Asymmetric dimethylarginine levels in patients with coronary artery ectasia

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Abstract

Background: Endothelial dysfunction might be one of the pathophysiological mechanisms in the development of coronary artery ectasia (CAE) although the exact mechanisms have not yet been demonstrated. Asymmetric dimethylarginine (ADMA), an endogenous competitive inhibitor of nitric oxide synthase, is also related to endothelial and structural dysfunction.

Aim: To asses the relationship between CAE and ADMA plasma concentrations.

Methods: Thirty patients with CAE in a mean age of 55.5 ± 3.6 years and 40 patients with normal coronary arteries in a mean age of 53.3 ± 11.6 years were studied. The ADMA levels of all patients were analysed by ELISA method.

Results: The mean ADMA level in the CAE group was found to be significantly higher than the mean ADMA level in the normal coronary artery group (2.26 ± 0.47 vs. 1.43 ± 0.40 µmol/l, $p < 0.001$). The elevated ADMA level (> 1.80 µmol/l) was present in 83.0% of patients from the CAE group and 25.0% of patients from the normal coronary artery group ($p < 0.001$). Having an increased ADMA level enhanced the risk of CAE 15-fold. The multiple-adjusted OR of the risk of CAE was 18.71 (95% CI 4.95-70.68) for the higher ADMA level compared to the lower level.

Conclusion: Asymmetric dimethylarginine level is significantly associated with the presence of coronary artery ectasia. These findings suggest that increased ADMA level may be associated with endothelial dysfunction leading to the development of coronary artery ectasia.

Keywords: asymmetric dimethylarginine, coronary artery ectasia, endothelial dysfunction

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Introduction

Coronary artery ectasia (CAE), an abnormality of the coronary anatomy, consists of localised and/or diffuse dilatation without a stenotic lesion exceeding 1.5 times the normal portion of the artery. Coronary artery ectasia is a relatively rare abnormality with the prevalence ranging from 1.2% to 4.9% in several angiographic series [1-3]. There is no consensus about the aetiology, prognosis, morbidity, and mortality related to this abnormality, although several studies have been performed. Congenital, inflammatory, and connective tissue disorders have been suggested as possible aetiologies, but atherosclerosis is the main causative entity in the majority of cases [2, 4, 5]. Clinically, there is a male preponderance, with a male to female ratio of 3 : 1 [1, 6, 7].

Although the whole spectrum of acute coronary syndrome might be seen in patients with CAE, the most commonly encountered symptom is chest pain. Selective coronary angiography seems to be the gold standard for the diagnosis of ectasia, providing information about the possible size, shape, location and number of dilatations.

L-arginine, a semi-essential basic amino acid, is involved in many physiological processes including protein synthesis, urea cycle, and synthesis of nitric oxide (NO). Nitric oxide synthesis from L-arginine is catalysed by NO synthase and is inhibited by endogenous methylated L-arginine analogues such as asymmetric dimethylarginine (ADMA). The ADMA is an endogenous competitive inhibitor of NO synthase. The ADMA competes with L-arginine. Therefore, NO levels decrease with increased ADMA levels.

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The main enzyme responsible for the metabolism and inactivation of ADMA is dimethylarginine dimethylaminohydrolase, which hydrolyses ADMA to dimethylamine and L-citrulline [8]. Recently, ADMA has been demonstrated to be a new and potentially independent marker of atherosclerosis and related cardiovascular disorders [9-11].

To the best of our knowledge, no previous study has examined the association between CAE and ADMA levels. Therefore, the aim of the present study was to assess serum ADMA concentrations in subjects with CAE, compared with well-matched healthy controls.

