Effects of stent implementation on plasma levels of asymmetric dimethylarginine in patients with or without ST-segment elevation acute myocardial infarction

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Abstract. The study was designed to compare the response pattern of plasma l-arginine and methylarginines to stent placement in patients with or without ST segment elevation myocardial infarction (STEMI). Two groups of patients with obstructive coronary artery disease (OCAD) undergoing percutaneous coronary intervention (PCI) with stenting were enrolled in the study. Group I consisted of 16 patients with STEMI, whereas group II included 24 patients without STEMI (controls). Before PCI and at <1 h, 5 and 30 days after reperfusion, blood samples were taken for measurement of l-arginine and methylarginines. L-arginine, asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), N-monomethylarginine (MMA) and l-ornithine plasma levels were measured by LC-MS-MS. Arginine methylation index (Arg-MI) was calculated according to the formula, Arg-MI = (ADMA+SDMA)/MMA. In patients without STEMI, stenting induced a prompt and sustained depression of ADMA ($p<0.000$), and l-ornithine ($p<0.000$) with simultaneous increase of l-arginine ($p<0.001$), l-arginine/ADMA ratio ($p<0.000$) and an inconsistent change in MMA. Arg-MI remained at the baseline value. By contrast, STEMI patients responded to stent placement with a variable increase in l-arginine ($p<0.01$), ADMA ($p<0.069$), SDMA, MMA ($p<0.01$) and l-ornithine ($p<0.000$), whereas there was an early fall of Arg-MI after stenting, followed by a steady increase approaching the initial values. The differences in the time-course for ADMA ($p<0.000$), MMA ($p<0.007$), Arg-MI ($p<0.01$) and l-ornithine ($p<0.003$) proved to be significant between the STEMI and control group. It can be concluded therefore, that stent placement improves endothelial dysfunction in patients with OCAD when it is not complicated by STEMI.

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Introduction

Percutaneous coronary intervention (PCI) with stenting is the standard therapy for acute ST segment elevation myocardial infarction (STEMI) (1). It ensures patency of the affected arteries, enhances blood supply to the stunned myocardium and improves long-term angiographic and clinical outcome (2-4). The structural and functional integrity of the endothelium, however, is further compromised by mechanical injury and detachement of endothelial cells from the arterial wall, altered hemodynamic forces, inflammation and oxidative stress (5,6).

As a combined effect of PCI and pre-existing cardiovascular risk factors, endothelial dysfunction is encountered as evidenced by reduced NO production/bioavailability and endothelial activation with increased production and expression of proinflammatory, procoagulatory and pro-proliferative substances (7,8). Endothelial acitvation is assumed to be accounted for by the re-endothelization of the injured arteries. This process can be achieved by resident endothelial cell proliferation and recruitment of circulating endothelial progenitor cells. Selective dysfunction and unlimited activation of regenerated endothelial cells may progress to neointima formation, vascular remodeling and in-stent restenosis (9,10).

Asymmetric dimethylarginine (ADMA) has been established as an early marker and mediator of endothelial dysfunction which is intimately involved in the initiation and progression of cardiovascular diseases. It has been shown to impair NO generation by inhibiting nitric oxide synthase (NOS) activity, by inhibiting the cellular uptake of l-arginine, the substrate of NOS, through the cationic amino acid transporter and by causing NOS uncoupling with subsequently enhanced vascular superoxide production that inactivates

endothelium-derived NO (11-13). Accordingly, elevated plasma ADMA levels were found in patients with acute coronary syndrome (14,15) and in patients undergoing PCI pre-procedural ADMA levels independently predicted adverse cardiovascular events over a follow-up period of 16 months (16).

Most recently, the research group of Hazen investigating the relationship of arginine, arginine methylation and the catabolic products of arginine to the cardiovascular risk provided evidence that the global arginine bioavailability ratio and the integrated quantification of methylation proved to be superior to ADMA alone in predicting long-term major cardiac events in stable patients undergoing elective cardiac evaluation (17,18).

Previously, we assessed the early effects of stent placement on plasma levels of ADMA in patients with coronary heart disease but without myocardial infarction. We demonstrated that in response to stenting there was a prompt and sustained reduction in ADMA levels with a simultaneous elevation of l-arginine and l-arginine/ADMA ratio (19).

