

Arginine deficiency measured by global arginine bioavailability ratio in patients with acute coronary syndrome

Koji Miyazaki, MD¹⁾, Nobuyuki Masaki, MD²⁾ and Takeshi Adachi, MD¹⁾

Abstract:

Background: L-arginine and its related metabolites are associated with arginine bioavailability and subsequent nitric oxide production. The global L-arginine bioavailability ratio (GABR), defined as the ratio of the level of L-arginine to the sum of the levels of its major metabolites (L-arginine/[L-citrulline + L-ornithine]), has been reported as an index of arginine bioavailability. GABR in acute coronary syndrome (ACS) has not been fully investigated. **Methods and results:** The serum levels of L-arginine, L-citrulline, L-ornithine, asymmetric dimethylarginine (ADMA), and symmetric dimethylarginine (SDMA) were assessed in 134 patients who underwent coronary angiography. The patients were classified into the following three groups based on clinical presentation, electrocardiogram, and coronary angiogram: stable patients without coronary artery disease (CAD (-), n = 38), stable patients with CAD (CAD (+), n = 56), and patients with ACS (n = 40). The ACS patients included 13 with acute myocardial infarction and 27 with unstable angina pectoris. L-arginine and L-ornithine levels were not significantly different among the three groups, whereas L-citrulline levels were significantly increased in ACS patients (CAD (-): 135 ± 62 , CAD (+): 148 ± 68 , ACS: 174 ± 79 $\mu\text{mol/L}$; $p = 0.043$), resulting in a significant decrease in GABR (CAD (-): 0.51 ± 0.19 , CAD (+): 0.49 ± 0.17 , ACS: 0.39 ± 0.12 ; $p = 0.003$). **Conclusion:** Increased serum citrulline and decreased GABR were observed in patients with ACS, suggesting the presence of relative arginine deficiency in ACS.

Key words:

Global arginine bioavailability ratio, GABR, Acute coronary syndrome, L-arginine, L-citrulline

Introduction

Nitric oxide (NO) is an important regulator of vascular tone and homeostasis, and in normal arteries, it plays important roles in vasodilation and in inhibition of platelet aggregation, leukocyte adhesion, and smooth muscle cell proliferation. Decreased bioavailability of NO in endothelial cells causes endothelial dysfunction, resulting in hypertension, atherosclerosis, and cardiovascular disease¹⁾. Because NO is produced by nitric oxide synthase (NOS) using L-arginine as the sole substrate, decreased bioavailability of L-arginine causes decreased NO production and subsequent endothelial dysfunction²⁾.

L-arginine is obtained from endogenous synthesis and degradation of body protein in addition to the diet, and so serum L-arginine concentration is generally maintained at a

level high enough for NO production^{3,4)}. However, despite having normal serum levels of L-arginine, patients with hypertension, hyperlipidemia, or diabetes mellitus can have decreased L-arginine bioavailability and subsequent endothelial dysfunction, which can be alleviated by exogenously supplied L-arginine. This phenomenon is called the “arginine paradox”⁵⁾.

One of the causes of the arginine paradox may be the elevated level of asymmetric dimethylarginine (ADMA)⁵⁾. ADMA is an endogenous inhibitor of NOS and is generated from methylation of L-arginine residues of intracellular proteins by protein arginine N-methyltransferases and subsequent breakdown of the proteins⁶⁾. ADMA competes with L-arginine as a substrate of NOS, resulting in decreased L-arginine bioavailability and endothelial dysfunction. Another cause of the arginine paradox may be consumption of L-

1) Department of Cardiology, National Defense Medical College

2) Department of Intensive Care Medicine, National Defense Medical College

Corresponding author: Koji Miyazaki, MD, kmiyazaki@tsc.u-tokai.ac.jp

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arginine by increased activity of arginase^{7,8}). L-arginine is converted to NO and L-citrulline by NOS and to L-ornithine and urea by arginase. Because L-arginine is the common substrate for NOS and arginase, increased activity of arginase in endothelial cells may decrease the intracellular L-arginine level, limiting bioavailability of L-arginine and causing endothelial dysfunction.

