Inflammatory response following peripheral endovascular treatment correlates with the extent of peripheral arterial injury

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Aims and objectives

Endovascular treatment (EVT), as a minimally invasive therapy, treats only a 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 damage [1]. These injuries are followed by inflammatory response that often ends with neointimal hyperplasia, a major culprit for long-term EVT failure [2]. Fig. 1 on page 2

It has been reported that higher postprocedural levels of inflammatory biomarkers indicate a higher risk for restenosis [3,4]. Both C-reactive protein (CRP) and fibrinogen have been established as biomarkers in atherosclerosis, but their exact role remains controversial [5].

The aim of this study was to examine whether the postprocedural change in CRP and fibrinogen levels is associated with the extent of periprocedural arterial injury measured by percutaneous transluminal angioplasty (PTA) treated segment length, balloon inflation time and stented segment length.

Images for this section:

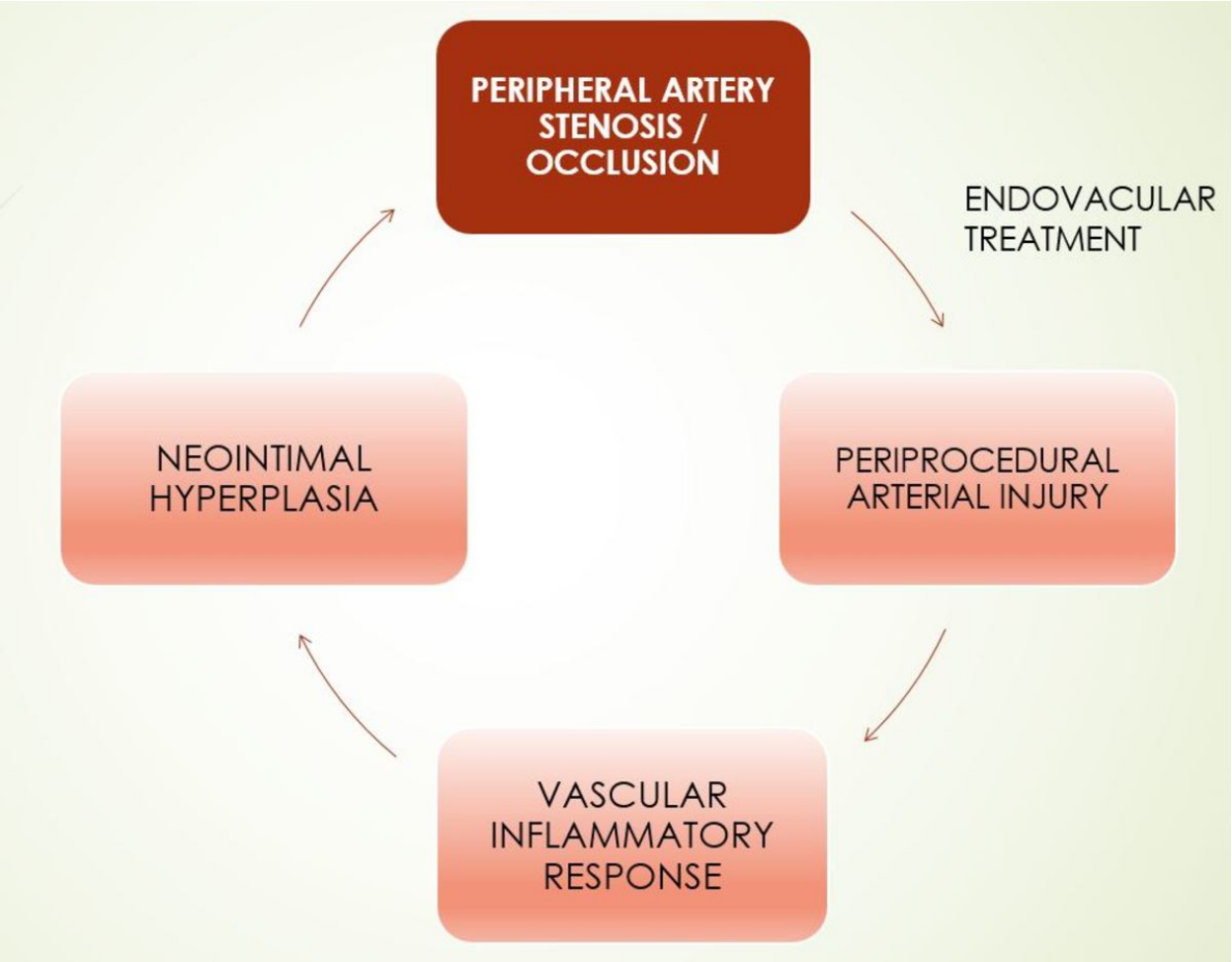

Fig. 1: EVT provokes neointimal hyperplasia

Methods and materials

Study design: observational single-center cohort study conducted between June 2014 and April 2017.

