

POST-INTERVENTION IMMUNE ACTIVATION REFLECTS THE DEGREE OF VASCULAR TISSUE DISRUPTION IN MINIMALLY INVASIVE LIMB PROCEDURES

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SUMMARY – This study explored whether changes in C-reactive protein (CRP) and fibrinogen levels after endovascular treatment (EVT) could reflect the extent of vascular injury caused during the procedure. A total of 71 patients undergoing EVT were analyzed, while 84 patients who had diagnostic angiography served as controls. CRP and fibrinogen levels were measured prior to the procedure and then at 8, 24, and 48 hours post-intervention. In those treated with EVT, procedural factors such as lesion classification, duration of balloon inflation, length of arterial segments treated by percutaneous transluminal angioplasty (PTA), and stent length were documented.

Results showed a significant increase in CRP and fibrinogen levels 48 hours after EVT ($p < 0.001$). No significant differences were observed across lesion complexity groups; however, CRP levels were notably higher in patients who received stents compared to those treated with PTA alone. A positive correlation was found between increases in CRP and procedural factors: the length of the PTA-treated segment ($r = 0.313$, $p = 0.02$), balloon inflation time ($r = 0.270$, $p = 0.03$), and the stented segment length ($r = 0.535$, $p = 0.01$). These findings suggest that inflammatory marker elevation following EVT may serve as an indicator of procedural vascular trauma.

Key words: *C-reactive protein; Fibrinogen; Stents; Angiography; Endovascular procedures; Angioplasty*

Introduction

Despite recent technical advances that have improved endovascular treatment (EVT) for peripheral arterial disease (PAD), neointimal hyperplasia and subsequent restenosis remain major culprits for failure. Balloon angioplasty leads to atherosclerotic plaque

rupture, exposure of its lipid rich core and activation of blood components¹. Stent implantation causes immediate biological response of protein, fibrinogen and blood cell deposition between stent struts and proliferation of granulation tissue and vascular smooth muscle cells². This process of endothelial healing leads to neointimal hyperplasia, which correlates with the extent of arterial wall injury³.

It has been reported that higher postprocedural levels of inflammatory biomarkers indicate a higher risk of restenosis^{4,5}. Both C-reactive protein (CRP) and fibrinogen have been established as biomarkers in

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Table 1. Patient characteristics

	Control group	Study group	p
Gender, n (%):			
male	64 (76.2)	52 (73.2)	0.71*
female	20 (23.8)	19 (26.8)	
Age (yrs), median (25%-75%)	64.5 (58-71.8)	62 (58-69)	0.29†
Fontaine stage, n (%):			
II A	17 (20.2)	17 (23.9)	0.84*
II B	58 (69)	49 (69)	
III	5 (6)	3 (4.2)	
IV	4 (4.8)	2 (2.8)	
TASC II lesion:			
A		38 (59.4)	
B		21 (32.8)	
C		5 (7.8)	
D		0	
DM, n (%)	30 (35.7)	26 (36.6)	>0.99*
Hypertension, n (%)	55 (65.5)	51 (71.8)	0.49*
CVD, n (%)	14 (16.7)	10 (14.1)	0.82*
CAD, n (%)	16 (19)	12 (16.9)	0.84*
Smoking, n (%)	45 (53.6)	35 (49.3)	0.63*
Dyslipidemia, n (%)	66 (95.7)	45 (77.6)	0.003*
Volume of contrast medium used (mL), median (25%-75%)	110 (93.5-127.5)	140 (80-180)	0.02†
Outcome, n (%):			
PTA		44 (72)	
stenting		27 (38)	
Balloon inflation time (s), median (25%-75%)	-	360 (180-431.3)	-
PTA treated segment length (cm), median (25%-75%)	-	8 (6-15)	-
Stented segment length (cm), median (25%-75%)	-	5 (4 - 6)	-

*Fisher exact test; †Mann Whitney U test; CAD = coronary artery disease; CVD = cerebrovascular disease; DM = diabetes mellitus; PTA = percutaneous transluminal angioplasty; TASC II = Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease

atherosclerosis, but their exact role remains controversial⁶. Although CRP is mainly synthesized in the liver, it is also produced by vascular smooth muscle cells and macrophages in the atherosclerotic plaque^{7,8}. Plasma concentration of CRP correlates with the level of its synthesis⁹. *In vitro* studies have shown that mechanical strain leads to local CRP expression in human arteries¹⁰. Fibrinogen was found to be associated with both the onset and progression of PAD^{11,12}. Apart from being the key determinant of blood viscosity and throm-

bus formation, fibrinogen is also responsible for neointimal growth by stimulation of vascular smooth muscle cells¹³.