The metabolites of L-arginine also affect arginine bioavailability. L-ornithine and L-arginine share the same plasma membrane transporter; therefore, in the setting of increased serum L-ornithine levels, L-ornithine competes for the transporter with L-arginine and limits the uptake of L-arginine by endothelial cells, resulting in decreased L-arginine bioavailability⁴).

The global L-arginine bioavailability ratio (GABR), defined as the ratio of the level of L-arginine to the sum of its major metabolite levels (L-arginine/[L-citrulline + L-ornithine]), has been reported as an index of arginine bioavailability in various clinical settings⁹⁻¹⁴), including stable coronary artery disease (CAD)^{15,16}). In acute coronary syndrome (ACS), GABR was reported to be lower in patients with cardiogenic shock due to acute myocardial infarction than in patients with stable CAD¹⁷). However, cardiogenic shock is reported to be associated with increased NO production¹⁸), which may alter GABR, so GABR in ACS has not been fully studied.

In this study, we measured serum levels of L-arginine, L-citrulline, and L-ornithine and then compared these values and GABR between patients with ACS and stable patients with or without CAD who underwent elective coronary angiography. Because ADMA can influence GABR through inhibition of NOS, ADMA concentration was simultaneously measured.

Methods

Patients

This study enrolled consecutive patients who underwent coronary angiography from November 2012 to November 2013 at the Department of Cardiology, National Defense Medical College (Tokorozawa, Japan). Patients undergoing hemodialysis, those receiving treatment for cancer, and those with infections, autoimmune disease, vasculitis, myocarditis, cardiomyopathy, congenital heart disease, pulmonary arterial hypertension, cardiac amyloidosis, or severe valvular heart disease were excluded from the study.

This study was approved by the Ethics Committee of National Defense Medical College (No. 1084) and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Coronary angiography and measurement of amino acids

Coronary angiography was performed using the 4Fr catheter system, and angiograms were obtained from 4 stan-

dard projections for each right and left coronary artery. Obstructive stenosis was defined as > 75% visual lumen narrowing. CAD was defined as the presence of coronary stenosis in at least 1 major coronary artery or its branches, or any clinical history of myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass surgery (CABG). Blood samples were collected through a guiding sheath during coronary angiography before intravenous heparin administration and immediately stored on ice. Serum was obtained by centrifugation at 3,000 rpm for 10 min at 4°C. Serum levels of hydroperoxides were measured as an index of oxidative stress using the reactive oxygen metabolites (d-ROMs) test¹⁹). Other serum aliquots were stored at -80°C until analysis. Serum levels of L-arginine, L-citrulline, L-ornithine, ADMA, and symmetric dimethylarginine (SDMA) were measured by high-performance liquid chromatography using a Shimadzu RF-20A system (Shimadzu Corp., Kyoto, Japan) with a Symmetry C18 column (3.9 × 150 mm, 5 µm particle size; Waters Corp., Milford, MA). The detection method was based on fluorescent derivatization with AccQ-Fluor™ reagent (Waters Corp.) according to previously described methods^{20,21}).

Patient classification

Patients were divided into three groups: the CAD (-) group included stable patients without coronary stenosis or history of coronary intervention; the CAD (+) group included stable patients with CAD; and the ACS group included patients with unstable angina pectoris (UAP) or with acute myocardial infarction (AMI). We diagnosed ACS according to American College of Cardiology/American Heart Association guidelines²²).

Coronary risk factors

Coronary risk factors were assessed using the following definitions. Hypertension was defined as blood pressure over 140/90 mmHg or prior diagnosis of hypertension with blood pressure-lowering medication. Diabetes mellitus was defined as fasting blood glucose > 126 mg/dL or use of insulin or oral hypoglycemic agents. Hyperlipidemia was defined as total cholesterol > 220 mg/dL, low-density lipoprotein (LDL) cholesterol > 140 mg/dL or prior diagnosis of hyperlipidemia with lipid-lowering medication. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation modified for the Japanese population^{23,24}).