Study population:

- **Inclusion criteria**: patients with PAD referred by vascular surgeon for diagnostic angiography and/or endovascular treatment. Fig. 2 on page 5
- **Exclusion criteria**: ongoing hemodialysis; malignant disease; history of surgery, myocardial infarction or coronary endovascular intervention in the past 3 months; history of endovascular intervention on the peripheral arteries in the last 2 weeks; ongoing immunosuppressant therapy; chronic inflammatory disease; clinical or laboratory signs of acute infection (baseline CRP #10 mg/l).
- 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 this study.
- **Study group**: 71 patients who underwent technically successful PTA with or without stent implantation.
- **Control group**: 84 patients who underwent diagnostic angiography of the lower limbs during the same period.
- **Severity of PAD**: categorized by Fontaine classification [6] . Fig. 3 on page 6
- **Complexity of treated lesions**: categorized by Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II) [7]. Fig. 4 on page 7

Methods: Lower limbs arteriography and interventional procedures were performed by an interventional radiologist using standardized protocol and femoral arterial ipsilateral or contralateral access. Interventional procedures were performed on iliac and femoropopliteal lesions 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%. Fig. 5 on page 7

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.

For all patients, localization and complexity of the lesion, balloon inflation time, PTA treated segment length, and stented segment length were recorded.

Blood sampling:

Baseline peripheral venous blood samples: drawn from each patient before angiography or endovascular treatment, in the morning after overnight fast.

Control venous blood samples: taken from each patient 8 hours, 24 hours and 48 hours after the procedure.

CRP and fibrinogen levels were measured in all blood samples.

For statistical analysis we used:

· Mann-Whitney and Kruskal-Wallis tests to compare samples

· Wilcoxon test and Friedman's test to detect the differences between dependent samples

· Spearman's rho test to determine the association between non-normally distributed variables

· The level of significance was set at Alpha of 0.05.

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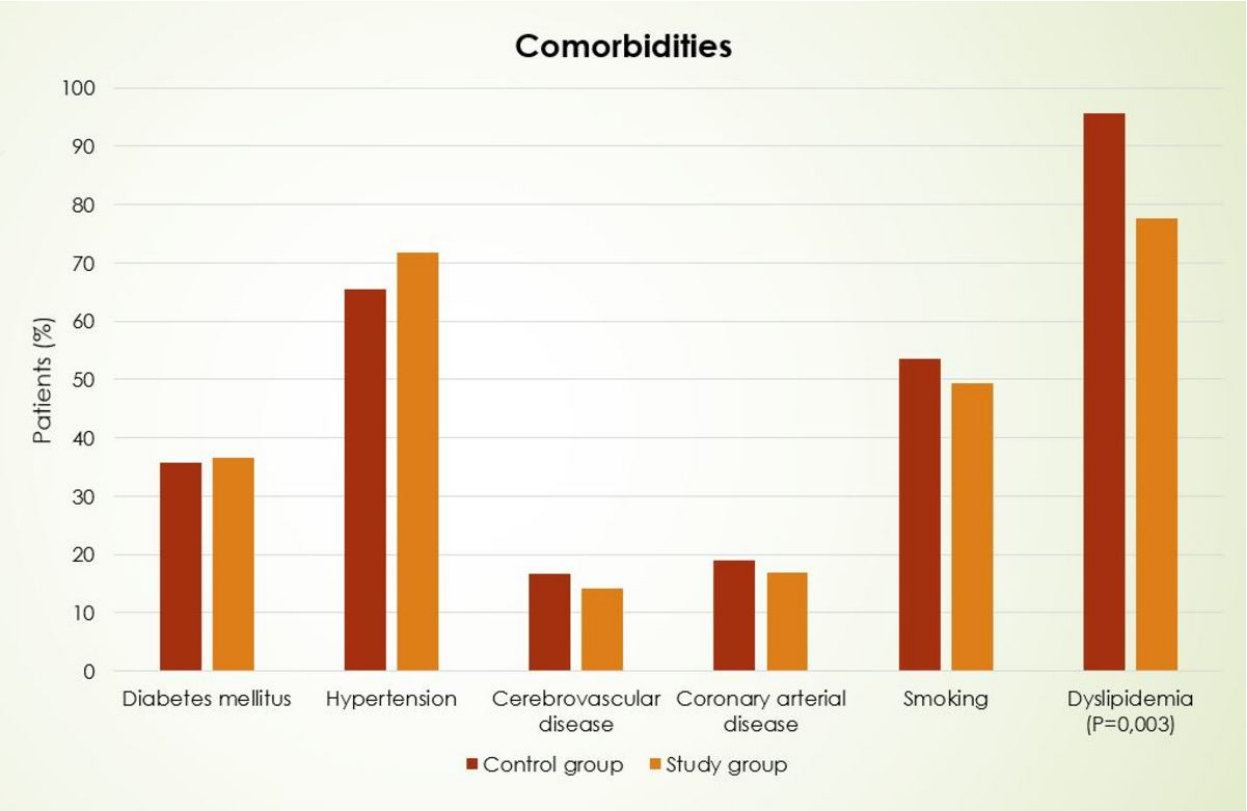

