

**Effect of coronary revascularisation on serum level of the endogenous
nitric-oxide synthase inhibitor asymmetric dimethyl-arginine**

PhD thesis

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1. INTRODUCTION

Cardiovascular complications are still the leading cause of death in Hungary (664,5 death/100 thousand person in 2004). Although the mortality of cardiovascular diseases has decreased since then, several new questions have arisen in connection with the pathogenesis of atherogenesis.

Endothelial dysfunction is thought to be the initial step of atherosclerosis. During this process, endothelium produces large amount of endothelin and small amount of nitric-oxide (NO) resulting in vasoconstriction and thrombogenesis.

Several studies suggest that endogenous competitive inhibitors of nitric oxide synthase (NOS) may play crucial role in the pathogenesis of endothelial dysfunction in coronary artery disease (CAD). These substances are asymmetric dimethyl-arginine (ADMA) and N-monomethyl-arginine (MMA). Since clinical trials provided firm evidences that serum concentration of ADMA is approximately 10-fold higher than the concentration of MMA, in this study we investigated the response pattern of ADMA in patients who underwent coronary revascularisation.

2. AIMS OF THE STUDY

1. In this study we planned to follow up serum level of ADMA, L-arginine, symmetric dimethyl-arginine (SDMA) and L-ornithine in patients who underwent elective coronarography or elective percutan coronary intervention (PCI) with stent implantation.
2. Our aim was to measure serum concentration of the above mentioned biomarkers in patients who suffered from acute myocardial infarction (MI) with ST-segment elevation (STEMI). Furthermore, we examined the effect of stent implantation on the newly introduced arginine methylation index (Arg-MI).
3. Finally, based on earlier observations referring to different oxidative stress caused by coronary artery bypass graft surgery (CABG) during coronary revascularization, we investigated the response pattern of ADMA and its metabolites in patients who underwent on-pump or off-pump CABG operation.

3. DETERMINATION OF SERUM ADMA LEVELS IN PATIENTS WHO UNDERWENT ELECTIVE PERCUTAN CORONARY INTERVENTION AND STENT IMPLANTATION

3.1. Patients and methods

30 consecutive patients with CAD were hospitalized at the Heart Institute of the Clinical Centre, University of Pécs, Hungary for elective coronary angiography and PCI as it was required. 20 patients who underwent elective coronary angiography without CAD or PCI were included as control. Coronary angiography was performed because the non-invasive data suggested or proved coronary disease.

From the blood standard estimation of risk parameters of ischemic heart disease according to the current guidelines was performed for each patient on the day they were hospitalized. During the 24 hours before PCI or elective coronary angiography we drew blood from CAD patients and controls in order to determine ADMA, SDMA, L-arginine and L-ornithine levels. These parameters were then measured again less than 1 hour, 5 days and 30 days after performing the PCI or elective coronary angiography.

Blood samples for the measurement of the above mentioned biomarkers were centrifuged in half an hour (3 minutes, 3000 turns). Fasting plasma samples were stored at -70°C until analysis. Plasma L-arginine, SDMA, and ADMA were determined with liquid chromatography – tandem mass spectrometry (LC-MS-MS) in collaboration with Institute of Clinical Pharmacology, University Hospital, Otto-von-Guericke University, Magdeburg.

Statistical analysis. Data are presented as mean value \pm SEM, with sample size (n) being indicated for each reported value. A value of $p < 0.05$ was considered statistically significant. t-tests were used to compare coronary risk parameters of the stent group with control. Repeated measures ANOVA with intrasubject factor time (baseline, 1 h, 5 days and 30 days) and intersubject factor group (stent vs. control) was performed for L-arginine, ADMA, SDMA, and L-ornithine and L-arginine/ADMA ratio. Greenhouse-Geisser correction was used where necessary to account for non-sphericity of the data.

3.2. Results

At baseline, patients in the stent group had significantly elevated plasma concentrations of ADMA, SDMA and L-ornithine compared to the control group, whereas L-arginine plasma level and L-arginine/ADMA ratio were markedly decreased (Table I).

Table 1: Response pattern of ADMA-, L-arginine-, SDMA-, MMA-, L-ornithin-, L-arginine/ADMA ratio.