Statistical analysis

Summary data are presented as the mean ± standard deviation with 95% confidence interval for parametric variables or the median (interquartile range) for non-parametric variables. The Kolmogorov-Smirnov test was used to identify distribution patterns. Cross-table analyses were performed using chi-squared test or Fisher's exact test when appropriate. Analysis of variance with the Bonferroni post-hoc test was used for comparisons among more than three

Table 1. Baseline characteristics

	CAD (-) (n=38)	CAD (+) (n=56)	ACS (n=40)	p-value
Age (years)	66 ±13	69 ±8	68 ± 8	0.253
Sex (women/men), n (%)	8/30 (21/79)	9/47 (16/84)	4/36 (10/90)	0.404
BMI (kg/m ²)	24 ± 4	23 ± 4	24 ± 3	0.625
Hypertension, n (%)	24 (63)	42 (75)	27 (68)	0.451
Hyperlipidemia, n (%)	19 (50)	39 (70)	25 (63)	0.156
Diabetes mellitus, n (%)	13 (34)	22 (39)	17 (43)	0.751
Current smoking, n (%)	13 (34)	16 (29)	16 (40)	0.503
<i>Previous condition</i>				
OMI, n (%)	0	16 (29)	10 (25)	0.002
CABG, n (%)	0	4 (7)	1 (3)	0.178
PCI, n (%)	0	27 (48)	10 (25)	<0.001
Atrial fibrillation, n (%)	7 (18)	0	0	0.001
<i>Coronary angiography and treatment</i>				
Syntax score	0 (0, 6)	15 (6, 23)	18 (11, 26)	<0.001
AMI, n (%)	0	0	13 (33)	<0.001
Revascularization, emergent, n (%)	0	0	20 (50)	<0.001
Revascularization, total, n (%)	0	14 (25)	38 (95)	<0.001
<i>Medication</i>				
Beta-blocker, n (%)	7 (18)	22 (39)	17 (43)	0.048
ACE inhibitor, n (%)	4 (11)	4 (7)	2 (5)	0.645
ARB, n (%)	11 (29)	34 (61)	16 (40)	0.007
Calcium channel blocker, n (%)	16 (42)	28 (50)	11 (28)	0.086
Furosemide, n (%)	5 (13)	5 (9)	2 (5)	0.451
Spironolactone, n (%)	1 (3)	2 (4)	1 (3)	0.944
Statins, n (%)	10 (26)	43 (77)	21 (53)	<0.001
Insulin, n (%)	3 (8)	4 (7)	2 (5)	0.866
Aspirin, n (%)	13 (34)	45 (80)	22 (55)	<0.001

Emergent revascularization indicates percutaneous or surgical coronary intervention subsequently performed after emergent coronary angiography. Total revascularization includes emergent and ad-hoc coronary interventions performed before discharge.

CAD: coronary artery disease, ACS: acute coronary syndrome, BMI: body mass index, OMI: old myocardial infarction, CABG: coronary artery bypass surgery, PCI: percutaneous coronary intervention, AMI: acute myocardial infarction, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker.

Significant p-values are shown in bold.

groups. Kruskal-Wallis test was employed for non-parametrical variables. Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL). A 2-sided p-value of less than 0.05 was considered statistically significant.

Results

Study population

A total of 134 patients including 40 with ACS were enrolled (**Table 1**). Among the 94 stable patients who underwent elective coronary angiography, 38 and 56 patients were included in the CAD (-) and CAD (+) groups, respectively. Atrial fibrillation was observed only in patients in the CAD (-) group. The CAD (+) group included 11 patients in whom no significant coronary stenosis remained at angiography. Fourteen patients in the CAD (+) group required coronary intervention; 12 and 2 patients underwent PCI and CABG, respectively. The ACS group comprised 13 patients with AMI and 27 patients with UAP. Among the 40 ACS patients, 20 underwent emergent revascularization on the

same day as coronary angiography (PCI 18, CABG 2), another 18 patients underwent coronary intervention during the same hospital admission (PCI 13, CABG 5), and the remaining 2 patients were treated with medication alone because their coronary stenosis was not suitable for intervention.

There were no differences in age or medical history of hypertension, hyperlipidemia, or diabetes mellitus among the groups. However, angiotensin receptor blockers, statins, and aspirin were used less frequently in the CAD (-) group. Laboratory examination revealed that the high-density lipoprotein cholesterol level was higher in CAD (-) patients compared with the other groups, whereas LDL cholesterol level was not different among the three groups (**Table 2**). Other measurements of coronary risk factors such as hemoglobin A_{1c}, eGFR, and brain natriuretic peptide did not show any significant differences among the groups.