Fig. 2: Comorbidities

	Number (%) of patients			P*
	Control group (N=84)	Study group (N=71)	Total (N=155)	
Gender				
Male	64 (76.2)	52 (73.2)	116 (74.8)	0.71
Female	20 (23.8)	19 (26.8)	39 (25.2)	
Disease severity by Fontaine classification				
II A	17 (20.2)	17 (23.9)	34 (21.9)	0.84
II B	58 (69)	49 (69)	107 (69)	
III	5 (6)	3 (4.2)	8 (5.2)	
IV	4 (4.8)	2 (2.8)	6 (3.9)	

Fig. 3: Demographics

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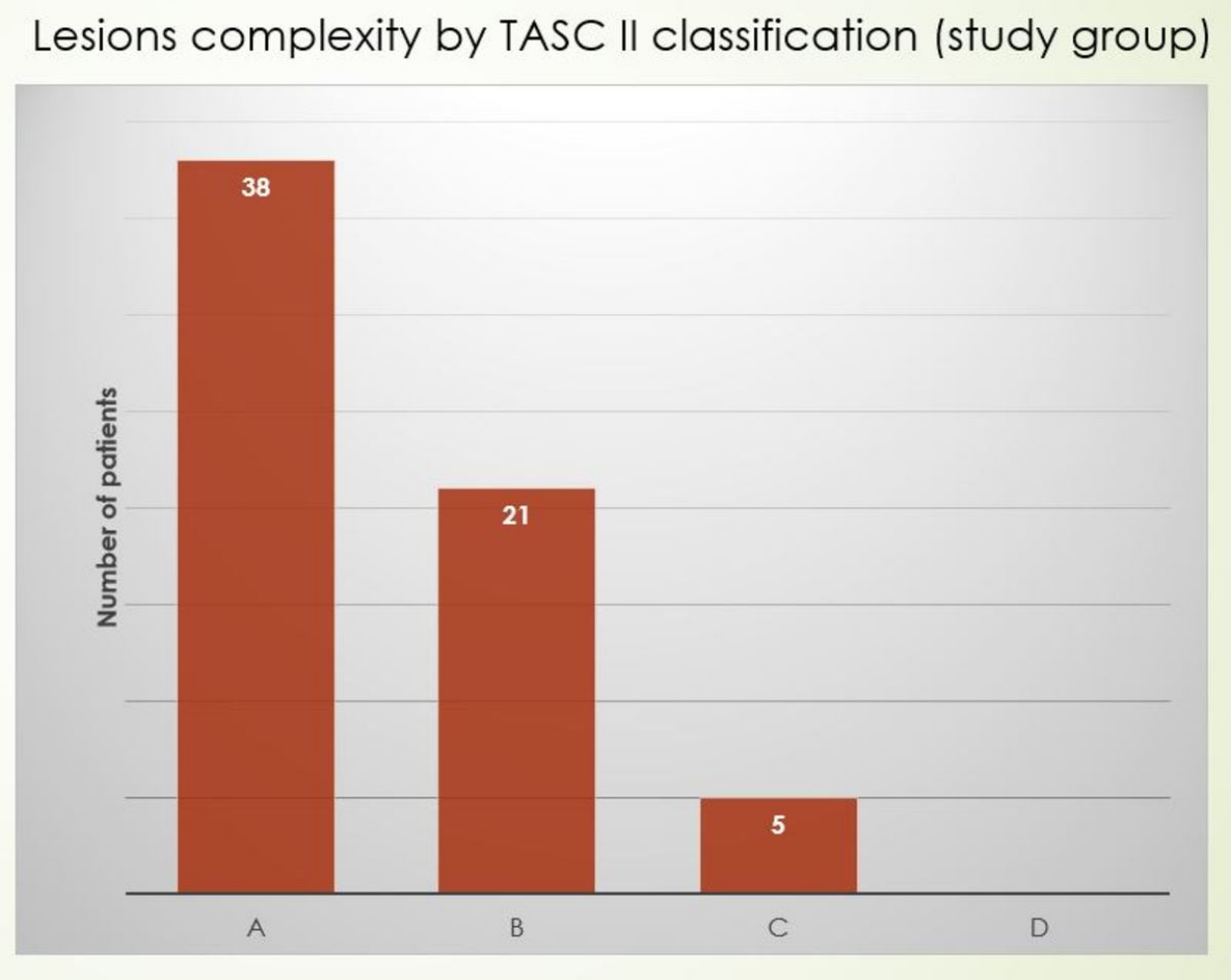

