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Letter to the Editor

Methylated arginines in stable and acute patients with coronary artery disease before and after percutaneous revascularization

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Abstract

Background: Impairment of the nitric oxide synthase (NOS) pathway independently predicts cardiovascular events. We investigated whether plasma levels of the NOS inhibitor asymmetric dimethylarginine (ADMA), of symmetric dimethylarginine (SDMA) and of the nitrogen oxide substrate L-arginine can serve as additional staging biomarkers in stable coronary artery disease, non-ST-segment myocardial infarction (NSTEMI) and ST-segment myocardial infarction (STEMI).
Materials and methods: Consecutive patients referred for percutaneous coronary intervention (PCI) were studied. Peripheral blood samples were drawn immediately before, immediately after and 24 h following PCI and analyzed by means of high-performance liquid chromatography.
Results: Seventy-four patients were studied: 27 patients with stable angina pectoris (7 women, 61.4±1.9 years), 23 NSTEMI patients (9 women, 61.8±2.3 years) and 24 STEMI patients (7 women, 61.3±2.8 years). Plasma concentrations of ADMA and SDMA were elevated following PCI compared to before PCI but there were no differences in concentrations between STEMI, NSTEMI and stable angina patients. Plasma concentrations of L-arginine rose after PCI but remained lower in patients with STEMI than in those with NSTEMI or in stable angina patients. Medication might influence L-arginine concentrations and the use of HMG CoA reductase inhibitors and β-adrenoceptor antagonists at study inclusion was significantly less common in STEMI patients compared to NSTEMI and stable angina patients.
Conclusion: L-arginine levels were lower in patients with STEMI and we found changes in ADMA levels over shorter time periods than previously considered possible. We speculate that these variations may be related to the natural history of myocardial infarction or to peri-procedural stress related to PCI.

Keywords: Coronary artery; Endothelium; Ischemic heart disease; Myocardial markers

1. Introduction

Impairment of the nitric oxide synthase (NOS) pathway independently predicts cardiovascular events [1]. Asymmetric dimethylarginine (ADMA) is the major NOS inhibitor [2] and a strong predictor of cardiovascular events [3–6] whereas symmetric dimethylarginine (SDMA) competes with the nitric oxide (NO) precursor L-arginine for uptake into cells. L-arginine is the major substrate for NO and a partial deficiency of L-arginine may exist in patients with severe ischemic heart disease [7].

It remains unknown whether plasma levels of methylated arginines might differ dependent on the acuteness of coronary artery disease. Furthermore, it is uncertain if plasma levels of methylated arginines vary significantly over short time periods [2]. We investigated if plasma levels of ADMA, SDMA and L-arginine can serve as additional staging biomarkers in three different settings of cardiovascular disease: stable coronary artery disease, non-ST-segment myocardial

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infarction (NSTEMI) and ST-segment myocardial infarction (STEMI).

2. Materials and methods

We assessed blood samples immediately before, immediately after, and 24 h following successful percutaneous coronary intervention (PCI). All participants gave informed consent before the invasive procedure and the protocol was approved by the local ethical committee. Concentrations of L-arginine, ADMA and SDMA were assessed by high-performance liquid chromatography and precolumn derivation with *o*-pthaldialdehyde (OPA) according to previous studies [8,9]. All data are presented as mean±SEM. Comparisons between groups were made with a one-way analysis of variance and in case of statistical significance a Tukey post hoc test was applied. Comparisons within groups were made with a one-way repeated measures analysis of variance and a Dunnett's post hoc test. The significance of differences in proportions was tested with the χ^2 statistic. Bivariate associations were examined by least square linear regression. Differences were considered statistically significant when $P<0.05$.

3. Results

Baseline characteristics for the 74 patients in the three groups are listed in Table 1. The patients with stable angina pectoris were in CCS-class 1–3 (mean 1.8±0.1). At study inclusion HMG CoA reductase inhibitor (statin) use and β-adrenoceptor antagonist use were significantly less frequent in STEMI patients compared to NSTEMI and stable angina patients.