In the present study an attempt was made to extend our previous observations by measuring the immediate response pattern of l-arginine, ADMA and symmetric dimethylarginine (SDMA) to stent placement in patients with acute STEMI. In addition, we determined the stent-induced changes in the recently introduced arginine-methylation index (Arg-MI) in this group of selected patients. It was expected that our study might provide new information clinically relevant to the functional recovery of endothelium in STEMI patients receiving stent placement.

Materials and methods

Patients. Sixteen consecutive patients with ST-segment elevation acute MI admitted to the Heart Institute of Faculty of Medicine, University of Pécs, Hungary were included in the study. Admissions were made within 24 h after the onset of acute MI. STEMI was defined as typical ischemic chest pain lasting longer than 30 min, evidence of new persistent ST segment elevation in ≥2 contiguous leads and elevation of cardiac enzymes (CK-MB, troponin I) at least two times over the upper limit of normal. Coronary angiography was performed immediately after admission. Perfusion status of the infarct-related artery was assessed according to current recommendation. The invasive examinations were performed using a Philips BH 5000 monoplane or biplane system. Recordings were analysed afterwards independently by two well-trained invasive cardiologists. The type and location of the culprit lesion and the degree of stenosis of the coronary vessels are illustrated in Table II. Stenosis of coronary arteries (75%) was considered as significant. The recanalization was done by implementation of bare metal stents in all STEMI patients. The periprocedural medication was as follows. Prior to PCI 300-600 mg clopidogrel, 300 mg aspirin and 60 IU/kg sodium-heparin was given. On days 2 and 4-5 after the intervention 75 mg clopidogrel and 100 mg aspirin were introduced, respectively. Patients with prior coronary artery bypass surgery, old MI and PCI history were excluded.

From the blood chemistry, standard estimation of risk parameters of ishemic heart disease was performed for each patient prior to coronarography. Twenty-four patients with coronary heart disease who underwent PCI with stent placement but had no MI served as controls. The major clinical, laboratory and angiographic characteristics of the study and control patients are summarized in Tables I and II.

Table I. Clinical characteristics of patients with obstructive coronary artery disease who underwent percutaneous coronary intervention with stent placement with (STEMI group) or without (control group) ST segment elevation myocardial infarction.

Variable	Control group (n=24)	STEMI group (n=16)	p-value
Age (years)	63±9	61±13	0.671
Male, n (%)	20 (67)	9 (56)	0.486
Diabetes mellitus, n (%)	9 (30)	1 (6)	0.063
Smoking, n (%)	7 (23)	5 (31)	0.56
Body mass index (kg/m^2)	27.5±4.0	28.8±2.9	0.314
LDL-cholesterol (mmol/l)	2.93±1.17	2.91±0.86	0.947
Fibrinogen (g/l)	3.45±1.17	4.29±1.51	0.027
hsCRP mg/l	9.34±9.3	34.55±44.9	0.007
Leukocytes (G/l)	7.28±2.26	11.3±2.98	<0.0001
Neutrophil granulocytes (%)	65.35±9.95	75.76±8.16	0.002
Homocysteine (μmol/l)	15.04±6.49	20.3±16.04	0.18
Creatinine (μmol/l)	97.75±28.88	86.27±24.97	0.201
Microalbuminuria, n (%)	4 (17)	3 (19)	0.865
EF (%)	50.24±11.63	47.07±9.68	0.37
RR syst (mmHg)	136±26	132±29	0.765
RR diast (mmHg)	78±11	88±16	0.021
Treatment, n (%)			
Nitrate	11 (37)	11 (69)	0.038
Statin	24 (80)	16 (100)	0.055
ACEI	21 (70)	10 (63)	0.605
ARB	6 (20)	2 (13)	0.523
Troponin I	ng/ml <0.4	10.2±17.54	
LDH	U/l <450	1106.7±838.1	
CK	U/l <200	1327±1228.18	
CK-MB	U/l <25	147.04±161.5	

Before PCI and at <1 h, 5 and 30 days after reperfusion blood samples were withdrawn for measurement of l-arginine, ADMA, SDMA, N-monomethylarginine (MMA) and l-ornithine plasma levels.