Comparison of L-arginine and its related metabolites

Box plots of L-arginine metabolites are shown in **Figure 1**. There were no significant differences in serum L-arginine and L-ornithine levels between the groups (**Table 2, Figure**

Table 2. Amino acids and biomarkers

	CAD (-) (n=38)	CAD (+) (n=56)	ACS (n=40)	p-value
L-arginine (μmol/L)	88 ± 21	91 ± 21	86 ± 26	0.514
L-ornithine (μmol/L)	58 ± 31	63 ± 31	63 ± 31	0.657
L-citrulline (μmol/L)	135 ± 62	148 ± 68	174 ± 79*	0.043
L-homocysteine (μmol/L)	6.7 ± 4.6	6.1 ± 2.8	5.9 ± 2.2	0.976
L-cysteine (μmol/L)	179 ± 48	190 ± 57	173 ± 49	0.279
ADMA (μmol/L)	0.52 ± 0.15	0.57 ± 0.21	0.54 ± 0.20	0.435
SDMA (μmol/L)	0.73 ± 0.30	0.72 ± 0.34	0.72 ± 0.35	0.989
ADMA/SDMA	0.80 ± 0.30	0.86 ± 0.26	0.84 ± 0.33	0.639
L-arginine/ADMA	178 ± 67	173 ± 76	165 ± 76	0.714
L-arginine/L-citrulline	0.74 ± 0.28	0.70 ± 0.25	0.55 ± 0.19**	0.001
L-arginine/L-ornithine	1.94 ± 1.02	1.75 ± 0.81	1.68 ± 0.89	0.408
GABR	0.51 ± 0.19	0.49 ± 0.17	0.39 ± 0.12**	0.003
D-ROMs (U.CARR.)	356 ± 74	324 ± 80	323 ± 93	0.129
WBC (μL)	5626 ± 1435	6144 ± 1499	7517 ± 2540**	<0.001
Hb (mg/dL)	13.5 ± 1.7	13.4 ± 1.6	13.8 ± 1.9	0.590
LDL cholesterol (mg/dL)	109 ± 30	99 ± 26	103 ± 31	0.231
TG (mg/dL)	118 (80, 181)	114 (88, 175)	98 (81, 168)	0.760
HDL cholesterol (mg/dL)	60 ± 21 [#]	50 ± 12	49 ± 13	0.001
HbA _{1c} (mg/dL)	6.1 ± 1.6	6.0 ± 1.1	6.0 ± 0.8	0.722
Uric acid (mg/dL)	5.7 ± 1.6	6.1 ± 1.7	6.0 ± 1.5	0.381
CPK (mg/dL)	85 (67, 124)	101 (58, 152)	118 (69, 197)	0.254
eGFR (mL/min)	71 ± 23	62 ± 18	65 ± 17	0.074
CRP (mg/dL)	0.3 (0.3, 0.6)	0.3 (0.3, 0.3)	0.3 (0.3, 0.4)	0.702
Log ₁₀ BNP	1.58 ± 0.67	1.59 ± 0.56	1.67 ± 0.60	0.777

CAD: coronary artery disease, ACS: acute coronary syndrome, ADMA: asymmetric dimethylarginine, SDMA: symmetric dimethylarginine, D-ROMs: derivatives of the reactive oxidative metabolites, LDL: low-density lipoprotein, TG: triglyceride, HDL: high-density lipoprotein, HbA_{1c}: hemoglobin A_{1c}, CPK: creatine phosphokinase, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, BNP: brain natriuretic peptide, Log₁₀BNP: log-transformed brain natriuretic peptide (pg/ml).

Significant p-values are shown in bold.

*: p<0.05 vs CAD (-), **: p<0.05 vs CAD (-) and CAD (+), #: p<0.05 vs CAD (+) and ACS in Bonferroni's post-hoc test.

