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Antioxidant effects of statins in patients after coronary angioplasty

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Abstract

Background: Oxidative stress, characterized by an imbalance between the generation reactive oxygen species (ROS) and the capacity of the intrinsic antioxidant defense system, may be implicated in the pathogenesis of cardiovascular diseases. Percutaneous transluminal coronary angioplasty (PCI) followed by the implantation coronary stents may be associated with a process of ischemia and reperfusion related injury. PCI and stent deployment induce production of vascular reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to post-procedural pathophysiological changes, including restenosis, stent thrombosis, and endothelial dysfunction.

The aim of the present study was to demonstrate, through the analysis of such parameters as Malondialdehyde (MDA), Superoxide dismutase (SOD) and Catalase, those early changes in oxidative stress take place in stable coronary artery disease (CAD) patients undergoing elective PCI with implantation of coronary stents.

Material and methods: In this study 120 consecutive chronic stable angina pectoris patients (mean age 59 ± 0,63 years, 80% male) undergoing PCI for management of single and multi -vessel CAD were included. Malondialdehyde, Superoxide dismutase and Catalase enzymes activity were measured before and after the procedure, as well as 24 hours later, then after 1, 3, 6 months. Simvastatin was administered at different doses: group I received – 20 mg, group II received – 40 mg of simvastatin and group III – 80 mg 12 hours before the angioplasty with stent implantation.

Results: The obtained outcomes indicate that the oxidative stress activity increased in the patients with CAD versus control group. Traumatic impact by expanding stent pressure was observed within 24 hours after angioplasty by raising MDA and lowering SOD and Catalase.

Conclusions: Pleiotropic antioxidant effects of simvastatin administered to patients after revascularization, manifested by abolishing oxidative stress (DAM) and raising antioxidant enzymes (SOD, Catalase) in the next steps 1, 3, 6 months after PCI.

Key words: oxidative stress, revascularization, atherosclerosis**.**

Introduction

Atherosclerosis is a chronic immuno-inflammatory and fibroproliferative disease of the medium and large arteries. The natural history of atheroma plaque counts three stages – initiation, progression and complications.

The initiation stage begins with the changes of homeostatic functions and molecular alterations of vascular endothelial cells triggered by atherogenic stimuli. The progression is the result of fibroproliferative response to inflammation and involves accumulation of intimal smooth muscle cells (SMCs). SMCs release macromolecules of the extracellular matrix forming a collagen-rich network that provides stability to the plaque. The atherosclerosis progression frequently causes fibrosis and calcium accumulation, wih a stabilizing

effect on the plaque, meanwhile the neovascularization occurs. Both processes – fibrosis and certain calcification patterns are currently considered dynamic phenomena that can equally express plaque stability, but also its vulnerability.

The complications stage or vulnerable, unstable plaque has a multifactorial etiology. Complex biological processes such as inflammation and fibrous head and necrotic lipid core remodeling are essential. Plaque remodeling is a result of both the matrix synthesis reduction and the increased degradation of collagen and elastin [1].

Intravascular view of the vulnerable atheroma plaque. *Intravascular ultrasound* (IVUS) is a conventional method used for the assessment of coronary artery atherosclerosis, which has the advantage of providing tomographic images in real time cross-section. The vulnerability is indicated by the eccentric pattern, the presence of ecolucent nucleus, positive remodeling, the presence of thrombi, as well as by quantitative information like the plaque length and lumen narrowing.

Optical coherence tomography (OCT) has the advantage of high resolution in *ex vivo* experiments reaching the sensitivity between 71-96% and the specificity between 90-98% for identifying the plaque morphology. At patients with PCI, the IVUS proved to be superior because it can recognize the thin head of the plaque, rupture and thrombi. OCT is the only method capable of recognizing eroded plaques.

The *Spectroscopy* uses the field in the vicinity of the infrared, is based on the absorption and scattering of light of different organic molecules.

The *Thermography* has the principle of heat production by the vulnerable plaque in the presence of inflammation and neovascularization. The main disadvantage is the cooling effect produced by the bloodstream.