The study protocol was reviewed and approved by the Institutional Ethics Committee of the Faculty of Medicine of

Table II. Results of coronary angiography in patients with obstructive coronary artery disease who underwent percutaneous coronary intervention with stent placement with (STEMI group) or without (control group) ST segment elevation myocardial infarction.

Control patients					STEMI patients				
Patients (n=24)	Type of lesion	Stenosis (%)	Location	No. of stents	Patients (n=16)	Type of lesion	Stenosis (%)	Location	No. of stents
1	A	58	RCA	1	1	C	100	LAD	3
2	B	81	LAD	4	2	C	100	LAD	3
3	C	57	LAD-DIAG	1	3	C	100	LAD	3
4	C	100	LAD-DIAG	4	4	C	100	RCA	3
5	C,B	62	LAD	3	5	B	75	CX	2
6	B	86	CX	1	6	C	98	LAD	2
7	C	70	LAD	3	7	B	75	LAD	1
8	A	55	CX	1	8	B	85	CX	1
9	B,A	81	LAD	2	9	C	100	RCA	1
10	B,C	100	RCA	2	10	B	98	RCA	3
11	C	90	RCA	3	11	C	100	LAD	2
12	C	95	CX	1	12	C	100	RCA	1
13	C	95	RCA	2	13	C	100	RCA	1
14	C	71	LAD	2	14	C	100	RCA	3
15	B	55	LAD-DIAG	2	15	C	100	RCA	4
16	C	100	LAD	4	16	C	100	RCA	3
17	C	95	CX	1					
18	B	95	CX	1					
19	B	95	CX	2					
20	C	52	LAD	1					
21	C	73	CX	1					
22	C	75	CX	4					
23	B	82	CX	2					
24	B	62	LAD	1					

University of Pécs. Written informed consent was obtained from all patients who participated in the study. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Laboratory measurements. Fasting plasma samples were obtained and stored at -70˚C until analysis. Plasma l-arginine, SDMA, ADMA and MMA were determined with liquid chromatography-tandem mass spectrometry (LC-MS-MS) as previously described (20). The intra-day precision was 4.5% for l-arginine, 5.5% for ADMA, 3.9% for SDMA and 3.98% for MMA. The respective values for inter-day precision were 4.7, 7.7, 4.9 and 7.58%. For the determination of l-ornithine concentration the recently published LC-MS-MS method was adapted (21). The intra-day and inter-day relative standard deviations were 1.1 and 3.5%, respectively.

The routine biochemical parameters were measured by using standard laboratory procedures. The integrated index of arginine methylation (Arg-MI) was calculated according to the formula, Arg-MI = (ADMA+SDMA)/MMA as proposed by Wang *et al* (18).

Statistical analysis. Data are presented as mean values ±SEM, with sample size (n) indicated for each reported value. A value of $p<0.05$ was considered statistically significant. t-tests were used to compare risk parameters of the group with or without STEMI but undergoing PCI and stent placement. Repeated measures using ANOVA with intrasubject factor time (baseline, <1 h, 5, and 30 days) and intersubject factor group (with or without STEMI) was performed for l-arginine, ADMA, SDMA, MMA, l-ornithine, l-arginine/ADMA ratio and Arg-MI. Greenhouse-Geisser correction was used when appropriate to account for non-spherocity of the data.

Results

The major clinical characteristics of the STEMI and control patients undergoing PCI with stenting are summarized in Table I. As is shown STEMI patients had significantly higher plasma fibrinogen, hsCRP, leukocytes, neutrophil granulocytes and diastolic blood pressure, and received more nitrate and statin therapy than patients in the control group. Moreover, troponin I, LDH, CK, CK-MB in STEMI patients much exceeded the upper limit of the normal values in our laboratory

