

Plasma asymmetric dimethylarginine and L-arginine levels in Chinese patients with essential hypertension without coronary artery disease

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ABSTRACT

Objective: To investigate the plasma asymmetric dimethylarginine (ADMA) levels and L-arginine in the essential hypertension (EH) patients without coronary artery disease. **Patients and Methods:** A total of 86 Chinese patients were enrolled in this study. All patients received coronary multidetector-row computed tomography to exclude distinct coronary stenosis and treadmill exercise testing to exclude microvascular angina pectoris. The patients with normal blood pressure (n = 26) were set as the control group. The EH patients were divided into three subgroups: the prehypertension group (n = 26), the stage 1 hypertension group (n = 26) and the stage 2 hypertension group (n = 8). The plasma ADMA and L-arginine concentrations were measured by a validated high-throughput liquid chromatographic tandem mass spectrometric assay. **Results:** There was a significantly higher ADMA level [0.028 (0.016) mmol/L vs. 0.021 (0.010) mmol/L, $P = 0.002$] and lower L-arginine to ADMA ratio [1.42 (0.58) vs. 2.01 (0.99), $P < 0.001$] in the EH group compared with the control group. Among the EH patients, the ADMA levels were increased by grades of hypertension [0.028 (0.011) mmol/L, 0.027 (0.014) mmol/L, 0.035 (0.024) mmol/L, respectively, $P < 0.001$]. The ADMA level was independently related to the systolic blood pressure ($r = 1.047$, $P = 0.001$). **Conclusion:** The plasma ADMA levels were significantly elevated with grades of hypertension in EH patients and were positively related to the systolic blood pressure levels.

Key words: Asymmetric dimethylarginine, essential hypertension, L-arginine

INTRODUCTION

Endothelium-derived nitric oxide (NO) is a potent vasodilator that plays a critical role in maintaining vascular homeostasis through its anti-atherogenic and antiproliferative effects on the vascular wall. NO is synthesized from its precursor, L-arginine, by endothelial NO synthase (NOS). Asymmetric dimethylarginine

(ADMA) is a naturally occurring amino acid and is produced by methylation of arginine residues of the intracellular proteins.^[1] It inhibits the NOS activity, leading to the derangement of vasoprotective and vasodilatory effect of NO. ADMA contributes to the cardiovascular disease pathogenesis related to endothelial dysfunction, including atherosclerosis, hyperlipidemia, diabetes mellitus, and others.^[2] A low ratio of L-arginine to ADMA is a marker of endothelial dysfunction and is also associated with all-cause mortality.^[3]

The present study included a highly selected group with essential hypertension (EH) without the coronary disease. The relationship of the ADMA levels between the EH patients and the controls (with normal blood pressure), and

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also different ADMA levels among the different stages of hypertension were both investigated.

PATIENTS AND METHODS

Patients

A total of 86 Chinese patients were enrolled in this study. All patients received the coronary multidetector-row computed tomography to exclude the distinct coronary stenosis and the treadmill exercise testing to exclude the microvascular angina pectoris. None of the patients had family history of hypertension. The patients with suspected secondary causes of hypertension were eliminated by necessary laboratory measurements. The exclusion criteria included ischemic heart disease, congestive heart failure, atrial fibrillation, chronic renal insufficiency, and a history of stroke. Ischemic heart disease was defined as being present in patients with >50% stenosis of a major coronary artery on coronary angiography or a history of myocardial infarction or percutaneous coronary intervention. Heart failure was defined as a history of dyspnea or exercise intolerance associated with signs of pulmonary congestion or peripheral edema. Cardiac enlargement or dysfunction shown by chest radiography or echocardiography was also a diagnostic criterion. The study was approved by the institutional review board of the First Affiliated Hospital of Bengbu Medical College.

Definition of hypertension

Blood pressures of the patients were measured at the brachial artery with an automatic pressure gauge after a resting period of at least 5 min. The same physician performed all measurements. The mean of the measurements on two sides of brachial artery was used as the systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hypertension was defined as SBP >140 mmHg and/or DBP >90 mmHg on the repeated measurements with or without any oral anti-hypertension drug. The patients with normal blood pressure ($n = 26$) were set as the control group. According to current hypertension guideline,^[4] the EH patients were divided into three subgroups: the prehypertension group ($n = 26$), the stage 1 hypertension group ($n = 26$) and the stage 2 hypertension group ($n = 8$).