Noninvasive view of the vulnerable atheroma plaque. *Multidetector CT angiography* is a method that allows the study of the characteristics and extension of the intramural atherosclerosis, certain vulnerable plaque features identification such as the positive remodeling, the increased proportion of non-calcium or mixed components in plaque, the stained appearance of calcifications, plaque low density. However, assessing density of the fibrous plaques versus those with a rich content of fat has limitations, as well as thin fibrous head plaques identification.

Positron emission tomography is addressed in the first line to the identification of the atherosclerosis plaque components throughout the arterial tree. One advantage is the reproducibility of assessment that would allow monitoring progress under treatment in large arteries. The technique has limitations at the coronary artery level due to the intense intake of the tracer by the myocardium.

Nuclear magnetic resonance is particularly suitable for large arteries, such as carotid arteries. At present, it is considered a potential method for evaluating both plaque morphology and composition but new technical performances are needed to increase reproducibility, usability for coronary atherosclerosis and, of course, determine the clinical predictive value for acute vascular events. Current literature makes premature the routine application of nuclear magnetic resonance for useful molecular imaging in characterizing the vulnerability.

Contrast ultrasound is a method applicable to the characterization of atheroma plaque due to the use of specific contrast agents. The small size allows seizure at microvascular level, implicitly in vessels of neoformation from the vulnerable plaque [2].

In a series of autopsies with human implants, Inoue et al. have reported that significant changes occur in neointima as BMS. The arteries that were stented from 2 to 3 years showed endothelial coverage with smooth muscle and collagen, rich neointima. Chronic inflammation was observed and was characterized by macrophages, T cells, and giant cell infiltration. At the stents implanted over 4 years, smooth muscle cells were rare, abundant collagen to lumen and foamy macrophages (so-called „neoatherosclerosis"), which expressed metalloproteinases. These data suggest that neointimal formation, which occurs after metallic stent implants is subject to the same atherosclerotic forces that affect the native vessels and macrophages mediate collagen degradation and ultimately could lead to the formation of necrotic core, and possible rupture and thrombosis. Atherosclerosis newly formed within the neointimal tissue of the stented segments, has been called „neoatherosclerosis". It contains the necrotic core with cholesterol crystal. The fibrous plaque covering the necrotic core is infiltrated with numerous foamy macrophages [3].

Recently, computerized coherent tomography is able to detect the development of new atherosclerosis in stented segments, at patients alive. In the register "CVTath stent registry" with a number of 299 autopsies, comprising 406 lesions (197 BMS, DES 209 [103 SES and PES 106]) – with implant duration over 30 days. The neoatherosclerosis pathological criteria were: peri-strut foam macrophages, fibroatheroma, thin fibrous atheromatous carcase, rupture with thrombosis. The neoatherosclerosis incidence was significantly higher at the DES (31%) vs. BMS (16%). The average lasting of neoatherosclerosis presence in stent was at the DES vs. BMS (420 days vs. 2160). The independent determinant of the neoatherosclerosis includes long lasting of implantation and type of stent [4].

Another study assessed the neointimal tissue at patients treated with DES between 9 months and 2 years of follow-up. A total of 76 DES were assessed. From which 23 with SES (Cypher), 20 PES (Taxus), 25 SEZs (Endeavor), 8 EES (Xience). This study that used serial OCT suggested that intrastent neoatherosclerosis, including conversion to neointima loaded with fat, can progress further during follow-up after implantation of DES. Regardless of DES type, the lipid loaded neointima was more frequently detected after 2 years of folow-up compared to 9 months (27.6% vs 14.5%, $p = 0.009$) [5].

W. Gerritsen et al. (2006, 2008) considers DAM as a marker of global and useful oxidative stress in assessing myocar-

dial injuries in patients undergoing PCI, including assessing effectiveness of different technical methods applied for this purpose [6, 7].

The role of oxidative stress (OS) in cardiovascular pathology is confirmed by registers from clinical and basic studies concerning the development of atherosclerosis, heart disease coronary, congestive heart failure, cardiac arrhythmias, hypertension, stroke, etc. [8].