Methods

Study population

This study is a cross-sectional study. A total of 2245 consecutive selective coronary angiograms were evaluated. Among them, 70 subjects (57 men; 13 women; mean age 54.2 ± 9.1 years; range 35-76 years) were included in the study. All patients underwent treadmill testing with Bruce protocol. A fasting peripheral venous blood samples from all patients were obtained before entering the study. According to the results of coronary angiograms, patients were divided into two groups: CAE and normal coronary artery (controls) groups. The CAE group consisted of 30 subjects (25 men; 5 women; mean age 55.5 ± 3.6 years) whereas the control group comprised 40 subjects (32 men, 8 women; mean age 53.3 ± 11.6 years). Hypertension was defined as blood pressure ≥ 140/90 mmHg or being on treatment, and diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dl on two occasions or being on treatment. All patients were surveyed for any cardiovascular drug use and smoking habit, and underwent transthoracic echocardiography for left ventricular ejection fraction (LVEF) assessment. Vital signs of each patient were also recorded during the study.

Exclusion criteria included the following: refusal to participate in the study; known coronary artery disease; LV dysfunction (LVEF < 50%) and hypertrophy; unstable ischaemic conditions (unstable angina pectoris and myocardial infarction); valvular heart disease; cardiac rhythm other than sinus; metabolic syndrome; renal or hepatic dysfunction (creatinine > 1.2 mg/dl, AST and ALT more than twice the upper limit of normal, respectively); systemic diseases; and detection of coronary atherosclerotic lesion and/or coronary slow flow (CSF) after selective coronary artery angiography. The Institutional Ethics Committee approved the study protocol and all patients gave informed consent to participate in the study.

Cardiac catheterisation

All patients in the study underwent selective coronary artery angiography after appropriate patient preparation. Femoral artery and sometimes radial or brachial artery cannulation was used for the arterial access site and a Judkins system was applied for cannulation of the left and right coronary arteries. All angiograms were evaluated by two experienced physicians blinded to the study. Angiograms without stenotic lesions in any major epicardial coronary arteries including LM, LAD, LCX and RCA were considered normal angiograms. Angiograms with localised and/or diffuse dilatation without a stenotic lesion exceeding 1.5 times the normal segment of the artery were diagnosed as CAE. Ectasia diameter was calculated by quantitative angiography on digital angiograms (Vepro, Medimage, The Image Managing System, Pfungstadt, Germany). In addition, CSF was investigated by using the TIMI frame count method described by Gibson et al. Previously published normal TIMI frame counts were 21.1 ± 1.5 frames for LAD (after correction), 22.2 ± 4.1 frames for LCX, and 20.4 ± 3.0 frames for RCA [12]. For a given artery, any value above this published range was considered as CSF and accepted as an exclusion criterion. The CAE classification, previously described by Markis et al., was used in the study [1].

Laboratory data

Fasting peripheral venous blood samples were obtained for the measurement of fasting plasma glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, fibrinogen levels, and complete blood count including haemoglobin, haematocrit, platelet count, and mean platelet volume (MPV) (22 parameters). Blood samples were centrifuged and plasma was obtained. Fasting blood glucose, total cholesterol, HDL cholesterol and triglyceride levels were measured enzymatically by the auto-analyser (Hitachi 911, Japan). Plasma glucose was measured with the glucose oxidase technique. Measurement of LDL cholesterol level was done through application of a formula as described by Friedewald et al. [13].

Measurement of ADMA

Collected blood samples for the measurement of ADMA concentration were centrifuged for 10 min at 2000 g at 4°C and stored at –75°C until analysis. The ADMA levels were analysed using an ADMA direct enzyme linked immunosorbent assay kit (Immundiagnostik AG, Bensheim, Germany). The analytic sensitivity of the test was 0.05 µmol/l. The ELISA method has been validated and compared with the gas chromatography-mass spectrometry method and liquid chromatography-mass spectrometry/mass spectrometry method in various experimental studies. Linear regression analysis across the relevant concentration ranges showed the ELISA method to correlate well with both the gas chromatography-mass spectrometry and the liquid chromatography-mass spectrometry/mass spectrometry methods [14-16].

Anthropometric measurement

Height and weight of patients were measured and body mass index (BMI) was calculated by dividing weight

in kilograms by height in metres squared and described as kg/m^2.