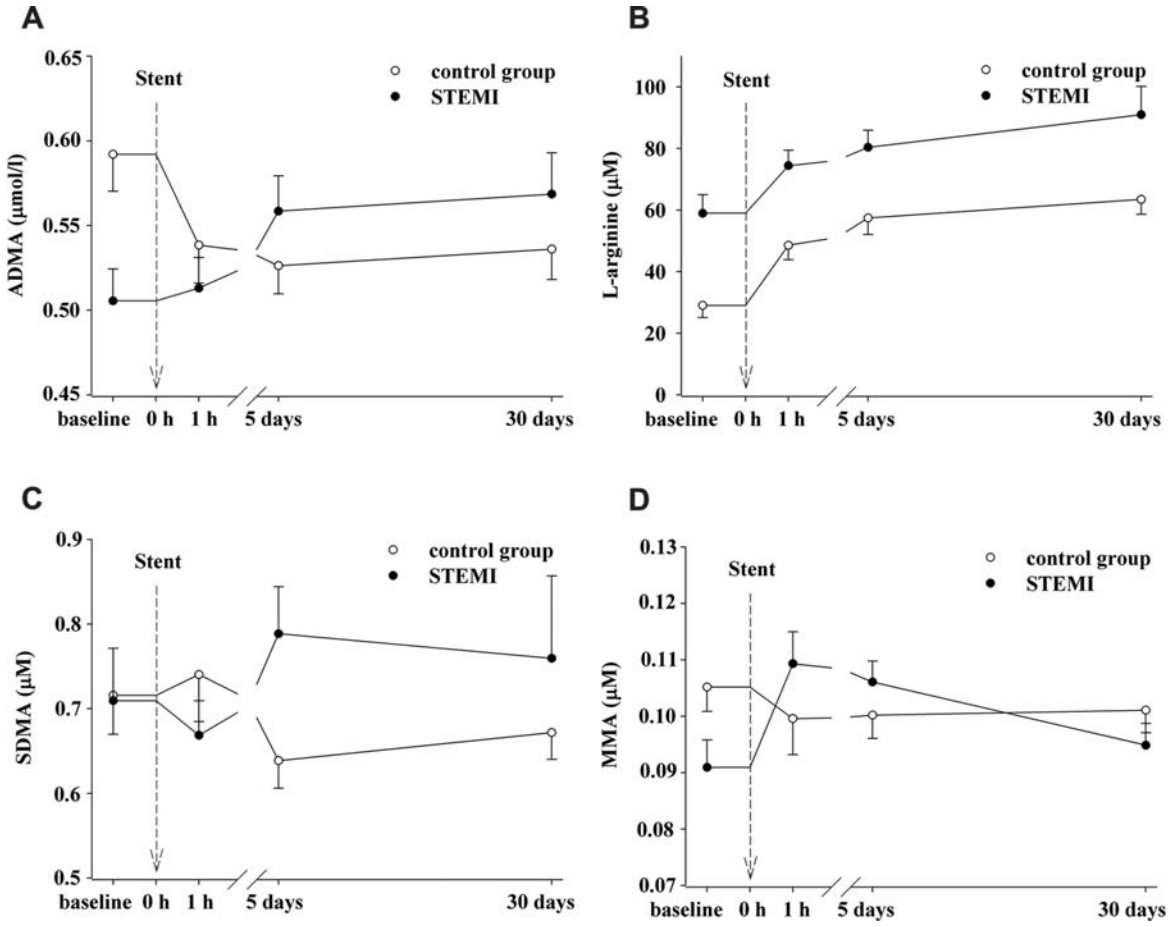

Figure 1. Plasma levels of asymmetric dimethylarginine (ADMA) (A), l-arginine (B), symmetric dimethylarginine (SDMA) (C) and monomethylarginine (D) in patients with obstructive coronary artery disease who underwent percutaneous coronary intervention with stent placement with (STEMI group) or without (control group) ST segment elevation myocardial infarction.

(given in the control group). Coronary angiography revealed that 11 of 16 STEMI patients had complete and 5 patients highly significant coronary artery obstruction. In the control group only 3 out of 24 patients were found to have complete obstruction (Table II).