Fig. 4: Lesions complexity

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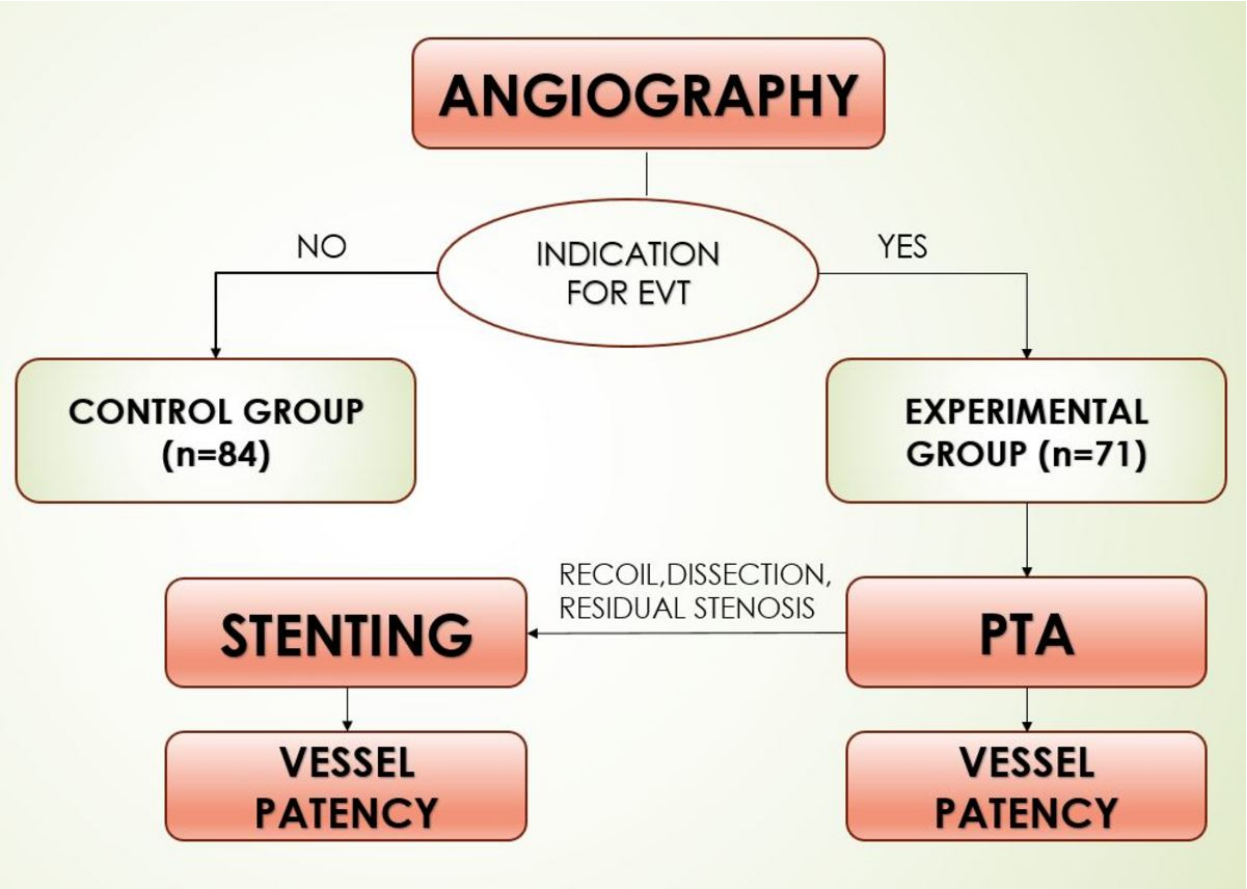