Statistical analysis

Data were analysed with the software SPSS version 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables are presented as mean ± SD and categorical variables as frequency and percentage. Student's t-test was used to compare normally distributed continuous variables and the Mann-Whitney U test for variables without normal distribution. The χ^2 test was used to compare categorical variables. Any correlation between ADMA and clinical, anthropometric, blood pressure, and laboratory measurements was analysed by linear regression. In addition, multiple logistic regression analysis was used to evaluate the independent associates of CAE. The odds ratios (OR) and 95% confidence intervals (CI) were calculated. A two-tailed p-value of < 0.05 was considered significant.

Table I. Baseline demographic, clinical, and laboratory characteristics of the study population

	CAE group (n = 30)	Control group (n = 40)	p
Age [years]	55.5 ± 3.6	53.3 ± 11.6	0.308
Male gender, n (%)	25 (83)	32 (80)	0.723
Hypertension, n (%)	15 (50)	15 (38)	0.296
Smoking habit, n (%)	12 (40)	15 (38)	0.832
Diabetes, n (%)	3 (10)	5 (13)	0.745
Family history of CAD, n (%)	14 (47)	10 (25)	0.059
Hyperlipidaemia, n (%)	10 (33)	15 (38)	0.719
Body mass index [kg/m^2]	27.3 ± 3.7	28.1 ± 4.9	0.498
ASA use, n (%)	9 (30)	6 (15)	0.130
Beta blocker use, n (%)	10 (33)	7 (18)	0.126
ACE-I use, n (%)	7 (23)	5 (13)	0.234
ARB use, n (%)	5 (17)	5 (13)	0.622
Statin use, n (%)	5 (17)	10 (25)	0.400
Fasting plasma glucose [mg/dl]	93 ± 10	95 ± 11	0.557
Cholesterol [mg/dl]			
total	188 ± 54	199 ± 19	0.237
LDL	107 ± 38	110 ± 23	0.627
HDL	47 ± 10	45 ± 12	0.333
Triglycerides [mg/dl]	186 ± 115	229 ± 111	0.123
Fibrinogen [mg/dl]	3.90 ± 0.01	3.67 ± 0.74	0.496
Haemoglobin [g/dl]	15.2 ± 0.9	14.4 ± 2.1	0.148
Haematocrit [%]	45.6 ± 2.2	42.9 ± 6.1	0.102
Platelets [/mm^3]	282667 ± 10189	260625 ± 57305	0.147
MPV [fl]	8.7 ± 0.4	8.5 ± 1.9	0.644
LVEF [%]	62.3 ± 2.1	62.7 ± 3.2	0.555
Heart rate [bpm]	81 ± 7	78 ± 10	0.248
Blood pressure [mmHg]			
systolic	122 ± 21	124 ± 21	0.669
diastolic	83 ± 11	80 ± 5	0.188
mean	96 ± 14	95 ± 10	0.718
pulse	39 ± 12	45 ± 17	0.167
Ectasia diameter [mm]	5.18 ± 0.77	-	-

Abbreviations: ACE-I – angiotensin-converting enzyme inhibitor, ARB – angiotensin II receptor blocker, ASA – acetylsalicylic acid, CAD – coronary artery disease, CAE – coronary artery ectasia, HDL – high--density lipoprotein, LDL – low-density lipoprotein, LVEF – left ventricular ejection fraction, MPV – mean platelet volume, NCA – normal coronary artery

Results

Baseline characteristics

Baseline demographic, clinical, and laboratory characteristics of patients in both groups are outlined in Table I. In the CAE group 83% of patients were male, with a mean age of 55.2 ± 3.9 years, and 17% were female, with a mean age of 57.0 ± 0.1 years. In the control group 80% of patients were male and 20% were female with a mean age of 53.4 ± 11.7 and 52.8 ± 11.9 years, respectively. There were no significant differences between the two groups concerning age, sex and other cardiovascular risk factors including hypertension, diabetes, hyperlipidaemia, and smoking. However, the prevalence of family history of CAD tended to be higher in the CAE group (p = 0.059). In addition, the two groups did not significantly differ in BMI, fasting plasma glucose, total, HDL and LDL cholesterol, triglyceride, fibrinogen, haemoglobin and haematocrit levels, platelet count, mean platelet volume, LVEF, cardiovascular drug use, and haemodynamical parameters.