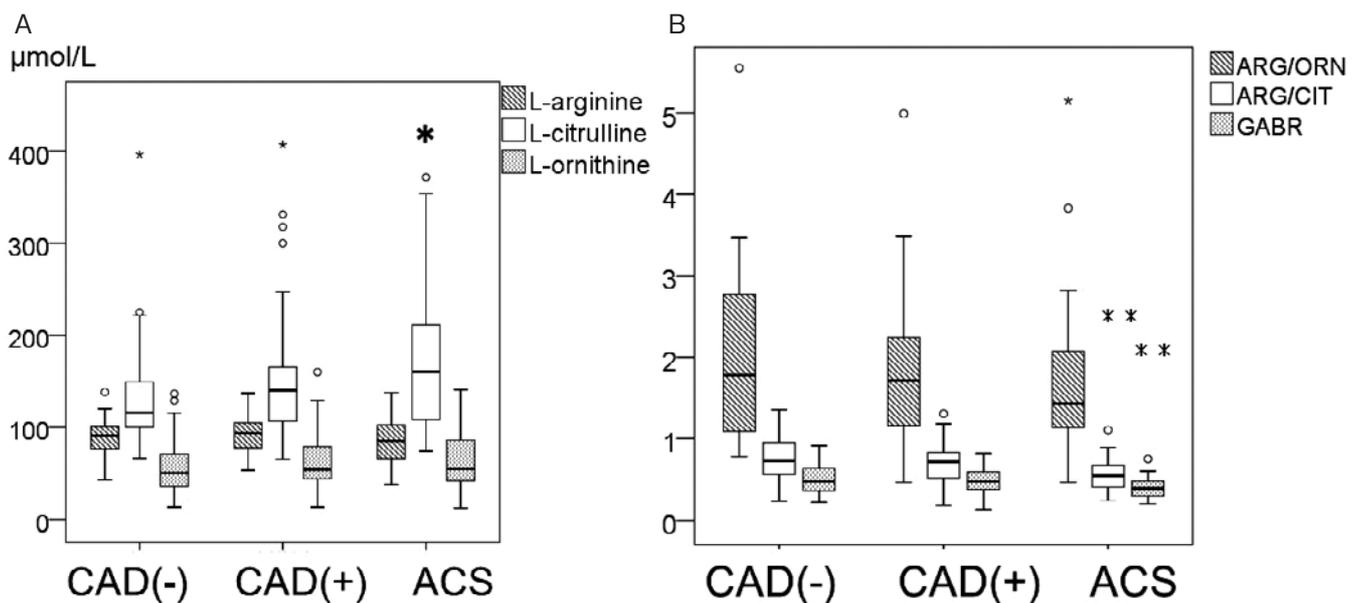


Figure 1. L-arginine and its metabolites

A: Serum concentrations of L-arginine, L-citrulline, and L-ornithine, B: GABR and L-arginine to L-citrulline ratio.

CAD: coronary artery disease, ACS: acute coronary syndrome, ARG: L-arginine, CIT: L-citrulline, ORN: L-ornithine, GABR: global L-arginine bioavailability ratio (defined as L-arginine/[L-ornithine+L-citrulline]).

*: p<0.05 vs CAD (-), **: p<0.05 vs CAD (-) and CAD (+).

1A), whereas serum L-citrulline levels were increased in the ACS group. The levels of ADMA, SDMA, and d-ROMs were not significantly different among the groups (**Table 2**). The ratio of L-arginine to L-citrulline and GABR were lowest in the ACS group (**Figure 1B**). In the ACS group, there were no differences between AMI (n = 13) and UAP (n = 27) in GABR (AMI: 0.38 ± 0.12 , UAP: 0.40 ± 0.13 ; $p = 0.724$), L-arginine to L-citrulline ratio (AMI: 0.51 ± 0.19 , UAP: 0.57 ± 0.19 ; $p = 0.348$), or L-arginine to L-ornithine ratio (AMI: 1.94 ± 1.09 , UAP: 1.55 ± 0.76 ; $p = 0.196$).

Discussion

The major findings of this study are as follows. In patients with ACS, GABR was significantly decreased compared with stable patients with or without CAD, suggesting the presence of decreased arginine bioavailability in patients with ACS. Reduced GABR was due to the elevated serum level of L-citrulline with no change in serum level of L-arginine, which could be explained by relative L-arginine deficiency due to increased NO production. The serum levels of L-ornithine and ADMA and the L-arginine to L-ornithine ratio were not significantly different among the three groups.