Fig. 1 and Table III illustrate the response pattern of the plasma levels of ADMA, l-arginine, SDMA and NMA to stent implementation in the STEMI and control groups. At baseline ADMA and MMA were significantly lower, l-arginine significantly higher in the STEMI than in the control group, while no discernible difference was detected between the two groups in SDMA. ADMA values increased moderately after stent placement in the STEMI group, in the controls the time-course was statistically significant; its early fall until day 5 was followed by a moderate increase during the rest of the study period. *Post-hoc* ANOVAs revealed a significant intrasubject time effect in the control group ($F=9.594$, $p<0.0001$) and showed only a statistical trend in the STEMI group ($F=2.982$, $p<0.069$). The time-course of ADMA between the two groups was markedly different ($F=9.431$, $p<0.0001$). L-arginine increased at about the same rate in both groups, so the intra-subject time effects were significant ($F=4.55$, $p<0.01$ and $F=6.71$, $p<0.001$ for the STEMI and control groups, respectively). However, no intersubject time effect was detected ($F=0.232$, $p<0.874$). SDMA appeared to increase in the STEMI group, whereas it appeared to decrease in the control group, these changes proved to be most pronounced at days 5 and 30 after PCI. However, these response patterns were not significantly different (group by time interaction for SDMA $F=2.766$, $p<0.074$). The *post-hoc* ANOVA showed that the SDMA values were not statistically significant in either group. MMA responded in the STEMI group to stenting with an immediate rise followed by a steady decline approaching the initial value by the end of the study. By contrast, no consistent changes were detected in the control group. The group by time interaction for MMA ($F=4.987$, $p<0.007$) and the intra-subject time effect in the STEMI group ($F=5.232$, $p<0.012$) proved to be significant.

Fig. 2 demonstrates that after stenting there was a drop in Arg-MI but it regained its initial value by day 5 and increased further at a slow rate thereafter in patients with STEMI, but neither STEMI patients nor control patients had significant changes with time in Arg-MI ($F=2.998$, $p<0.071$; $F=1.505$, $p<0.235$). However, the intersubject time effect was significant ($F=4.453$, $p<0.012$). The baseline values of l-arginine/ADMA ratio were higher in the STEMI group compared to those in the control group. In response to stent implementation this ratio rose rapidly within 1 h and remained elevated later on in both groups. The increase of l-arginine/ADMA ratio over time reached statistical significance in the STEMI ($F=3.65$, $p<0.023$)

Table III. Plasma levels of asymmetric dimethylarginine (ADMA), l-arginine, symmetric dimethylarginine (SDMA), monomethylarginine (MMA), and l-ornithine, as well as the l-arginine/ADMA ratio and arginine methylation index (Arg-MI) in patients with obstructive coronary artery disease who underwent percutaneous coronary intervention with stent placement with (STEMI group) or without (control group) ST segment elevation myocardial infarction.

	Control group (n=24)				STEMI group (n=16			
Variable	Baseline	<1 h	5 days	30 days	Baseline	<1 h	5 days	30 days
ADMA (μM/l)	0.592±0.020[b]	0.538±0.020	0.526±0.020	0.536±0.020	0.505±0.020	0.513±0.020	0.559±0.020	0.569±0.020
L-arginine (μM/l)	29±4.0[c]	48.6±4.7[c]	57.5±5.4[b]	63.5±4.9[b]	59±6.1	74.4±5.1	80.4±5.5	91±9.2
L-arginine/ADMA ratio	51.8±7.6[c]	94.7±9.8[c]	112.1±11.2[a]	120.5±9.3[a]	117.3±11.8	148.3±12	146.6±11.3	161.6±16.2
SDMA (μM/l)	0.716±0.050	0.74±0.06	0.639±0.030[a]	0.672±0.030	0.709±0.060	0.669±0.040	0.789±0.060	0.76±0.10
MMA (μM/l)	0.105±0.004[a]	0.100±0.006	0.100±0.004	0.101±0.004	0.091±0.004	0.109±0.006	0.106±0.004	0.095±0.004
Arg-MI	12.7±0.6x	13.2±0.8[c]	11.9±0.5[b]	12.3±0.5[a]	13.8±1.0	11.1±0.6	13.1±0.9	14±1.1
L-ornithine (μM/l)	157.4±12.2[c]	99.2±9.5[c]	116.7±8.3[c]	105.2±5.9[b]	67.2±4.5	47.8±3.2	67.3±6.3	76.3±5.0

Independent t-test for intersubject comparison. [a] 0.05; [b]p<0.01; [c]p<0.001.

