outcomes are lacking.

Here we employed liquid chromatography tandem mass spectrometry (LC-MS/MS) to analyze ARA metabolites in the plasma of ACS

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patients suffering from recurrence of MACE, comparing with those ACS patients who didn't suffer from recurrence of MACE, to find out the prognostic value of ARA metabolites in ACS.

2. Methods

2.1. Study population

2.1.1. ACS (acute coronary syndrome)

The diagnosis of ACS was made according to American and European guidelines [12,13]. ST segment elevation ACS were characterized in ECG by new or presumed new LBBB or ST segment elevation at the J point in two or more contiguous leads with the cut-off points of ≥0.2 mV in leads V1, V2, or V3 and ≥0.1 mV in other leads [14]. In contrast, NSTE-ACS patients present with acute chest pain but without persistent ST-segment elevation [15]. The ECG shows persistent or transient ST-segment depression or T-wave inversion, flat T waves, pseudo-normalisation of T waves, or no ECG changes at presentation.

2.1.2. MACE (major adverse cardiovascular event)

MACE was defined as (1) cardiac death: including death caused by heart failure, arrhythmia, and myocardial infarction; (2) non-lethal myocardial infarction; (3) unplanned coronary revascularization.

This is a mono-center retrospective nested case-control study. There were 1135 patients who signed written consent for this study from all 3527 hospitalized ACS patients who underwent PCI to treat severe coronary artery stenosis in the cardiac-cathlab of Peking University Third Hospital (PUTH) from January 1st 2010 to December 31st 2012 (Fig. 1). Of them, 513 patients met our inclusion criteria. The inclusion criteria were (1) age > 18 years old; (2) symptoms compatible with ACS (ST segment elevation and Non-ST segment elevation) within 24 h; (3) at least one of electrocardiographic (ECG) changes, abnormal cardiac biomarkers and (4) excluded by the exclusion criteria. The exclusion criteria were (1) prior ACS; (2) myocardial ischemia caused by reasons other than coronary stenosis(such as arrhythmia, severe anemia, hypoxia, hypotension, valvular heart disease); (3) chronic kidney disease stage 4 and 5; (4) active liver disease with ALT (glutamic-pyruvic transaminase) > 3.0*ULN (upper limits of normal) or TBIL (total bilirubin) > 1.5*ULN; (5) NYHA stage III-IV or Killip III-IV heart

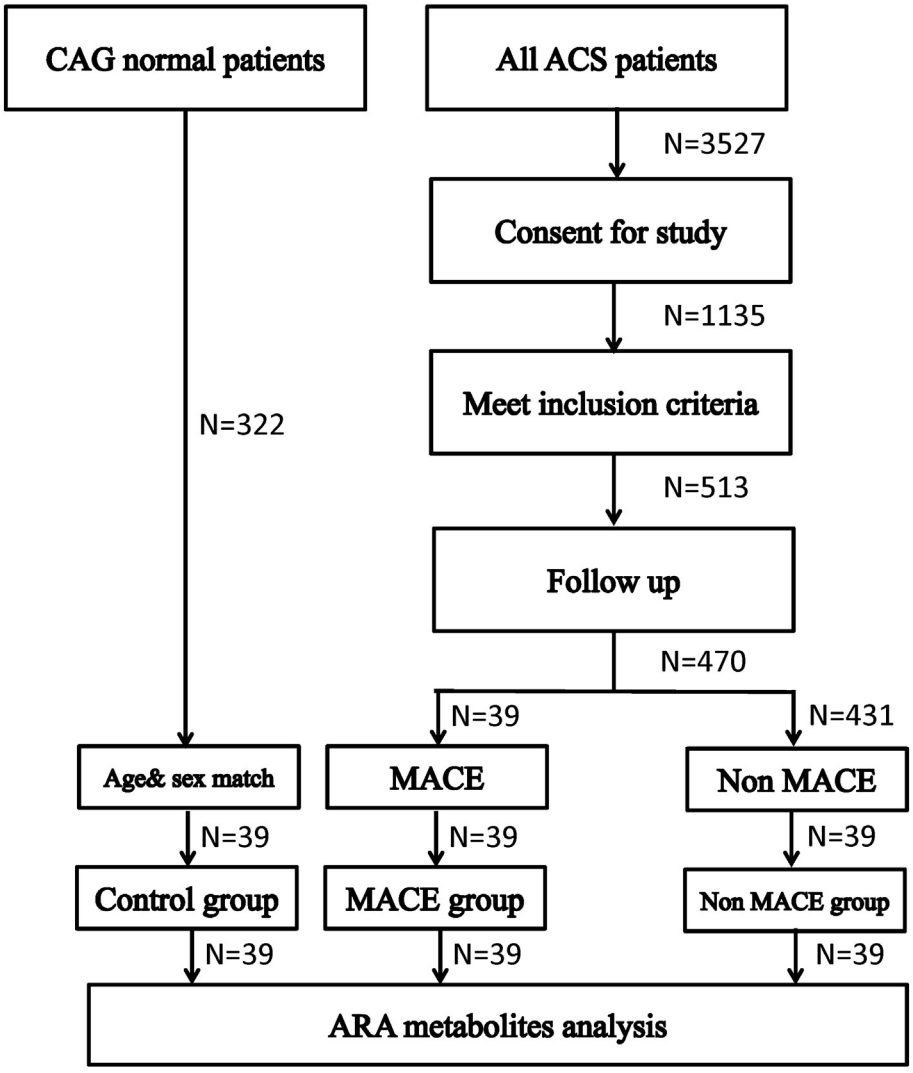

Fig. 1. Research flowchart. There were 1135 patients who signed written consent for this study of all 3527 hospitalized ACS patients who underwent PCI. Of them, 513 patients met our inclusion criteria (We excluded patients with disease or conditions that would interfere ARA metabolites concentrations.) We successfully followed up 470 ACS patients. Of them 39 patients had MACE (MACE group). We recruited 39 patients without MACE while matched with MACE group (Non-MACE group). We also recruited 39 patients with normal coronary angiography and excluding diagnosis of CHD, while matched with MACE group (Control group).