Fig. 5: Study design

Results

Endovascular procedures summary: 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 a 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).

Postprocedural CRP and fibrinogen increase: 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 ($P<0.05$). Fig. 6 on page 9

Postprocedural CRP and fibrinogen levels regarding the lesion complexity: 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. Fig. 7 on page 10

Postprocedural CRP and fibrinogen levels regarding the type of EVT: significant increase in CRP ($P<0.001$) and fibrinogen levels ($P=0.001$) was found in a subgroup of patients who underwent PTA, as well as in a subgroup who underwent stenting ($P<0.001$). CRP levels were significantly higher ($P=0.03$) in stent subgroup compared to PTA subgroup 48 hours following EVT. Fig. 8 on page 11

Postprocedural CRP and fibrinogen levels regarding the extent of periprocedural arterial injury: significant positive correlation was found between PTA treated segment length and CRP increase between 8 hours and 24 hours following EVT ($r=0.313$, $P=0.02$), balloon inflation 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 ($r=0.535$, $P=0.01$). No significant positive correlation was found between fibrinogen levels and the extent of periprocedural arterial injury. Fig. 9 on page 12

Images for this section:

	Median (interquartile range)					
	Control group	P*	Study group	P*	Total	P†
CRP 0	3 (1.9 – 4.7)	0.13	3.7 (2.05 - 6)	**<0.001**	3.2 (1.9 - 5.2)	0.17
CRP 8h	3.1 (1.8 – 5.3)		3.7 (1.9 - 6.75)		3.3 (1.9 - 6)	0.42
CRP 24h	4.75 (2.83 - 6.8)		6.2 (3.4 - 11.5)		5 (2.9 - 9.4)	**0.03**
CRP 48h	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 8h	3.5 (3.2 - 4.18)		3.6 (3.13 - 4.1)		3.55 (3.2 - 4.1)	0.76
Fibrinogen 24h	3.8 (3.33 - 4.7)		4 (3.45 - 4.9)		3.9 (3.4 - 4.7)	0.42
Fibrinogen 48h	4.3 (3.3 - 5.3)		4.3 (3.7 - 5.2)		4.3 (3.7 - 5.2)	0.93

CRP (mg/l) and fibrinogen (g/l) median by groups

Fig. 6: Plasma levels of inflammatory biomarkers after angiography (control group) and endovascular treatment (study group)

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

CRP (mg/l) and fibrinogen (g/l) median by TASC II classification

Fig. 7: Correlation of plasma levels of inflammatory biomarkers and lesion complexity according to TASC II classification

	Median (interquartile range)					P†
	PTA	P*	Stent	P*	Total	
CRP 0	3.6 (2 - 5.9)		4.6 (2.13 - 7.65)		3.7 (2.05 - 6)	0.33
CRP 8h	3.3 (1.65 - 5.75)	**<0.001**	4.6 (2.1 - 12)	**<0.001**	3.7 (1.9 - 6.75)	0.09
CRP 24h	6.2 (3.4 - 9.85)		10.1 (3.08 - 14.73)		6.2 (3.4 - 11.45)	0.18
CRP 48h	7 (3.65 - 14.05)		12.8 (8.05 - 23.9)		9.1 (4.3 - 17.7)	**0.03**
Fibrinogen 0	3.8 (3.4 - 4.5)		3.8 (3.28 - 4.93)		3.8 (3.3 - 4.7)	0.91
Fibrinogen 8h	3.55 (3.2 - 4.03)	**<0.001**	3.7 (3 - 4.35)	**<0.001**	3.6 (3.13 - 4.1)	0.94
Fibrinogen 24h	4.05 (3.43 - 4.68)		4 (3.35 - 5.15)		4 (3.45 - 4.85)	0.77
Fibrinogen 48h	4.3 (3.6 - 5)		4.9 (3.7 - 5.4)		4.3 (3.7 - 5.2)	0.15

CRP (mg/l) and fibrinogen (g/l) median by type of EVT

Fig. 8: Plasma levels of inflammatory biomarkers after PTA and stent implantation

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

Fig. 9: Correlation between elevation of plasma levels of inflammatory biomarkers and the extent of periprocedural arterial injury

Conclusion

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.