Although the source of increased serum L-citrulline in patients with ACS observed in this study is unknown, one possibility is that it could in part be caused by increased production of NO by inducible NOS (iNOS) due to systemic inflammation in ACS. ACS is known to be accompanied by a systemic inflammatory response, as indicated by increased circulating levels of inflammatory markers such as high-sensitivity C-reactive protein (CRP), interleukin-6, and tumor necrosis factor α^{25-27} . Systemic inflammation induces iNOS expression in various types of cells and augments NO production. Sánchez de Miguel et al reported higher protein expression levels of iNOS and increased NO production in neutrophils from patients with ACS compared with those from healthy donors²⁸. They measured accumulation of tritium-labeled citrulline in tritium-labeled arginine-loaded neutrophils as a marker of NO production and showed that the amount of tritium-labeled citrulline accumulated in neutrophils from patients with ACS was significantly higher than in neutrophils from healthy donors. In our study, the increased white blood cell counts in patients with ACS suggested the presence of systemic inflammation, so the possibility that increased serum levels of L-citrulline could be derived from increased production of L-citrulline by iNOS induced by systemic inflammation in the setting of ACS cannot be excluded.

Among the stable patients who underwent coronary angiography in the present study, GABR was not different between those with and without CAD, which may be due to similar prevalence of coronary risk factors such as diabetes mellitus. There have been two reports regarding GABR in patients with stable CAD^{15,16}. Tang et al measured plasma levels of L-arginine and its related metabolites in 1010 con-

secutive patients who underwent coronary angiography¹⁵. They found lower plasma L-arginine, higher plasma L-ornithine and L-citrulline, and lower GABR in patients with compared to those without obstructive CAD. After adjusting for Framingham risk score, CRP, and creatinine clearance, high levels of L-ornithine and L-citrulline and low GABR, but not low L-arginine levels, remained significantly associated with obstructive CAD. Only high L-citrulline level and low GABR were associated with subsequent risk of major adverse cardiovascular events (MACE) over 3 years. Sourij et al measured GABR in 2236 patients who underwent coronary angiography and reported that decreased GABR was associated with increased cardiovascular mortality during 7.7 years of follow-up¹⁶, which was consistent with the findings of Tang et al¹⁵. As for the association between GABR and prevalence of obstructive CAD, however, the results of Sourij et al¹⁶ were not consistent with those of Tang et al. In their analysis, although GABR was associated with the prevalence of obstructive CAD in the crude logistic model, this association was no longer significant after adjustment for the presence of diabetes mellitus. In the present study, the prevalence of diabetes mellitus was not significantly different between patients with and without obstructive CAD, and GABR was not associated with the presence of obstructive CAD, which is consistent with the results of Sourij et al¹⁶.

ADMA is an endogenous inhibitor of NOS, and its serum level is reported to be increased in patients with stable CAD or with ACS²⁹, which is also associated with subsequent incidence of cardiovascular events³⁰. In this study, however, serum levels of ADMA were not different between the three groups. Increased serum ADMA level causes endothelial dysfunction and was reported to be associated with increased risk of cardiovascular events in a broad range of patients, including stable patients with or without CAD and in patients with ACS, as well as in healthy individuals³⁰. However, whether increased serum ADMA level is an independent predictor of the presence of CAD remains controversial. Wang et al measured plasma ADMA levels in 1011 consecutive patients who underwent elective coronary angiography, and reported that after adjusting for Framingham risk score, CRP, and creatinine clearance, plasma ADMA level was no longer associated with prevalence of obstructive CAD, although it remained an independent predictor of incident MACE³¹. Xuan et al performed a meta-analysis of 16 case-control studies, which included 4713 participants in 20 cohorts. They found that 12 cohorts demonstrated a positive association and the remaining 8 cohorts a negative association between ADMA and the risk of CAD, and overall, it was concluded that ADMA level is significantly increased in patients with CAD compared with healthy controls²⁹. However, Wang et al noted that they could not adjust for several confounding factors such as smoking, age, and sex, which could have overestimated the association between ADMA and CAD. The serum ADMA level is reported to be increased by oxidative stress in the presence of coronary risk

factors such as hypertension, hyperlipidemia, diabetes mellitus, and smoking. In the present study, the prevalence of these risk factors was not significantly different among the three groups. The levels of oxidative stress measured by d-ROMs test were also not different, which was consistent with unchanged ADMA levels among the three groups. In patients with coronary risk factors, endothelial dysfunction of the coronary artery indicated by vasoconstrictive response to intracoronary acetylcholine infusion preceded the development of atherosclerosis detectable by intracoronary ultrasound imaging, suggesting that endothelial dysfunction may have a role in the initiation of atherosclerosis³². Because decreased GABR or elevated serum ADMA levels are causes of endothelial dysfunction, they may be useful predictors of initiation and progression of atherosclerosis rather than markers of the presence of atherosclerosis.