ADMA levels

The mean ADMA level was significantly higher in the CAE group compared with controls (2.26 ± 0.47 vs. 1.43 ± 0.40 µmol/l, p < 0.001).

Distribution of the ectasia type is shown in Table II. Type 4 CAE was the most commonly seen type in our study (37%).

In multivariate logistic regression analysis, no significant association was found between CAE and coronary artery disease risk factors including age, gender, hypertension, diabetes, hyperlipidaemia, family history of CAD, cigarette smoking, and BMI.

The mean ADMA level showed a significant positive correlation with age, total cholesterol, triglyceride, fibrinogen levels, heart rate, and diastolic blood pressure (Table III). No significant correlation was detected between mean ADMA concentration and BMI, fasting plasma glucose, LDL cholesterol, HDL cholesterol, haemoglobin, haematocrit, platelet count, MPV, LVEF, and systolic, mean, and pulse pressure measurements (Table III).

No significant correlation was also detected between mean ADMA level and ectasia diameter in the CAE group (β = 0.053, r^2 = 0.003, and p = 0.803).

There was no significant effect of gender on the ADMA level–CAE relationship in our study: women – 2.06 ± 0.45 µmol/l; men – 2.33 ± 0.47 µmol/l, p = 0.243.

According to BMI, neither in the control group nor in the control group were there any significant correlations between BMI and ADMA level (R = 0.182 and p = 0.260; R = 0.143 and p = 0.450 in the control and CAE groups, respectively).

A cut-off point of 1.80 µmol/l was used for increased ADMA concentration. Higher ADMA level was significantly associated with the risk of CAE such that 83.0% of patients in the CAE group had higher ADMA, whereas 25.0% of patients in the control group had increased ADMA (p < 0.001). Having elevated ADMA (> 1.80 µmol/l) increased the risk of CAE 15-fold (95% CI 4.53-49.68). After adjustment for age, gender, BMI, the presence of hypertension, diabetes mellitus, and smoking, serum levels of total, LDL and HDL cholesterol, triglycerides, fasting plasma glucose, fibrinogen, and current use of cardiovascular drugs, the multiple-adjusted OR of the risk of CAE was 18.71 (95% CI 4.95-70.68) for the increased ADMA level compared to the lower level (Figure 1).

The mean ADMA levels in each type of CAE group were similar (differences NS) (Figure 2).

Discussion

In our study, we found for the first time that patients with CAE had significantly increased ADMA levels compared to control subjects. In addition, this association was independent of risk factors for coronary artery disease.

The endothelium of the vascular tissue has many functions for the continuation of normal vascular physiology. The endothelium plays a key role in maintaining vascular homeostasis through balancing endothelial-derived relaxing and contracting factors, growth, thrombogenicity, and inflammation. The role of the endothelium in controlling the vascular tone, especially vasodilatation, has been shown via the endothelial-derived relaxing factor, which was later identified as NO [17, 18]. Endothelial dysfunction occurs when NO activity in the vascular tissue is decreased, resulting in decreased endothelium-dependent vasodilatation. Thus, decreased NO activity might result in vasoconstriction, smooth muscle cell proliferation, platelet adhesion and aggregation [19, 20]. Endogenous ADMA is assumed to be a key regulator of NO synthase activity, notably of the endothelial NO synthase isoform.