Assays for ADMA, L-arginine, and other biomarkers

Laboratory assessment of several biomarkers was conducted on samples drawn in the morning after at least 12 h of fasting. Plasma samples were stored at -80°C and used for mass spectrometric determination of ADMA

and L-arginine using a validated high-throughput liquid chromatographic tandem mass spectrometric assay.^[5] All plasma samples were measured by the same assay. Glucose, uric acid, total cholesterol, triglyceride, and high-density lipoprotein cholesterol levels were measured by the enzymatic colorimetric method with an Olympus AU600 auto-analyzer using reagents from Olympus Diagnostics.

Statistical analysis

The variables with normal distribution were reported as mean \pm standard deviation and were compared using Student's *t*-test. The variables with non-normal distribution were reported as median (quartile range) and were compared by Wilcoxon's test. Discrete variables were compared by chi-square or Fisher's exact test. ADMA-related analysis used multivariate logistic regression analysis. A value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SAS software (Version 9.1, SAS Institute Inc., Cary, NC, USA).

RESULTS

Clinical characteristics

Table 1 shows the clinical characteristics in the EH group and the control group. There were no statistical differences between the EH group and the control group in terms of sex, age, glucose, uric acid, triglycerides, total cholesterol and high-density lipoprotein cholesterol.

Plasma ADMA and L-arginine concentrations

There was a significantly higher ADMA level [0.028 (0.016) mmol/L vs. 0.022 (0.010) mmol/L, $P = 0.002$] and lower L-arginine to ADMA ratio [1.42 (0.58) vs. 2.01 (0.99), $P < 0.001$] in the EH group compared to the control group. Among the patients, the ADMA levels were increased by grades of hypertension [0.028 (0.011) mmol/L, 0.027 (0.014) mmol/L, 0.035 (0.024) mmol/L, respectively, $P < 0.001$]. There was no significant difference in the L-arginine levels among the patients [Table 1 and Figure 1]. The ADMA concentrations were found to be independently related to the SBP levels ($r = 1.047$, $P = 0.001$) after multivariate logistic regression analysis.

DISCUSSION

The results of this study, which was performed in EH patients without coronary disease, showed that the plasma ADMA levels were significantly elevated in EH patients and were positively related to the SBP levels.

Table 1: The patients' clinical characteristics

	EH group (n = 34)	Control group (n = 52)	X/t value	P value
Sex (male/%)	20/58.2	24/46.5	1.32	0.251
Age (years)	58.9±12.5	53.5±16.1	2.06	0.056
Blood glucose (mmol/L)	4.8±0.6	4.8±0.5	-0.27	0.787
Uric acid (mmol/L)	354.9±115.2	340.8±139.2	-0.49	0.626
Triglycerides (mmol/L)	1.99±0.79	1.80±1.03	-0.91	0.366
Total cholesterol (mmol/L)	4.87±1.05	4.63±0.95	-1.12	0.265
High-density lipoprotein (mmol/L)	1.29±0.28	1.25±0.33	-0.70	0.483
SBP (mmHg)	140 (20)	120 (10)	62.28	<0.001
DBP (mmHg)	100 (20)	80 (5)	59.91	<0.001
Heart rate (bpm)	75±8	70±10	8.09	0.054
ADMA (mmol/L)	0.028 (0.016)	0.021 (0.010)	14.44	0.002
L-arginine (mmol/L)	0.045±0.008	0.047±0.009	0.99	0.323
L-arginine to ADMA ratio	1.42 (0.58)	2.01 (0.99)	16.95	<0.001