Parameter	Control group (n = 20)				Stent group (n = 30)			
	Baseline	1 hour	Day 5	Day 30	Baseline	1 hour	Day 5	Day 30
ADMA ($\mu\text{M/l}$)	0.46 \pm 0.03	0.48 \pm 0.02	0.48 \pm 0.02	0.51 \pm 0.03	0.59 \pm 0.02	0.54 \pm 0.02	0.53 \pm 0.02	0.54 \pm 0.02
L-arginine ($\mu\text{M/l}$)	70.7 \pm 4.1	63.9 \pm 4.1	78.8 \pm 5.9	64.7 \pm 5.1	35.9 \pm 4.2	51.7 \pm 4.0	60.8 \pm 4.6	63.5 \pm 4.9
L-arginine/ ADMA ratio	157 \pm 10.5	134 \pm 7.1	165 \pm 11.6	124 \pm 9.1	64.3 \pm 7.9	100 \pm 8.4	116 \pm 9.1	120 \pm 9.3
SDMA ($\mu\text{M/l}$)	0.43 \pm 0.02	0.43 \pm 0.02	0.48 \pm 0.03	0.47 \pm 0.02	0.66 \pm 0.04	0.68 \pm 0.05	0.59 \pm 0.03	0.67 \pm 0.03
L-ornithine ($\mu\text{M/l}$)	62.6 \pm 4.5	57 \pm 3.9	78.6 \pm 5.7	101 \pm 6.1	157 \pm 12	99.2 \pm 9.5	117 \pm 8.3	105 \pm 5.7

ADMA decreased dramatically immediately after stent placement and remained decreased even 30 days after PCI. In the control group ADMA increased throughout the observation period, even if the elevated ADMA levels of the stent group were not reached. The difference between the groups proved to be statistically significant ($F=12.8$, $p<0.0001$). The stent group showed a significant decrease of ADMA ($F=10.8$, $p<0.0001$). On the other hand, the control group showed a statistically significant increase of ADMA ($F=4.4$, $p=0.009$).

L-arginine levels in the stent group were low at baseline, but showed an increase after stent placement and remained elevated throughout 30 days. The control group had normal L-arginine plasma levels at baseline that increased 5 days after coronarography. Post-hoc ANOVAs with factor time showed significant increases of L-arginine in both groups ($F=6.7$, $p=0.001$ in the stent group, and $F=5.3$, $p=0.004$ in the control group).

The L-arginine/ADMA ratio increased in the stent group coming from a low baseline level, whereas in the control group the time course was similar to the L-arginine course. The

repeated measures ANOVA indicated a significant group by time interaction for the L-arginine/ADMA ratio ($F=7.1$, $p<0.001$).

SDMA appears to decrease in the stent group whereas SDMA appears to increase in the control group, especially 5 and 30 days after intervention. The time courses were significantly different (group by time interaction for SDMA $F 5.5$, $p=0.013$).

Finally, L-ornithine behaved similarly to ADMA (significant group by time interaction $F=12.5$, $p<0.0001$) with a significant increase in the control group ($F=28.3$, $p<0.0001$) and a significant decrease from baseline in the stent group ($F=9.1$, $p<0.0001$).

Moreover, ADMA showed a direct relationship to L-ornithine ($r=0.71$, $p=0.0001$) when pooling data pairs from all 4 time points.

3.3. Discussion

The present study provides evidences for the first time that restoration of coronary circulation by stent placement in patients with CAD induces a rapid and sustained decrease in the level of ADMA that is maintained during the 30 days follow-up period after stenting. Furthermore, L-ornithine shows a significant decrease after stent implantation. In contrast, the plasma concentration of L-arginine increases significantly contributing to a substantial rise of L-arginine/ADMA ratio that remains at this high level until the end of the study. This phenomenon may increase the activity of endothelial NOS which may restore the NO formation rates at physiological levels to promote the revascularization process. Clinically, the revascularization procedure improves the general condition, including cardiac output, ejection fraction and myocardial contractility as well as the short- and long-term outcomes.

In the control group, plasma levels of L-arginine were not correlated with L-ornithine, and the direct relationship of ADMA with L-ornithine was much weaker. This indicates that stent implementation presumably increases ADMA and L-ornithine transport into the cell whereas L-arginine transport out of the cell seems to be enhanced.