Although the correlation between postprocedural levels of inflammatory biomarkers and EVT has been investigated in several studies, the association with the extent of periprocedural arterial injury has not been completely elucidated.

The aim of this study was to examine whether the postprocedural change in CRP and fibrinogen levels

was associated with the extent of periprocedural arterial injury measured by percutaneous transluminal angioplasty (PTA) treated segment length, balloon inflation time and stented segment length.

Subjects and Methods

Study design

This observational single-center cohort study was conducted at Department of Diagnostic and Interventional Radiology, Osijek University Hospital Centre, Osijek, Croatia between June 2014 and April 2017. Before enrolment, all patients provided their written informed consent. The study was approved by the Ethics Committee of the Osijek University Hospital Centre.

Study population

Patients were referred by vascular surgeon for diagnostic angiography and/or EVT for PAD. Seventy-one patients who underwent technically successful PTA with or without stent implantation were recruited. Eighty-four patients who underwent diagnostic angiography of lower limbs during the same period served as a control group. Their demographic characteristics are listed in Table 1. Fontaine classification¹⁴ was used to categorize the severity of PAD. The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II)¹⁵ classification was used to categorize the complexity of lesions to be treated. Patients on hemodialysis treatment, patients with malignant disease, those with a history of surgery, myocardial infarction or coronary endovascular intervention in the past 3 months or endovascular intervention on peripheral arteries in the last 2 weeks, patients on immunosuppressant therapy and those suffering from or treated for chronic inflammatory diseases, and patients with clinical or laboratory signs of acute infection (CRP ≥ 10 mg/L) were excluded from the study. Patients who underwent any other form of EVT besides balloon angioplasty and bare metal stent implantation (such as drug coated balloon angioplasty, drug eluting stent implantation, stent graft implantation, thrombolysis, thrombectomy, etc.) were not included in the study.

Methods

Lower limb arteriography and interventional procedures were performed by an interventional radiolo-

gist (T.T., O.R., G.S. or T.M.) using standardized protocol and femoral arterial ipsilateral or contralateral access. The procedures were performed on iliac and femoropopliteal arteries according to TASC II guidelines. PTA balloon and stent diameters and length were selected according to the vessel diameter and diseased segment length.

Stenting was performed in case of elastic recoil, flow-limiting dissection or residual stenosis greater than 30%. During EVT, all patients received a bolus of 5000 IU of heparin intra-arterially. After EVT, all patients received 40 mg of subcutaneous enoxaparine for three days. In all patients, localization and complexity of the lesion, balloon inflation time, PTA treated segment length, and stented segment length were recorded.

Clinical data

In all patients, demographic data and medical history were determined using a questionnaire and medical records. Hypertension was defined as blood pressure of $>130/90$ mm Hg or a history of treatment for hypertension. Dyslipidemia was defined as a serum high-density lipoprotein (HDL) level <1 mmol/L, low-density lipoprotein (LDL) level >3 mmol/L, cholesterol level >5 mmol/L, and triglyceride level >1.7 mmol/L. Diabetes mellitus was defined as having fasting blood glucose level >6.4 mmol/L or hemoglobin A_{1c} $>6\%$ or a history of treatment with antidiabetic medications. Coronary artery disease was defined as a history of myocardial infarction, angina pectoris, or coronary revascularization procedures. Cerebrovascular disease was defined as a history of transient ischemic attacks, cerebral hemorrhage, stroke, or carotid artery revascularization procedure.