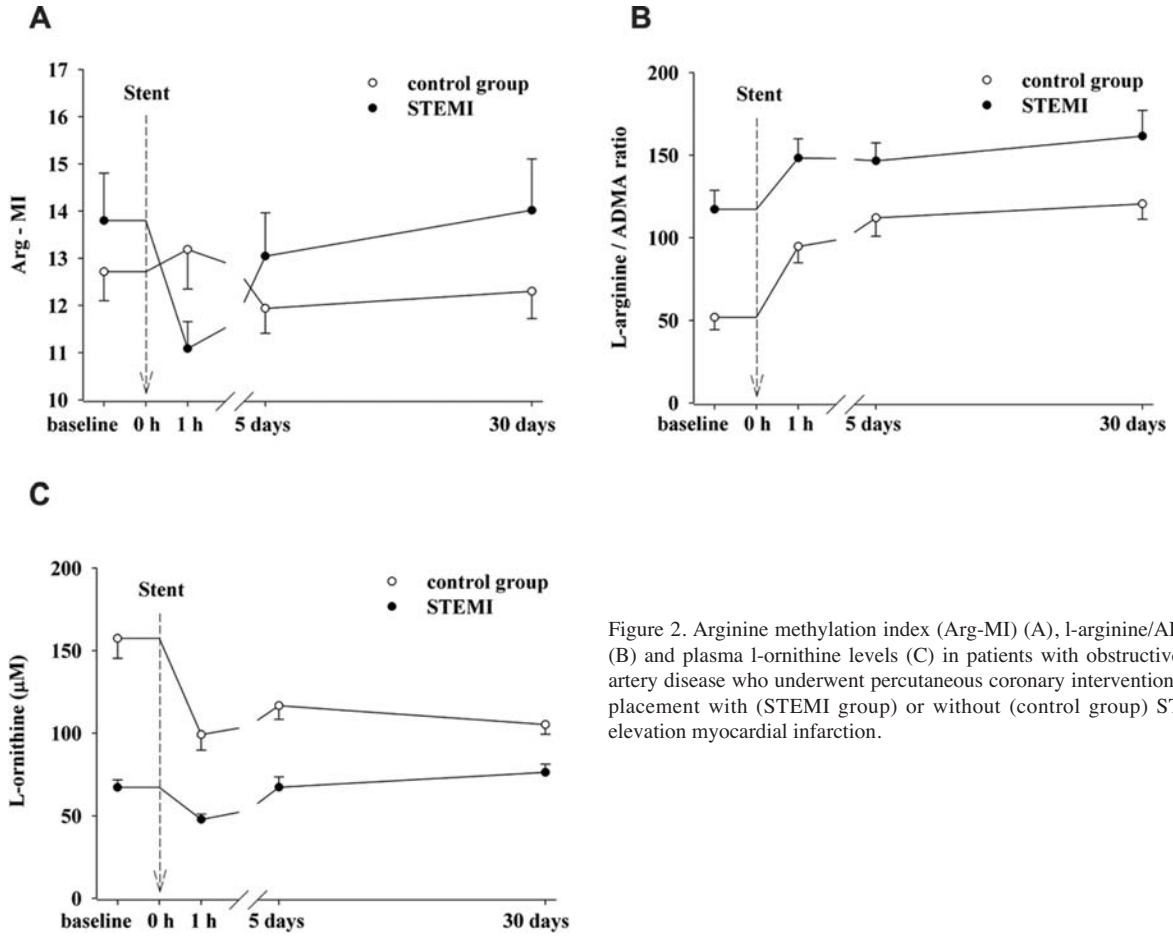

Figure 2. Arginine methylation index (Arg-MI) (A), l-arginine/ADMA ratio (B) and plasma l-ornithine levels (C) in patients with obstructive coronary artery disease who underwent percutaneous coronary intervention with stent placement with (STEMI group) or without (control group) ST segment elevation myocardial infarction.