We showed no consistent changes in SDMA during the whole follow-up. Because SDMA is not metabolized by DDAH, the plasma levels of SDMA returned to initial value after 30 days, which could be associated with a non-significant decrease of L-ornithine plasma levels between 5 days and 30 days. A further explanation could be the decreased renal function due to the application of contrast medium during stent implantation leading to an increase of SDMA and the consecutive decrease of SDMA after 5 days.

Based on our data we suggest that in patients with CAD, stent placement may decrease the level of the new cardiovascular risk factor ADMA. We speculate that changes in CAT and in DDAH activity may be responsible for the observed effect.

4. EFFECTS OF STENT IMPLEMENTATION ON PLASMA LEVELS OF ASYMMETRIC DIMETHYLARGININE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION (STEMI)

4.1. Patients and methods

16 consecutive patients with ST-segment elevation acute MI admitted to the Heart Institute of Clinical Centre, University of Pécs, Hungary were included into the study. Admissions were made within 24 hours after the onset of acute MI. Coronary angiography was performed immediately after admission. Perfusion status of the infarct-related artery was assessed according to current recommendation. Patients with prior coronary artery bypass surgery, prior MI and PCI history were excluded.

From the blood chemistry standard estimation of risk parameters of ischemic heart disease was performed for each patient prior to coronarography. 24 patients with coronary heart disease who underwent PCI with stent placement but had no MI served as controls. Before PCI and at <1 hour, 5 days and 30 days after reperfusion blood samples were withdrawn for measurement of L-arginine, ADMA, SDMA, MMA and L-ornithine plasma levels.

Laboratory measurements and statistical analysis were performed as discussed before.

4.2. Results

At baseline ADMA and MMA were significantly lower, L-arginine significantly higher in the STEMI than in the control group, while no discernible difference could be detected between the two groups in SDMA (Table 2).

Table 2: Response pattern of ADMA-, L-arginine-, SDMA-, MMA-, L-ornithin-, L-arginine/ADMA ratio and Arg-MI in the control and the STEMI group.

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

x $p < 0.05$

xx $p < 0.01$

xxx $p < 0.001$

In the STEMI group there was an early increase in the ADMA values after stent placement and it remained elevated, while its serum concentration decreased in the control group after coronary angiography. Post-hoc ANOVAs revealed a significant intrasubject time effect in the control group ($F=10.75$, $p<0.0001$) and in the STEMI ($F=2.98$, $p<0.04$). The time-course of ADMA between the two groups was markedly different ($F=10.35$, $p<0.0001$).

L-arginine increased at about the same rate in both groups ($F=4.55$, $p<0.01$ and $F=6.71$, $p<0.001$ for the STEMI and control groups, respectively).

SDMA appeared to increase in the STEMI group, whereas it appeared to decrease in the control group, these changes proved to be the most pronounced at days 5 and 30 after PCI.

MMA responded in the STEMI group to stenting with an immediate rise followed by a steady decline to approach the initial value by the end of the study. By contrast, no consistent changes could be detected in the control group. The group by time interaction for MMA ($F=4.987$, $p<0.007$) and the intrasubject time effect in the STEMI group ($F=5.232$, $p<0.012$) proved to be significant.

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, these results proved to be statistically significant ($F=2.96$, $p<0.048$). Control patients did not have significant changes with time in Arg-MI ($F=1.49$, $p<0.22$). The intersubject time effect was significant ($F=4.41$, $p<0.05$).

The baseline values of l-arginine/ADMA ratio were higher in the STEMI as compared to those in the control group. In response to stent implementation this ratio rose rapidly within 1 hour and remained elevated later on in both groups. The increase of l-arginine/ADMA ratio over time reached statistical significance in the STEMI ($F=3.65$, $p<0.023$) and also in the control group ($F=8.25$, $p<0.0001$).

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 ($F=14.97$, $p<0.0001$). 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 and in control patients where this association proved to be particularly strong ($r=0.70$, $p<0.0001$).

4.3. Discussion

The present study demonstrated that there is a striking difference in the response of L-arginine, its methylated metabolites 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.

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. Our findings suggest that the ongoing deterioration of endothelial dysfunction in STEMI is not attenuated by stent implementation.

5. RESPONSE OF ASYMMETRIC DIMETHYLARGININE LEVELS TO CORONARY ARTERY BYPASS GRAFT SURGERY

5.1. Patients and methods

Twenty consecutive patients with CAD admitted to the Heart Institute of Clinical Centre, University of Pécs, Hungary, who underwent elective CABG with CPB surgery and twenty-one patients with CAD admitted to the Department of Cardiac Surgery, Zala County Hospital, Hungary who underwent elective CABG with OPCAB surgery were included in the present study. Patients with preoperative poor left ventricular function, rhythm disturbances and anticipated concomitant interventions were excluded from the study.