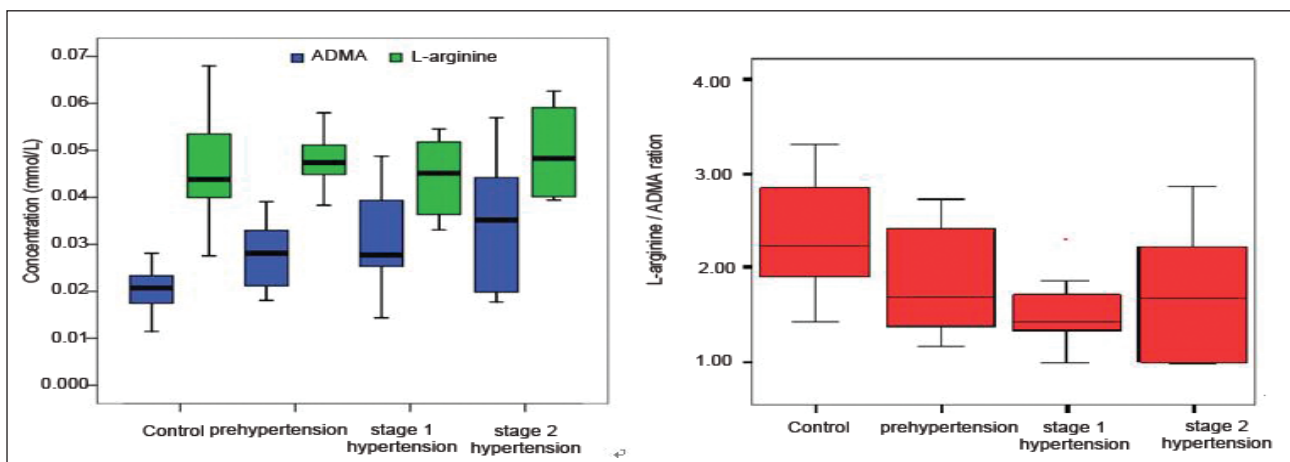


Figure 1: The ADMA, L-arginine levels (left) and the L-arginine to ADMA ratio (right) in EH patients with different stages of hypertension and the control group

Endothelium-derived NO is the most potent endogenous substance exerting its beneficial effects by stimulation of soluble guanylate cyclase to produce cyclic GMP.^[6] It is synthesized by the endothelial enzyme NOS from L-arginine. A large amount of data indicates that ADMA may be responsible for endothelial dysfunction in subjects with vascular diseases and in those with cardiovascular risk factors in whom ADMA plasma levels have been found to be elevated.^[7]

The ADMA has been identified as an independent predictor of morbidity and mortality in patients with different cardiovascular diseases.^[3] Elevated ADMA levels have been documented in different clinical conditions such as dyslipidemia, high BP, diabetes and acute coronary syndrome, all associated with endothelial dysfunction.^[8] We found in our previous study that the plasma ADMA concentrations are increased in acute coronary syndrome.^[9] We also found that the ADMA levels are positively correlated to the degree of coronary atherosclerosis.^[10]

NO plays an important role in the regulation of vascular tonus and blood pressure. NOS inhibition has been shown to cause a decrease in renal sodium excretion, which may also contribute to hypertension. ADMA has potent vasoconstrictor/pressor effects by inhibiting NOS. Further, exogenously administered ADMA was reported to decrease renal sodium excretion in healthy human subjects.^[11] Thus, we hypothesized that ADMA may be involved in the pathogenesis of hypertension. Our data indicated that ADMA levels were higher in a high selected EH patients than that in the control group after excluded from coronary artery disease. In a recent study, ADMA levels were found to be significantly higher in 30 younger males with EH.^[12] However, that study did not exclude coronary atherosclerotic heart disease which is an important influencing factor of ADMA testified by our previous research.^[10]

L-arginine is the substrate for the endothelial NOS synthase to generate NO. The plasma L-arginine level varies according to the daily diet. The L-arginine to ADMA ratio has been used to represent the NO bioavailability.^[13] A

lower L-arginine to ADMA ratio is associated with high risk of death and cardiovascular disease events in the general population.^[8] In a large community-based sample, the ratio of L-arginine to ADMA is significantly associated with the all-cause mortality.^[3] Our previous study also indicated that the ratio of L-arginine to ADMA decreased in patients with acute coronary syndrome.^[9] Reduced L-arginine to ADMA ratio is found to correlate with a decreased endothelial-dependent flow-mediated vasodilatation in patients with hypercholesterolemia,^[14] hyperhomocysteinemia^[15] and hypertriglyceridemia.^[16] In this study, we found that a lower L-arginine to ADMA ratio existed in EH patients without coronary artery disease. Inhibition of NOS activity may be overcome by increased extracellular L-arginine to ADMA ratio through excess substrate. So, supplementation with L-arginine may be able to restore the physiological status by normalizing the extracellular L-arginine to ADMA ratio. This implicates further therapeutic options for L-arginine supplementation for EH patients.

Limitations

There were several limitations of the present study. Many of the EH patients in our study received anti-hypertension drugs such as the vasodilatation drugs, which can influence the results. Furthermore, we did not assess the diastolic function of left ventricle, and it is conceivable that plasma ADMA is associated with left ventricular diastolic dysfunction. Blood pressure is also responsive to many factors such as alcohol assumption, smoking, diet and exercise, body mass index, air pollution, etc. which we did not analyze in this study.

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