Blood sampling

Baseline peripheral venous blood samples were obtained from each patient before angiography or EVT, in the morning after overnight fast. Subsequently, venous blood samples were obtained at 8 hours, 24 hours and 48 hours after the procedure. CRP levels were measured by an immunoturbidimetric method (Olympus AU480, Beckman Coulter, Tokyo, Japan). Fibrinogen levels were measured by a coagulometric method (BCS XP, Siemens Healthcare Diagnostics, Marburg, Germany). Laboratory values were recorded for each patient and compared between the groups.

Statistical analysis

Data were processed using descriptive statistical methods. Mann-Whitney and Kruskal-Wallis tests were used on sample comparison. Wilcoxon test and Friedman's test were used to detect differences between dependent samples. Spearman's rho test was used to determine the association between non-normally distributed variables. The level of significance was set at alpha of 0.05. Statistical analysis was performed using MedCalc Statistical Software version 14.12.0 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2014).

Results

The indication for EVT was mild intermittent claudication (Fontaine stage IIA) in 17 (23.9%), moderate to severe claudication (Fontaine stage IIB) in 49 (69%) and limb ischemia (Fontaine stages III and IV) in five (7%) patients. Lesions to be treated were classified as TASC II A in 38 (59.4%), TASC II B in 21 (32.8%) and TASC II C in five (7.8%) patients. There were no patients with TASC II D lesion. No complications occurred during or following EVT. PTA was performed in 44 (72%) and stenting in 27 (38%) patients. The median balloon inflation time during PTA was 360 seconds (s) (interquartile range [IQR] 180-431.3). Balloon inflation time for a single patient was calculated as the sum of duration of all balloon inflations performed during vascular intervention. The median length of PTA treated segment was 8 cm (IQR 6-15) and the median stented segment length was 5 cm (IQR 4-6).

There was significant increase in both plasma CRP and fibrinogen levels in the first 48 hours following EVT ($p < 0.001$). The increase in CRP and fibrinogen levels was also recorded in the control group, but it was not statistically significant. CRP levels were significantly higher in the study group 24 hours following EVT compared to the control group 24 hours following angiography ($p < 0.05$). No other statistically significant difference regarding CRP and fibrinogen levels was found between the groups at different time points (Table 2).

Among patients with different lesion complexity (Table 3), significant increase in both CRP and fibrinogen levels was noted in patients with lesions classified as TASC II A and B. Patients with TASC II C lesions showed significant increase in CRP ($p < 0.05$), but not in plasma fibrinogen levels ($p > 0.05$). No significant difference in CRP and fibrinogen levels was found at examined time points following EVT between different TASC II groups.

Regarding the location of pathology, there was a significant postprocedural increase in plasma CRP and fibrinogen levels ($p < 0.001$) in patients with femoropopliteal interventions and in patients with iliac interventions. However, there was no significant difference in postprocedural CRP and fibrinogen elevation between these two subgroups.

Significant increase in CRP ($p < 0.001$) and fibrinogen ($p = 0.001$) levels was found in the subgroup of patients who underwent PTA, as well as in the subgroup that underwent stenting ($p < 0.001$) (Table 4). CRP levels were significantly higher ($p = 0.03$) in the stent

Table 2. Plasma levels of CRP (mg/L) and fibrinogen (g/L) after angiography (control group) and endovascular treatment (study group)

	Median (interquartile range)					p [†]
	Control group	p [*]	Study group	p [*]	All patients	
CRP 0	3 (1.9-4.7)	0.13	3.7 (2.05-6)	<0.001	3.2 (1.9-5.18)	0.17
CRP 8 h	3.1 (1.8-5.33)		3.7 (1.9-6.75)		3.3 (1.88-6)	0.42
CRP 24 h	4.75 (2.83-6.8)		6.2 (3.4-11.45)		5 (2.9-9.4)	0.03
CRP 48 h	6.5 (3.25-8.4)		9.1 (4.3-17.7)		7.85 (3.85-14.5)	0.09
Fibrinogen 0	3.7 (3.3-4.3)	0.18	3.8 (3.3-4.7)	<0.001	3.8 (3.3-4.5)	0.38
Fibrinogen 8 h	3.5 (3.2-4.18)		3.6 (3.13-4.1)		3.55 (3.2-4.1)	0.76
Fibrinogen 24 h	3.8 (3.33-4.68)		4 (3.45-4.85)		3.9 (3.4-4.7)	0.42
Fibrinogen 48 h	4.3 (3.3-5.3)		4.3 (3.7-5.2)		4.3 (3.68-5.23)	0.93