The revascularization in the OPCAB group was performed on the beating heart using the Chase™ stabilizer (Chase Medical Inc., Dallas, USA). A standard CPB technique was used for the on-pump CABG group. The CPB circuit was composed of a roller pump (Sarns, USA) and a hollow fiber polypropylene oxygenator with an incorporated cardiotomy reservoir (Cobe Optima XP, Cobe Cardiovascular Inc., USA). All operations (CPB and OPCAB) were performed via midline sternotomy and pedicled left internal thoracic artery (LITA). Saphenous veins were used as bypass grafts. After pericardiotomy, a routine coronary sinus (CS) catheter (15 Fr., Medtronic DLP, Grand Rapids, MI, USA) was inserted into the right atrium through a small purse string. The tip of the catheter was guided with intraoperative TEE to the ostium of the coronary sinus.

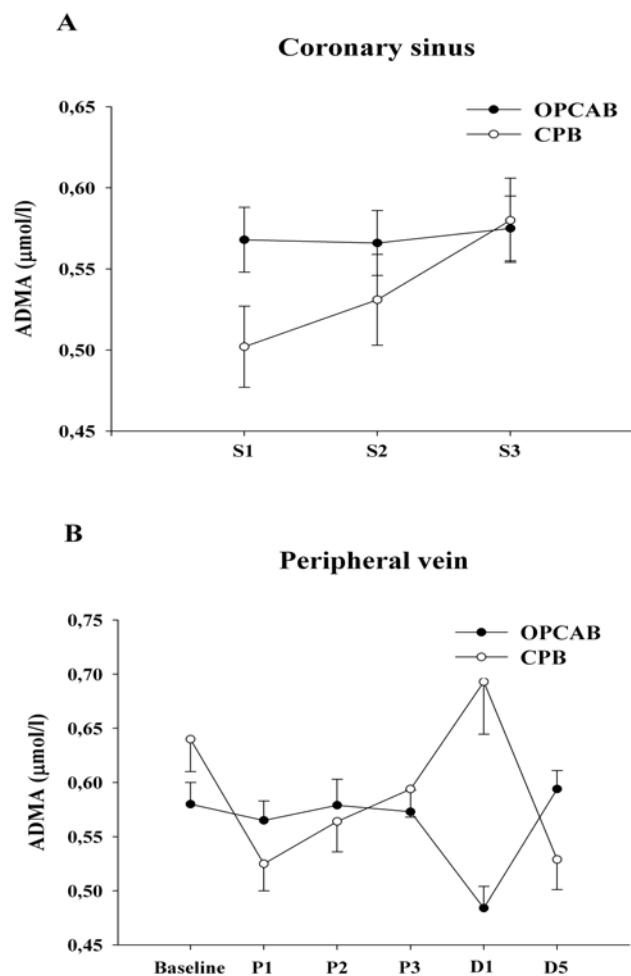
Blood samples for measurements of ADMA, SDMA and L-arginine were withdrawn from the CS and from peripheral vein immediately after the insertion of CS catheter (S1 and P1 respectively), immediately after the completion of the first distal anastomoses (S2 and P2 respectively), and immediately after completion of the last distal anastomoses (S3 and P3 respectively). In addition, before CABG surgery, on the first and fifth postoperative day (baseline, D1 and D5 respectively) blood was withdrawn from the peripheral vein to determine the above-mentioned parameters.

5.2. Results

There was no significant baseline difference in the peripheral plasma concentrations of ADMA between the CPB and OPCAB groups. In contrast, on the first postoperative day (D1), a significant increase of peripheral ADMA levels was observed in the PCB group, when compared to the OBCAB group of patients (0.693 ± 0.049 vs. 0.484 ± 0.024 ; $p < 0.001$). The time-course of ADMA, as measured from blood samples obtained from the peripheral vein proved to be markedly different between the two groups ($F=6.99$, $p < 0.002$). Intersubject analysis revealed similar significant difference in CS ADMA level between the two groups of patients ($F=6.991$, $p < 0.002$).