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 [3,8-11]. In the control group, the increase in CRP and fibrinogen levels following angiography was evident, although not statistically significant and could be attributed to the arterial puncture and contrast media application.

In a 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 the morphometric studies [12,13] in porcine models where more intimal hyperplasia was found after stenting compared to balloon angioplasty, suggesting a more pronounced inflammatory response.

Limitations to the study: relatively small number of patients, concomitant use of various drugs not directly related to atherosclerotic disease; different diameters, designs and structures of used stents could modulate the inflammatory response; no follow-up to study the correlation with restenosis rate.

Present study has 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.

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References

1. Ross R. The Pathogenesis of Atherosclerosis - An Update. N Engl J Med. 1986 Feb 20;314(8):488-500.

2. O'Brien ER, Schwartz SM. Update on the biology and clinical study of restenosis. Trends Cardiovasc Med. 1994 Jul 1;4(4):169-78.

3. Schillinger M, Exner M, Mlekusch W, Rumpold H, Ahmadi R, Sabeti S, et al. Fibrinogen predicts restenosis after endovascular treatment of the iliac arteries. Thromb Haemost. 2002 Jun;87(6):959-65.

4. Schillinger M, Exner M, Mlekusch W, Rumpold H, Ahmadi R, Sabeti S, et al. Vascular Inflammation and Percutaneous Transluminal Angioplasty of the Femoropopliteal Artery: Association with Restenosis. Radiology. 2002 Oct 1;225(1):21-6.

5. Vrsalovi# M, Vu#ur K. Diabetes and critical limb ischemia: the deadly duo in patients with symptomatic peripheral artery disease. Acta Clin Croat. 2016 Jun 1;55.(2.):240-5.

6. Fontaine R, Kim M, Kieny R. [Surgical treatment of peripheral circulation disorders]. Helv Chir Acta. 1954 Dec;21(5-6):499-533.

7. TASC Steering Committee, Jaff MR, White CJ, Hiatt WR, Fowkes GR, Dormandy J, et al. An Update on Methods for Revascularization and Expansion of the TASC Lesion Classification to Include Below-the-Knee Arteries: A Supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Vasc Med Lond Engl. 2015 Oct;20(5):465-78.

8. Schillinger M, Exner M, Mlekusch W, Haumer M, Ahmadi R, Rumpold H, et al. Inflammatory response to stent implantation: differences in femoropopliteal, iliac, and carotid arteries. Radiology. 2002 Aug;224(2):529-35.

9. Araújo PV, Ribeiro MS, Dalio MB, Rocha LA, Viaro F, Joviliano RD, et al. Interleukins and Inflammatory Markers in In-Stent Restenosis after Femoral Percutaneous Transluminal Angioplasty. Ann Vasc Surg. 2015 May 1;29(4):731-7.

10. Schillinger M, Exner M, Mlekusch W, Haumer M, Rumpold H, Ahmadi R, et al. Endovascular Revascularization Below the Knee: 6-month Results and Predictive Value of C-reactive Protein Level. Radiology. 2003 May 1;227(2):419-25.

11. Kavitha S, Sridhar MG, Satheesh S. Periprocedural plasma fibrinogen levels and coronary stent outcome. Indian Heart J. 2015;67(5):440-3.

12. Elesbão JL de L, Pereira AH, Grüdtner MA, Meyer F. Morphometric analysis of swine carotid artery angioplasty with or without cobalt-chromium stent implantation. J Vasc Bras. 2010 Jun;9(2):40-6.

13. Castro Júnior C, Pereira AH, Pasa MB. Morphometric analysis of the intimal reaction after stent implantation in iliac arteries submitted to angioplasty in pigs. Acta Cir Bras. 2006 Jun;21(3):139-43.