*Friedman's test; †Mann Whitney U test; CRP = C-reactive protein

Table 3. Correlation of plasma levels of CRP (mg/L) and fibrinogen (g/L) with lesion complexity according to TASC II classification

	Median (interquartile range)						p [†]
	TASC II A	p*	TASC II B	p*	TASC II C	p*	
CRP 8 h	3.8 (2.5-7.3)	<0.001	2.6 (1.2-6.7)	0.001	3.05 (1.15-50.18)	0.03	0.32
CRP 24 h	6.2 (3.7-12.45)		6.2 (2.7-11.2)		6.35 (3.75-63.78)		0.64
CRP 48 h	8.75 (4.13-15.38)		9.1 (5-25.1)		7.25 (3.73-71.83)		0.80
Fibrinogen 8 h	3.6 (3.05-4)	<0.001	3.7 (3.23-4.35)	0.005	4.1 (3.7-6)	0.08	0.13
Fibrinogen 24 h	4 (3.4-5.15)		4 (3.6-4.65)		4.6 (3.9-6.3)		0.29
Fibrinogen 48 h	4.3 (3.5-5.05)		4.8 (3.68-5.43)		4.3 (4.3-5.4)		0.51

*Friedman's test; †Kruskal Wallis test; CRP = C-reactive protein; TASC II = Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease classification

Table 4. Plasma levels of CRP (mg/L) and fibrinogen (g/L) in patients undergoing PTA and stent implantation

	Median (interquartile range)					p [†]
	PTA	p*	Stent	p*	Total EVT	
CRP 0	3.6 (2-5.9)	<0.001	4.6 (2.13-7.65)	<0.001	3.7 (2.05-6)	0.33
CRP 8 h	3.3 (1.65-5.75)		4.6 (2.1-12)		3.7 (1.9-6.75)	0.09
CRP 24 h	6.2 (3.4-9.85)		10.1 (3.08-14.73)		6.2 (3.4-11.45)	0.18
CRP 48 h	7 (3.65-14.05)		12.75 (8.05-23.88)		9.1 (4.3-17.7)	0.03
Fibrinogen 0	3.8 (3.4-4.5)	0.001	3.8 (3.28-4.93)	<0.001	3.8 (3.3-4.7)	0.91
Fibrinogen 8 h	3.55 (3.2-4.03)		3.7 (3-4.35)		3.6 (3.13-4.1)	0.94
Fibrinogen 24 h	4.05 (3.43-4.68)		4 (3.35-5.15)		4 (3.45-4.85)	0.77
Fibrinogen 48 h	4.3 (3.6-5)		4.9 (3.7-5.4)		4.3 (3.7-5.2)	0.15

*Friedman's test; †Mann Whitney U test; CRP = C-reactive protein; EVT = endovascular treatment; PTA = percutaneous transluminal angioplasty

subgroup compared to PTA subgroup 48 hours following EVT.

Regarding the association between elevation of CRP and fibrinogen with the extent of periprocedural

arterial injury (Table 5), significant positive correlation was found between PTA treated segment length and CRP increase between 8 hours and 24 hours following EVT ($r=0.313$, $p=0.02$), between balloon inflation

Table 5. Correlation between elevation of inflammatory biomarker plasma levels and extent of periprocedural arterial injury