Recently, ADMA has emerged as a critically significant and powerful biochemical marker in basic and clinical sciences. Plasma, serum, and urine are the most relevant biological systems for measuring ADMA. Plasma ADMA concentration decreases from birth until about the second decade of life. After this, ADMA plasma concentration increases [21]. We have also demonstrated a positive relationship between ADMA level and age. Several drugs have been reported to be able to decrease plasma ADMA

Table II. Distribution of ectasia type

Ectasia type	Frequency, n (%)
Type 1	6 (20)
Type 2	9 (30)
Type 3	4 (13)
Type 4	11 (37)

Abbreviations: Type 1 – diffuse ectasia of two or three vessels, Type 2 – diffuse ectasia in one vessel and localised in another, Type 3 – diffuse ectasia of a single vessel, Type 4 – localised or segmental ectasia [1]

Table III. Correlation between mean ADMA level and clinical, anthropometric, blood pressure, and laboratory measurements

	Mean ADMA	
	R	p
Age	0.249	0.038
Body mass index	0.099	0.416
Fasting plasma glucose	0.268	0.060
Total cholesterol	0.303	0.011
LDL cholesterol	0.129	0.288
HDL cholesterol	0.047	0.701
Triglyceride	0.285	0.017
Fibrinogen	0.760	<0.001
Haemoglobin	0.058	0.677
Haematocrit	0.085	0.536
Platelets	0.112	0.416
MPV	0.124	0.368
LVEF	0.121	0.318
Heart rate	0.359	0.010
Systolic blood pressure	0.053	0.717
Diastolic blood pressure	0.289	0.042
Mean blood pressure	0.104	0.472
Pulse pressure	0.242	0.090

Abbreviations: as in Table I

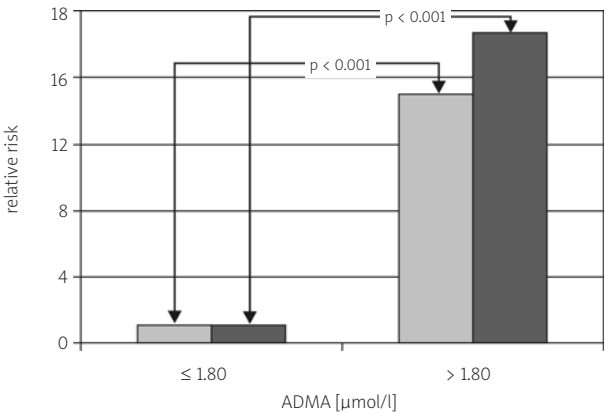

Figure 1. Relative risk of CAE using the cut-off value of 1.80 µmol/l of ADMA. The control group comprised subjects with an ADMA level ≤ 1.80 µmol/l. Dark bars indicate the results of multivariate analysis and grey bars indicate the results of univariate analysis

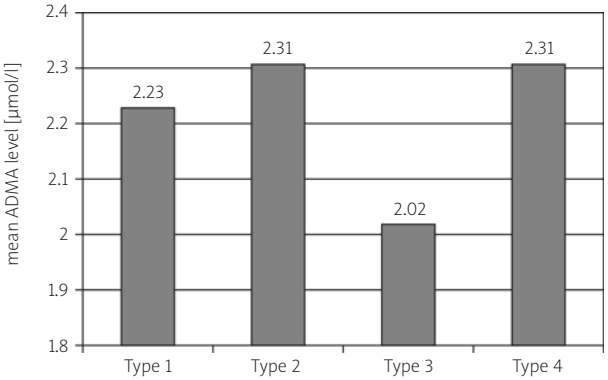

Figure 2. Distribution of mean ADMA levels in four types of CAE

Abbreviations: as in Table II

concentrations, such as angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, aspirin, and statins [22], however, in our study the usage of these agents was similar in the CAE and control groups.

Recently, an ADMA-endothelial dysfunction relationship has been reported [23, 24]. Evidence for a causal association between increased ADMA concentration and endothelial dysfunction has been found in hypercholesterolaemic subjects. In these subjects, increased ADMA levels were inversely correlated with endothelium-dependent vasodilatation in the forearm [23, 24]. However, there was no significant difference between the groups concerning hyperlipidaemia and cholesterol levels in our study, although a positive relation was demonstrated between total cholesterol/triglyceride and ADMA levels.