and also in the control group (F=8.25, p<0.0001). As the time-course was essentially the same in the two groups no group by time interaction was demonstrated. The initial values of l-ornithine levels were markedly depressed in STEMI patients relative to the controls and after a slight early decline it increased steadily until the end of the observational period (F=14.97,

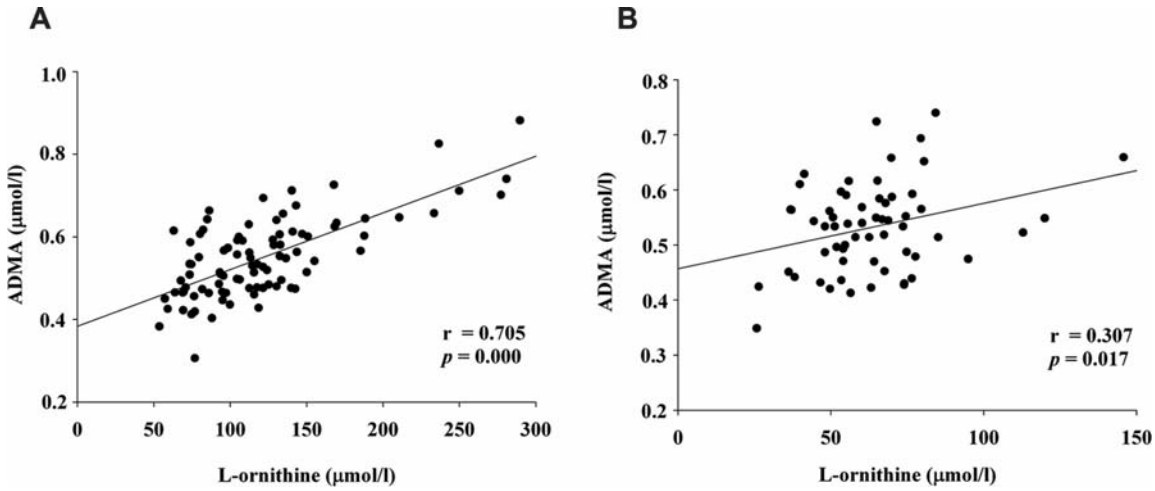

Figure 3. The relationship of plasma asymmetric dimethylarginine (ADMA) to l-ornithine levels in patients with obstructive coronary artery disease who underwent percutaneous coronary intervention with stent placement with (STEMI group) or without (control group) ST segment elevation myocardial infarction.

p<0.0001). In the control patients, a sharp reduction occurred in l-ornithine soon after stenting and after the 5th day it declined progressively until the end of the study (F=9.10, p<0.0001). The time-courses of the two groups were significantly different (group by time interaction for l-ornithine F=5.10, p<0.003).

Interestingly, significant positive correlation was found between ADMA and l-ornithine in the patients with STEMI (r=0.307, p<0.017) and in control patients where this association proved to be particularly strong (r=0.70, p<0.0001) (Fig. 3).

Discussion

The present study demonstrated that there is a striking difference in the response of l-arginine, its methylated metabolities and l-ornithine to stenting between patients with or without STEMI. Namely, in patients without STEMI this intervention induced a prompt and sustained depression of ADMA, and l-ornithine with simultaneous increase of l-arginine, l-arginine/ADMA ratio and an inconsistent change in MMA. Arg-MI remained at the baseline value. This metabolic profile appeared to be compatible with improved endothelial function possible due to high-grade shear stress and to the related changes in the activity of cationic amino acid transporters and DDAH (19).

By contrast, STEMI patients responded to stent placement with an increase in l-arginine, ADMA, SDMA, MMA and l-ornithine, whereas there was an early fall of Arg-MI after stenting followed by a steady increase to reach its initial value. The differences in the time-course for ADMA, MMA, Arg-MI and l-ornithine, as evaluated by the intersubject time effect, proved to be significant between the STEMI and control group. Our findings suggest that the ongoing deterioration of endothelial dysfunction in STEMI is not attenuated by stent implementation. The reason for this response pattern is not apparent, however, several underlying mechanisms are to be considered.