The oxidative stress reflects a status in which the reactive oxygen species (ROS) prevail antioxidant defense mechanisms [9]. SRO are involved in a large number of cardiovascular diseases including hypertension, atherosclerosis, myocardial infarction, and restenosis following angioplasty or by-pass [10]. PCI causes increased ROS removal of the affected artery wall place. Many of these mechanisms contribute to involvement in endothelial function [11]. **Thus, the purpose of the study** was to study the evolution of oxidative stress markers at patients exposed to coronary angioplasty.

Material and methods

The study selected 120 patients with stable pectoris angina who were treated for myocardial revascularization by coronary angioplasty with stent implantation and who received lipid-lowering preparation, simvastatin, according to the assigned lot. In addition to individual anti-ischemic treatment was administered Aspirin Clopidogrel (as the standard antiplanichetar treatment). Other classes of preparations were administered at the discretion of the attending physician.

The patients were under treatment within the Institute of Cardiology during 2012-2014. They were followed-up for 6 months with assessment at different stages: stage I – pre PCI, stage II – after PCI (24 hours), stage III – 1 month, stage IV – 6 months. Group I consisting of 62 patients received 20 mg of simvastatin, group II consisting of 26 patients received 40 mg of simvastatin and group III received 80 mg of simvastatin 12 hours before PCI.

To assess the activity of oxidative stress the following markers have been estimated:

1. lipid oxidation product – malondialdehyde (MAD);
2. antioxidant system parameters – superoxide dismutase (SOD) and catalase;

Results and discussions

Changes in circulating levels of oxidation products (MAD) in both the pre PCI stage and the following ones after PCI, 1, 3, 6 and 12 months are shown in table 1.

Malondialdehyde as one of the end products of lipid peroxidation, indicates the enabling of oxidative stress. Statistically speaking, DAM data at the initial stage in 3 groups were not different ($p > 0.05$): group I – 11.8 ± 0.99 μM/L, group II – 10.87 ± 2.29 μM/L and group III – 15.43 ± 4.21 μM/L, which reveals elevation against the statistically significative baseline. In all 3 groups of post-PCI, the DAM increased, showing an oxidative stress activation resulting from stent implantation and endothelial injury at coronary level. Thus, in group I the DAM level – 16.3 ± 3.49 μM/L, in group 20.19 ± 5.07 μM/L and group III – 19.71 ± 4.92 μM/L. Subsequently, the DAM decreased to 8.47 ± 0.86 μM/L in group I, in group II – 4.83 ± 0.81 μM/L, in group III 9.62 ± 3.8 μM/L. A statistically significant decrease in oxidant marker was recorded at the stage of 6 months in group I (7.63 ± 0.87 μM/L vs 11.8 ± 0.99 μM/L with $p < 0.05$) and in group III (5.47 ± 0.3 μM/L vs 15.43 ± 3.21 μM/L).

The catalase is an intracellular enzyme which is a true component of antioxidant system. Catalase, at patients with atherosclerotic coronary pathology enrolled in the study, demonstrates the compromised antioxidant system through its

Table 1

Malondialdehyde indices and their dynamics at all stages of the study
Control groups N = 37 M = 4.26 m = 0.20

PCI stages	Group I 20 mg simvastain			Group II 40 mg simvastatin			Group III 80 mg simvastatin			$P_{I.II}$	$P_{I,III}$	$P_{II,III}$
	N	M	m	N	M	m	N	M	m			
Pre	43	11.80***	0.99	17	10.87**	2.29	24	15.43***	3.21	> 0.05	> 0.05	> 0.05
Post	49	16.30***	3.49	22	20.19**	5.07	26	19.71***	4.92	> 0.05	> 0.05	> 0.05
1 month	46	12.47***	1.66	20	14.70**	3.04	22	12.82**	2.71	> 0.05	> 0.05	> 0.05
3 monts	14	8.47***	0.86	3	4.83	0.81	5	9.62**	3.8	< 0.05	> 0.05	> 0.05
6 months	19	7.63***	0.87	5	19.35	9.82	2	5.47**	0.30	> 0.05	< 0.05	> 0.05
$p_{d\ post}$	> 0.05			> 0.05			> 0.05					
$p_{d\ 1\ l}$	> 0.05			> 0.05			> 0.05					
$p_{d\ 3\ l}$	> 0.05			> 0.05			> 0.05					
$p_{d\ 6\ l}$	< 0.01			0.05			---					

Legend: p d.post – DAM dynamics at post PCI stage versus initial stage; p d.1 l. – DAM dynamics at the 1 month stage versus initial stage; p d 3 l. – DAM dynamics at the 3 months stage versus initial stage; p d 6 l. – DAM dynamics at the 6 months stage versus initial stage;

* – $p < 0.05$; ** – $p < 0.01$; *** – $p < 0.001$ – statistical significance compared to the baseline.