	Spearman's rank correlation coefficient Rho (p-value)		
	PTA treated segment length	Balloon inflation time	Stented segment length
ΔCRP (0-8 h)	0.015	-0.114	0.535 (0.01)
ΔCRP (8 h-24 h)	0.313 (0.02)	0.270 (0.03)	0.202
ΔCRP (24 h-48 h)	0.109	-0.035	-0.011
ΔFibrinogen (0-8 h)	0.131	0.081	-0.083
ΔFibrinogen (8 h-24 h)	-0.059	-0.117	0.173
ΔFibrinogen (24 h-48 h)	0.073	0.021	-0.076

CRP = C-reactive protein; PTA = percutaneous transluminal angioplasty

time and CRP increase in the aforementioned time frame ($r=0.270$, $p=0.03$), as well as between CRP increase in the first 8 hours following stenting and the stented segment length ($r=0.535$, $p=0.01$). There was no significant positive correlation between fibrinogen levels and the extent of periprocedural arterial injury.

Discussion

Endovascular treatment as a minimally invasive therapy treats only the diseased vessel segment. However, dilatation with high-pressure balloons and implantation of stents cause periprocedural injury of the arterial wall by endothelial denudation, as well as intimal and medial damage¹⁶. These injuries are followed by inflammatory response that often ends with neointimal hyperplasia, a major culprit for long-term EVT failure¹⁷.

Although CRP and fibrinogen are among the most studied inflammatory biomarkers associated with atherosclerosis, their exact role in the response to arterial injury remains unclear. In the current study, CRP level increase showed positive correlation with PTA treated segment length, balloon inflation time and stented

segment length, suggesting that the extent of periprocedural arterial injury correlates with vascular inflammatory response. However, we found no such correlation for fibrinogen. These results are consistent with a previous study of coronary arteries¹⁸, where postprocedural increase of CRP correlated with the total stented segment length. Conflicting results have been reported from the study performed by Wu *et al.*¹⁹, where CRP levels were highest 24 hours after percutaneous coronary intervention, but no statistical difference regarding inflammatory response was found between different dilatation pressures and different stented segment lengths. We found no similar studies assessing the increase in inflammatory biomarkers following EVT on peripheral arteries.

In this study, significant increase was detected in both CRP and fibrinogen levels in patients following EVT. Similar increase in inflammatory biomarkers was found after EVT in previous studies, both on coronary and peripheral arteries^{4,20-23}. In the control group, the increase in CRP and fibrinogen levels following angiography was evident, although not statistically significant. That mild increase could be attributed to arterial puncture and contrast media application.

On subgroup analysis, both PTA and stent groups showed statistically significant increase in postprocedural CRP and fibrinogen levels. Plasma CRP levels were found to be significantly higher in patients 48 hours following stent implantation compared to PTA group. These results can be correlated with morphometric studies^{24,25} in porcine models where more intimal hyperplasia was found after stenting compared to balloon angioplasty, suggesting a more pronounced inflammatory response.

The TASC II classification, with its latest update in 2015¹⁵, provides guidelines on optimal treatment modality for PAD based on lesion complexity and location. Although more complex lesions are more difficult to treat, requiring more endovascular manipulation, in our study no significant difference was found in CRP and fibrinogen levels between different lesion complexity assessed by TASC II classification. Previous studies by Schillinger *et al.*^{20,22} showed no correlation between postprocedural inflammatory response and lesion morphology either.

The present study showed that the arterial injury caused by EVT reflected on the level of inflammatory biomarkers. However, there were several limitations to

our study. Although the interventions were performed according to the TASC II guidelines, angioplasty balloons and stents, as well as balloon inflation time were determined by the operator. Results could have been influenced by the relatively small number of patients and the concomitant use of various drugs not directly related to atherosclerotic disease. Different diameters, designs and structures of stents could also modulate inflammatory response. There was no follow up to study the correlation of our findings with restenosis rate.

Although the inflammatory nature of atherosclerosis is well known for almost two decades²⁶, the role of inflammatory biomarkers has not yet been completely elucidated. The present study assessed the correlation between periprocedural arterial injury and inflammatory response measured by CRP and fibrinogen increase, suggesting that the extent of iatrogenic damage to the arterial wall could relate to future arterial remodeling and subsequent restenosis. Due to the complexity of vascular biology, future studies are warranted to clarify the inflammatory reactions observed.

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