It has been well-documented that local and systemic inflammation plays a prominent role in the pathomechanism of myocardial infarction (22,23). Postischemic tissue damage has been shown to initiate and maintain a cascade of inflammatory reactions. Certain products of tissue injury activate Toll-like receptors, transcription factors, such as NF-κB, and the complement system. Neutrophils and monocytes/macrophages are attracted to the site of injury and chemokines mediating the migration of inflammatory cells and pro-inflammatory cytokines are released (24). The severity of myocardial damage is related to the degree of infection (25,26). Pharmacological inhibition or targeted deletion of elements of inflammatory mediators has been proven to be effective in reducing infarction, improving myocardial function and survival (27-30). Pro-inflammatory cytokines are known to stimulate the formation of reactive oxygen species, which in turn amplify the inflammatory processes. This synergistic interplay between oxidative stress and inflammation aggravates endothelial dysfunction and further compromises the integrity of l-arginine-NO system. Namely, in endothelial cells from human and porcine coronary artery recombinant CD40L treatment induced superoxide generation with concomitant reduction in cellular NO levels. Moreover, eNOS mRNA expression and stability, eNOS protein levels and enzyme activity were markedly depressed. Additionally, superoxide may react with NO to form the highly toxic peroxynitrite, causing eNOS uncoupling with the subsequent eNOS-mediated superoxide production and may reduce the vascular reactivity to NO (31-33).

Endothelial dysfunction can also be attributed to accumulation of methylarginines. MMA and ADMA inhibits NOS activity and cellular l-arginine uptake via cationic amino acid transporters, whereas SDMA is a weak inhibitor of cellular l-arginine transport. In myocardial infarction, which is associated with inflammation and oxidative stress there are increases in the cellular/circulatory ADMA levels via enhancing the activity of methyltransferases, the synthesizing enzymes and simultaneously decreasing the activity of DDAH, the degrading enzyme (14-16,34).

In agreement with this notion in our STEMI patients the post-stent decline in plasma ADMA levels did not occur possibly due to the infarct-related inflammation and oxidative stress and to the subsequent ischaemia/reperfusion injury. In contrast to ADMA, the plasma levels of l-arginine after stenting proved to be quite similar in patients with or without STEMI. It

can be assumed to be due either to attenuated cellular l-arginine uptake (13) or to augmented proteolysis (25) with release of free amino acids including l-arginine and methylarginines.

Cytokine-induced expression and activation of arginase, the enzyme that metabolises l-arginine to l-ornithine and urea may also have a role in the depletion of cellular l-arginine pool. Arginase and NOS share a common substrate, l-arginine and they are reciprocally regulated. Arginase inhibition increases NO production and NOS inhibition in turn upregulates arginase and results in enhanced production of l-ornithin and urea. In fact, in our STEMI patients there was a steady increase in l-ornithine <1 h after stent placement, so it is speculated that through generation of proline and polyamines the arginase-ornithine pathway is of importance in inducing cell proliferation and tissue repair after myocardial injury (35,36). The close, positive correlation between ADMA and l-ornithine underlines the possibility that factors responsible for the generation and accumulation of ADMA may also stimulate arginase activity and may lead to enhanced l-ornithine production (37).

The recently introduced integrated quantification of arginine methylation, Arg-MI, as an independent risk factor for coronary artery disease and for future major adverse cardiac events in stable patients undergoing cardiac evaluation needs to be commented on. Wang *et al* reported a mean value of 22.5 and 28.6 for patients without or with significantly obstructive coronary artery disease, respectively (18). Our patients had severe coronary artery obstruction and were treated with stent placement with or witout STEMI. It is of note, that their Arg-MI averaged at 12-14, much less than those described by Wang *et al*. We have no clear explanation for this striking discrepancy. However, the numerator ADMA proved to be higher, the denominator MMA to be lower in the patients studied by Wang *et al* than in ours. These differences cannot be attributed to the clinical conditions of the patients and the validated laboratory analysis we used has long been accepted as appropriate. Therefore one must be cautious to apply Arg-MI as an estimate of cardiovascular risk and further studies need to be conducted to reconcile these apparently conflicting results.

Study limitations include only a small number of patients was selected for the study, and the follow-up period was relatively short. Pro-infammatory cytokines and markers of oxidative stress were not determined.

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