Table 2

Catalase indices and their dynamics at all stages of the study
Control groups N = 54 M = 26.061 m = 0.903

PCI Stages	Group I 20 mg simvastain			Group II 40 mg simvastatin			Group III 80 mg simvastatin			$P_{I,II}$	$P_{I,III}$	$P_{II,III}$
	N	M	m	N	M	m	N	M	M			
Pre	43	19.51***	1.35	17	14.23***	1.53	24	13.56***	1.02	< 0.05	< 0.001	> 0.05
Post	49	19.53***	1.56	22	16.38***	1.49	26	16.46***	1.37	> 0.05	> 0.05	> 0.05
1month	47	19.55***	1.53	20	15.92***	1.15	22	13.67***	1.07	> 0.05	< 0.01	> 0.05
3months	14	21.46*	1.86	3	16.77**	6.43	5	13.06***	2.18	> 0.05	< 0.05	> 0.05
6months	19	24.15	1.9	5	17.93*	4.43	2	18.70***	0.52	> 0.05	< 0.05	> 0.05
$p_{d\ post}$	> 0.05			> 0.05			> 0.05					
$p_{d\ 1l}$	> 0.05			> 0.05			> 0.05					
$p_{d\ 3l}$	> 0.05			> 0.05			> 0.05					
$p_{d\ 6l}$	> 0.05			> 0.05			---					

Legend: p d.post – catalase dynamics at PCI stage versus initial stage; p d.1 l. – catalase dynamics at the 1 month stage versus initial stage; p d 3 l. – catalase dynamics at the 3 months stage versus initial stage; p d 6 l. – catalase dynamics at the 6 months stage versus initial stage;

* – p < 0.05; ** – p<0.01; *** – p < 0.001 – statistical significance compared to the baseline.

low level of statistical significance (p < 0.001) compared to the pre PCI and compared to the reference group in all 3 groups of patients (19.51 ± 1.35 μM/L in group I, 14.23 ± 1.53 μM/L in group II and 13.56 ± 1.02 sample II μM/L vs. 26.0 ± in group III 0.90μM/L reference). For the pre PCI stage the catalase level was higher in group I (< 0.05) compared to group II and III, although patients have been divided into groups aimlessly with no certain principles (tab. 2).

Under the simvastatin treatment the catalase level began to rise from the post PCI stage even though statistically insignificant (19.53 ± 1.56 μM/L for group I, 16.38 ± 1.49μM/L for group II and 16.46 ± 1.37 μM/L for group III). This increase continued at next stages. The highest figures have been recorded at the stage of 6 months for all 3 groups (24.15 ± 1.9 μM/L, 17.93 ± 4,43 μM/L and 18.7 ± 0.52 μM/L respectively) being higher in group I (p I, III < 0.05).

Superoxide dismutase (SOD) is the enzyme that assures the transformation processes of superoxide anion into hydrogen peroxide and thus is recognized as an important component of the antioxidant system. Reducing the quantities of SOD compared to baseline denotes a compromised antioxidant system and indicates the activation of oxidative stress. Therefore, the reduction of SOD is associated with the elevation of malondialdehyde. A compromised antioxidant system is attested at the stage before the angioplasty in all groups of patients compared to the baseline group, sta-

Table 3

Superoxide dismutase indices and their dynamics at all stages of the study
Control groups N = 44 M = 1075.28 m = 16.49