Asymmetric dimethylarginine may also affect vascular structure as well as vascular endothelial reactivity. In an animal model, it has been shown that the intracellular concentrations of ADMA were directly related to intimal thickness of the injured vessel [25]. In contrast to the study performed by Sen et al., MPV values have not been found to be higher in our patients with CAE compared to controls [26]. Also, no gender or BMI effects on ADMA levels have been demonstrated in our study population.

Although endothelial dysfunction and atherosclerosis have been considered as the possible pathophysiological mechanisms for ectasia formation, the exact mechanism has not yet been discovered. In our study, we found no significant correlation between ADMA level and ectasia diameter, suggesting that increased ADMA concentrations are related to the presence of CAE and endothelial dysfunction rather than the severity and extent of ectasia. Previously, coronary blood flow has been shown to be reduced in patients with CAE using the TIMI frame count method, indicating endothelial dysfunction as the possible underlying pathophysiological mechanism [27, 28]. However, CSF was an exclusion criterion in our study. Coronary artery ectasia is not a benign condition considering its potential to cause ischaemia as well as acute coronary events due to coronary spasm, slow flow, and thrombus formation, all of which have been related to coronary endothelial dysfunction.

Limitations of the study

Although fluctuations of the L-arginine/ADMA ratio reflect changes in L-arginine rather than in the ADMA plasma concentrations, this ratio could be studied to obtain further data. Other limitations of this study were the small patient sample size and lack of long-term follow-up data. Since contrast angiography is a type of lumenography, diffusely diseased coronary arteries might not be detected properly, resulting in underestimation of lesions and overestimation of angiographically normal coronary arteries.

Conclusion

Our data suggest that high levels of ADMA are present in patients with CAE compared to patients with normal coronary arteries, supporting the hypothesis that ADMA might participate in the process of coronary ectasia development via endothelial and structural dysfunction. Prospective studies with large sample sizes using multivariate survival analysis are needed for prognostic evaluation of increased ADMA levels in patients with CAE during long-term follow-up.

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Stężenie asymetrycznej dwumetyloargininy u chorych z tętniakami tętnic wieńcowych

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Streszczenie

Wstęp: Zaburzenia funkcji śródbłonka mogą leżeć u podłoża powstawania tętniaków tętnic wieńcowych, choć dokładny mechanizm tego zjawiska nie został dotąd poznany. Asymetryczna dwumetyloarginina (ADMA), endogenny inhibitor syntazy tlenku azotu, jest związana z dysfunkcją śródbłonka.

Cel: Ocena stężenia ADMA u chorych z tętniakami tętnic wieńcowych i bez nich.

Metody: Do badania włączono 30 chorych (25 mężczyzn, wiek 55,5 ± 3,6 roku) z tętniakami tętnic wieńcowych. Grupę kontrolną stanowiło 40 osób (32 mężczyzn, wiek 53,3 ± 11,6 roku) z prawidłowymi tętnicami wieńcowymi. Stężenie ADMA badano przy użyciu testu ELISA.

Wyniki: Stężenie ADMA było statystycznie istotnie wyższe w grupie badanej niż w grupie kontrolnej (odpowiednio: 2,26 ± 0,47 *vs* 1,43 ± 0,40 μmol/l, $p < 0,001$). Określono punkt odcięcia 1,80 μmol/l, którego poziom wskazywał na 15 razy zwiększone ryzyko powstania tętniaków tętnic wieńcowych (OR 18,71, 95% CI 4,95–70,68). Podwyższone stężenie ADMA (> 1,80 μmol/l) stwierdzono u 83% chorych w grupie badanej i 25% osób w grupie kontrolnej.

Wnioski: Stężenie ADMA jest podwyższone u chorych z tętniakami tętnic wieńcowych. Wskazuje to na możliwość istnienia związku tak określonej dysfunkcji śródbłonka z powstawaniem tętniaków tętnic wieńcowych.

Słowa kluczowe: asymetryczna dwumetyloarginina, tętniaki tętnic wieńcowych, dysfunkcja śródbłonka

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