ADMA and SDMA did not differ between groups while ADMA, SDMA and L-arginine concentrations increased following PCI (Fig. 1). In the STEMI group, L-arginine concentrations were significantly lower at all three time points compared to the stable angina group and to the NSTEMI group. Levels of ADMA, SDMA or L-arginine did not correlate with levels of TnT, TnI or hsCRP. There was no statistically significant relation between Thrombolysis in Myocardial Infarction (TIMI) flow grade before intervention and methylated arginines across groups. There were no significant differences between ADMA levels in non-smokers (0.58±0.04 μmol/l, $n=12$), ex-smokers (0.54±0.02 μmol/l, $n=35$) and current smokers (0.55±0.03 μmol/l, $n=21$) ($P=0.59$, smoking habits were unknown for six subjects).

Table 1
Baseline data

	Stable angina ($n=27$)	NSTEMI ($n=23$)	STEMI ($n=24$)	*P*-value
Clinical characteristics				
Age, mean (SEM), y	61.4 (1.9)	61.8 (2.3)	61.3 (2.8)	0.99
Sex, male/female, *n*	20/7	14/9	17/7	0.59
Weight, mean (SEM)	76(3)	79 (4)	81 (3)	0.64
Systolic blood pressure (mm Hg)	139 (4)	126 (3)	132 (5)	0.09
Diastolic blood pressure (mm Hg)	80 (2)	72 (2)*	81 (3)	0.01
Hypertension, *n* (%)	17 (63)	10 (44)	9 (38)	0.23
Diabetes, *n* (%)	2 (7)	2 (9)	1 (4)	0.81
Duration from symptom onset to PCI (hours)	–	199 (26)	5.1 (1.1)	–
Medication prior to invasive procedure				
β-Blockers, *n* (%)	18 (67)	20 (87)	4 (17) *	<0.001
Calcium antagonists, *n* (%)	11 (41)	4 (17)	5 (21)	0.13
ACE-inhibitors or AII antagonists, *n* (%)	9 (33)	13 (55)	9 (37)	0.24
HMG CoA reductase inhibitors, *n* (%)	20 (74)	17 (74)	2 (8) *	<0.001
Biochemical variables				
Creatinine, mean (SEM), μmol/l	91 (2)	91 (4)	95 (4)	0.63
Total cholesterol, mean (SEM), mmol/l	5.1 (0.2)	4.8 (0.5)	5.7 (0.3)	0.12
Triglyceride, mean (SEM), mmol/l	1.5 (0.5)	1.5 (0.4)	1.9 (0.3)	0.62
HDL cholesterol, mean (SEM), mmol/l	1.4 (0.1)	1.1 (0.1)*	1.4 (0.1)	0.04
LDL cholesterol, mean (SEM), mmol/l	3.1 (0.2)	2.7 (0.4)	3.0 (0.3)	0.98

Values are mean and (SEM).
Differences were tested by one-way ANOVA (*P*-value) and a Tukey post hoc test (asterisk indicates differences compared with the other two groups). Data on lipid profiles were incomplete. Blood samples were obtained from 7 patients with stable angina, 11 with NSTEMI and 21 with STEMI.

4. Discussion

We found that patients with STEMI had lower levels of L-arginine than other patient categories with coronary artery disease. The differences can be explained by reduced L-arginine synthesis or increased breakdown. Arginine metabolism is highly complex and involves multiple pathways and tissues [10] and excretion is mainly renal [11]. However, renal function did not differ between our patient groups. L-arginine concentration might increase during lipid-lowering therapy [12] and β-adrenoceptor antagonists dose-dependently block splenic arginase activity which metabolizes L-arginine [13]. Thus, the infrequent use of statins and β-adrenoceptor antagonists in STEMI patients could have contributed to the lower levels in these patients. With L-arginine being the major substrate for NO another intriguing explanation of reduced concentrations in STEMI patients is the possibility that L-arginine is linked to the occurrence of myocardial infarction. This is supported by findings in hypercholesterolemic stroke-prone spontaneously hypertensive rats suggesting that NO deficiency induces myocardial infarction [14] and by another study in spontaneously hypertensive rats demonstrating a decrease in plasma L-arginine concentration following acute reduction in blood pressure [15]. In a human study of the vasodilatory response to coronary L-arginine infusion, dilation was more pronounced in complex stenoses than smooth stenoses in agreement with local deficiency of L-arginine at locations prone to myocardial