PCI stage	Group I 20 mg simvastain			Group II 40 mg simvastatin			Group III 80 mg simvastatin			$P_{I.II}$	$P_{I,III}$	$P_{II,III}$
	N	M	M	N	M	m	N	M	m			
Pre	43	874.04***	41.74	17	864.26**	77.34	24	878.29**	56.44	>0.05	> 0.05	> 0.05
Post	49	886.82***	40.22	22	936.11**	45.55	26	911.31**	57.69	>0.05	> 0.05	> 0.05
1month	47	948.35**	35.85	20	976.39	87.86	22	980.51	80.0	>0.05	> 0.05	> 0.05
3months	14	1069.33	80.00	3	1163.05	182.36	5	746.10***	63.36	>0.05	> 0.05	> 0.05
6months	19	1094.30	61.85	5	981.02	111.79	2	1038.91	151.75	>0.05	> 0.05	> 0.05
$p_{d\ post}$	> 0.05			> 0.05			> 0.05					
$p_{d\ 1l}$	> 0.05			> 0.05			> 0.05					
$p_{d\ 3l}$	> 0.05			> 0.05			> 0.05					
$p_{d\ 6l}$	0.05			> 0.05			---					

Legend: p d.post – SOD dynamics at PCI stage versus initial stage; p d.1 l. – SOD dynamics at the 1 month stage versus initial stage; p d 3 l. – SOD dynamics at the 3 months stage versus initial stage; p d 6 l. – SOD dynamics at the 6 months stage versus initial stage;

p < 0.05; ** – p < 0.01; *** – p < 0.001 – statistical significance compared to the baseline.

tistically significant ($p < 0.001$): 874.04 ± 41.74 u/c, 864.26 ± 77.34 u/c, 878.29 ± 56.44 u/c against the baseline 1075.28 ±16.49 u/c (tab. 3).

The antioxidant system has been activated since the first hours after PCI, having as impetus the impact provoked to the vessel when inflating the balloon to high pressure and stent implantation. The data on SOD at the pre PCI stage had no significant differences among groups. At subsequent stages 1, 3, 6 months were recorded figures for SOD. So at 6 months stage they reach 1094.3 ± 61.85 u/c for group I, 981.02 ± 111.79 u/c for group II and 1038.91 ± 151.75 u/c for group III, having statistical significance for group I ($p = 0.05$).

Activation of oxidative stress and antioxidant system incompetence is due to mechanical impact of angioplasty. Indices are modified especially in the first 24 hours. A cluster of pro-inflammatory cells are connected during the mechanical alteration of the covered coronary artery wall, with additional release of reactive oxygen.

Several authors report on compromised antioxidant system in cardiovascular diseases, especially in patients with ischemic heart disease and diabetes.

DAM is a final product resulting from the breakdown of arachidonic acid and polyunsaturated fatty acids by enzymatic or non-enzymatic means. DAM production by enzymatic processes is well known, but its biological functions and dose dependency have not been studied although DAM is chemically more stable and with a more permeable membrane than other SRO [13].

The catalase is, along with other 2 enzymes (fumarase and acetylcholinesterase), one of the most effective known catalysts, the reactions they catalyze being essential for life. The enzyme catalyzes a reaction every time it encounters a sulfur molecule. Relative speed and orientations of the interacting molecules are important for the reaction. The catalase acts in the conversion of hydrogen peroxide ($2H2O2 \rightarrow 2H2O + O2$) which is a strong oxidizing agent, with a toxic character for cells.

Superoxide dismutase is considered the most effective antioxidant. The importance of SOD is extremely high for the protection of our cells, which represent a substantial part of the proteins produced by the body. Deficiency in SOD/Catalase is the most notorious nutrient factor in most "inflammatory" processes. Given the strong link between free radicals and many health problems today, supplements that increase the activity of SOD/Catalase in the body offer a huge potential.

Conclusions

The oxidative stress activity is already at the initial stage compromised, which shows that in patients with stable angina pectoris prevail oxidant system indices (DAM) over the antioxidants (SOD, Catalase) versus the reference group.

The traumatic impact by expanding pressure of the stent was observed within 24 hours after angioplasty by raising DAM and by lowering the SOD and Catalase levels.

Antioxidant pleiotropic effects of simvastatin administered to patients after coronary angioplasty, manifested by abolishing oxidative stress (DAM) and raising antioxidants indices level (SOD, Catalase) at the next stages 1, 3, 6 months after PCI.

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