Based on the intraoperative (CS) samples, we did not observe a discernible increase of ADMA in the OPCAB group. In contrast, the corresponding intraoperative CS levels of ADMA showed a significant elevation in the CPB group ($F=0.416$, $p<0.685$ and $F=14.751$, $p<0.001$ for OPCAB and CPB groups, respectively). Similarly, a significant increase of ADMA was observed in the peripheral blood during CPB, while during OPCAB, ADMA remained largely unchanged. On the first postoperative day (D1) we observed a dramatic drop of ADMA levels in the peripheral blood of the OPCAB patients: these levels returned to the initial, baseline level by the end of the study (D5). In contrast, there was a massive increase of ADMA in the peripheral blood of the CPB patients, with ADMA levels subsequently decreasing below baseline level by the fifth postoperative day (Figure 1 A and B).

Figure 1. Serum level of ADMA in the coronary sinus and in the peripheral vein in patients undergoing coronary bypass surgery



OPCAB group exhibited a significant increase of L-arginine, both in plasma from CS and from peripheral vein. In the CPB group, however, a significant intraoperative increase of L-arginine was found in the peripheral blood, with a subsequent, further elevation until the end of the study (D5). In the OPCAB group a considerable decrease of L-arginine was

observed on the first postoperative day (D1), which was followed by a steady increase towards baseline values by the fifth postoperative day (D5).

The L-arginine/ADMA ratios were significantly higher in the OPCAB group at baseline and on the first postoperative day, as compared to the CPB group (178.29 ± 11.56 vs. 136.28 ± 13.72 at baseline and 129.43 ± 7.08 vs. 106.8 ± 6.9 and on the first postoperative day for OPCAB and CPB groups respectively). Similarly, significant differences were observed between the two groups when S1 and S3 values were compared. The L-arginine/ADMA ratio in the peripheral blood samples exhibited a continuous, slight decrease until the first postoperative day (D1) in both groups. Thereafter, a pronounced increase was observed on the fifth postoperative day (D5) ($F=10.09$, $p<0.001$ and $F=8.931$, $p<0.001$ for the OPCAB and CPB groups, respectively).

SDMA appeared to be significantly elevated in the OPCAB group compared to CPB group, both in the coronary sinus and in peripheral blood samples, but SDMA levels increased by a comparable extent in both groups.

5.3. Discussion

According to our examination the response pattern of asymmetric dimethyl-arginine to coronary bypass operation has revealed significant differences between the two surgical methods. Although extracorporeal circulation is a safe and effective way of revascularisation, many complications can occur. According to our experiences, systemic inflammation generated by extracorporeal circulation seems to be the major cause of these harmful effects. Activation of polymorphonuclear cells in response to cardiopulmonary bypass facilitates the production of reactive free radicals and expression of adhesion molecules, leading to a direct relationship between inflammatory cells and endothelial cells. Finally, this process attenuates tissue damage and vascular dysfunction.

7. SUMMARY OF NOVEL FINDINGS

1. We have first highlighted that stent implantation causes dramatic and rapid decrease in serum concentration of the new cardiovascular risk factor asymmetric dimethyl-arginine during elective percutan coronary intervention. ADMA remained decreased until the end of the study independently the type of the stent.
2. We found that ADMA, SDMA and L-ornithine levels increased significantly in the control group after elective coronary angiography possibly due to the altered vascular shear stress caused by the contrast agent used during the examination.
3. We pointed out, that elective percutan coronary intervention with stent placement caused a rapid and long-lasting decrease in the serum concentration of ADMA, SDMA and L-ornithine, in contrast significantly increased the serum level of L-arginine and L-arginine/ADMA ratio.
4. We demonstrated that there is a significant difference between the the above mentioned biomarkers to stent placement in patients with STEMI and in control patients also.
5. We revealed that serum levels of ADMA, SDMA, L-arginine, MMA and L-ornithine rise significantly in patients with acute myocardial infarction and ST- segment elevation.
6. Finally, we found evidence for the first time that there is significant difference in the serum concentration of asymmetric dimethyl-arginine during on-pump vs. off-pump CABG surgery, due to different oxidative stress. In contrast, there was no significant difference between the samples from coronary sinus and peripheral vein. In conclusion, we believe that this response pattern due to systemic inflammation generated by extracorporeal circulation.

8. PUBLICATIONS

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Cumulative Impact Factor : 48.951

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