Study limitations and clinical implications

In this study, blood samples were collected through a guiding sheath during coronary angiography, so in cases of acute coronary syndrome blood samples were obtained in the emergency setting and patients were not always fasted, which means that measured values were influenced by a meal. Plasma arginine is reported to exhibit a postprandial increase with a peak concentration approximately 3 h after the meal³³. This effect of a meal could cause overestimation and blunt the decrease in arginine level in patients with acute coronary syndrome. However, the increased L-citrulline levels in patients with acute coronary syndrome was not explained by the effect of a meal alone. Pharmacokinetic analysis showed that oral ingestion of L-citrulline increased its serum level with a peak within 1 h after ingestion. It has been reported that after entering the circulation, L-citrulline is rapidly converted to L-arginine and L-ornithine within 1 h, which increased both L-arginine and L-ornithine levels in proportion to the increase in L-citrulline levels³⁴. In the present study, serum L-citrulline level increased without a significant increase in either L-arginine or L-ornithine levels, resulting in decreased GABR in patients with acute coronary syndrome. The decreased GABR was attributed to decreased arginine bioavailability rather than the effect of a meal, because neither L-arginine nor L-ornithine levels were changed. To confirm this, however, further study is needed to clarify the effect of a meal on GABR.

In addition to the effect of a meal, circadian variation should be considered. The existence of cardiovascular circadian rhythms is well known. Endothelial function measured by endothelium-dependent flow-mediated vasodilation in brachial arteries (FMD) has been reported to show diurnal variation with a significant attenuation in the morning³⁵. It is speculated that serum concentration of arginine and its related metabolites may also show diurnal variation. Plasma arginine levels were reported to show circadian variation with an arginine-free diet. Plasma L-arginine concentration was relatively high in the morning, decreased during the

awake period, and returned to its baseline level overnight³³. To our knowledge, there have been no reports about circadian variation of GABR. Only one paper suggested that serum ADMA concentration has diurnal variation with a morning peak³⁶, which is the opposite pattern to that of endothelial function. In the present study, time of day of blood sampling varied depending on the schedule of coronary angiography, which could obscure the differences in GABR and ADMA values between patients with or without CAD because of diurnal variation. To use GABR or ADMA as markers of coronary risk, circadian variation of these values must be clarified.

In this study, levels of arginine and its metabolites were measured at the whole-body level and their intracellular levels were unknown. Thus, it is not clear whether the increased serum L-citrulline level observed in patients with ACS was derived from increased production of L-citrulline within NO-producing cells, such as endothelial cells, macrophages, and neutrophils. Although production of NO and L-citrulline are reported to be increased in neutrophils from patients with ACS, it is also unclear whether increased intracellular L-citrulline causes elevation of circulating L-citrulline, because intracellular citrulline is recycled to arginine for NO synthesis within the cell. Further study is needed to identify the source of increased serum citrulline observed in this study in patients with ACS.

To predict arginine bioavailability, which is one of the major determinants of endothelial function, we measured GABR but did not measure endothelial function as FMD or vasomotor responses to acetylcholine in coronary arteries. Therefore, the association between GABR and endothelial function has not been validated in this study. If decreased GABR is confirmed to be an index of endothelial dysfunction in ACS, those patients who will benefit from arginine supplementation could be identified. Although a previous study demonstrated that arginine supplementation in patients with acute myocardial infarction was not beneficial³⁷, supplementation may be beneficial for such patients with low GABR.

Conclusion

In conclusion, increased serum levels of L-citrulline and decreased GABR were observed in patients with ACS, suggesting the presence of relative arginine deficiency in ACS.

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Conflicts of Interest

None.

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