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Role of NOS and inflammatory markers in the early restenosis after the application of femoral arterial stent

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ABSTRACT

The objective of this research was to investigate the role of inflammatory markers, including the interleukin-6 (IL-6), matrix metalloprotease 9 (MMP-9), tumor necrotic factor α (TNF-α), endothelin-1 (ET-1) and nitric oxide synthase (NOS) in the early restenosis after the application of femoral arterial stent. According to this, serum samples were collected from the patients who accepted the implantation of arterial stents due to the atherosclerotic occlusive disease in the lower extremities at the following timepoints: 24 h before implantation, 24 h, 1 month, 3 months and 6 months after implantation. With the samples, we detected the levels of IL-6, TNF-α and MMP-9 by using the enzyme-linked immunosorbent assay (ELISA) in serum, levels of ET-1 in plasma by using the non-balanced method of radioimmunity assay and the activity of NOS by using the chemical analysis. Results showed that during the 6-month follow-up, 15 patients (15.31%) reported restenosis; at postoperative 24 h, the level of IL-6 in the restenosis group was much lower than that of the non-restenosis group ($P < 0.05$), while the level of MMP-9 was higher than that of the non-restenosis group ($P < 0.01$); besides, at postoperative 24 h, 1, 3, and 6 months after the operation, the average level of ET-1 in the restenosis group was higher than that in the non-restenosis group ($P < 0.05$ or 0.01). In the restenosis group, the level of NOS in the serum of patients after the implantation of the stent decreased evidently, which was rescued by the treatment of atorvastatin in a dose-dependent manner ($P < 0.05$). In conclusion, at postoperative 24 h, the levels of IL-6 and MMP-9 increased, while the level of NOS decreased, and the level of ET-1 in the plasma of restenosis patients keeps higher than the baseline.

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Introduction

Atherosclerosis obliterans (ASO) in lower extremities is a type of chronic arterial occlusive disease caused by atherosclerosis, with the clinical manifestation of ischemia in lower extremities caused by the arterial lumen stenosis or occlusion due to atherosclerosis, secondary thrombosis and medial degeneration of artery (1). ASO in the lower extremities could not only affect the life quality of patients but also increase the risk of coronary heart disease, cerebral hemorrhage and cerebral infarction (2). Moreover, ASO, as reported, is one of the major causes of the amputation of lower extremities, taking up nearly 40% to 60% of amputation patients (3). Thus, a timely, safe and effective method is quite important for the treatment of ASO.

So far, clinical treatment for ASO in the lower extremities includes vascular intervention and bypass operation that usually cause surgical trauma which could hardly be tolerated by the elders and is generally adverse to the prognosis (4). However, microinvasive interventive surgeries, including percutaneous transluminal angioplasty, balloon dilatation and in-stent implantation, have become the first choice for vascular surgeons due to the advantages, like small trauma, rapid recovery, repeatability and immediate effect (5). Nevertheless, the arising problem of "in-stent restenosis" has now become a major issue affecting the long-term efficacy of intracavitary therapy for atherosclerotic vessels. The prevalence of ISR within 1 year after the implantation of a stent in the femoral artery has risen to 18% to 40%, according to the published literatures (6-7). Therefore, the prevention of ISR is one of the major challenges for patients after PTA.

ISR is a quite complicated pathophysiological process involving a variety of aspects, including immune inflammation, intimal hyperplasia and remodeling of extracellular matrix, where inflammation is associated closely with ISR.

Restenosis after PTA has been considered a unique pathophysiological process, instead of the accelerated form of atherosclerosis after the intervention. Adhesion of inflammatory cells, aggregation, deposition of extracellular matrix and hyperplasia and migration of endothelial cells and vascular smooth muscle cells are associated directly with the ISR-caused vascular wall damage and the key factors for the restenosis after the vascular intervention (8-9). In addition, the damaged endothelial cells can release more endothelin 1, angiotensin II and growth factor but less nitric oxide, which may further promote the endothelial hyperplasia and proliferation of smooth muscle cells, thereby triggering the ISR (10,11). Existing data, though, have confirmed various clinical factors are related to ISR, but little is known about the molecular mechanism of ISR. In this study, we detected the levels of inflammatory cytokines in the serum and NOS activity of patients before and after femoral stent implantation, aiming to uncover the relationship between these indicators and the ISR.

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Materials and Methods

Selection of patients

This study was approved by the Ethical Board of Nanping First Hospital Affiliated to Fujian Medical University and conducted in accordance with the Declaration of Helsinki. All participants signed the written informed consent. In this study, a total of 103 patients who accepted the implantation of the arterial stent due to the ASO in the lower extremities, including 56 males, with an average age of (62.58± 6.49) years old, aged between 52 and 76 years. Among these patients, 5 patients were excluded from this study due to the failure in fulfilling the 6-month follow-up, while the remaining 98 patients completed it. Color Doppler Ultrasound Detector was applied to detect the site and degree of stenosis for the femoral artery in the lower extremity of patients. ISR was indicated by the degree of in-stent restenosis ≥50%. Criteria for inclusion: Patients aged between 40 and 80 years old; patients with sclerosis and occlusion in the femoral arteries of the lower extremities; patients who were classified as Rutherford III to V; patients with no evident stenosis in the proximal inflow channel, or with no lesion that could affect the blood flow evidently after treatment, or at least one of three arteries (the artery beneath the knee and in front of the tibia, the artery in the rear of the tibia and the femoral artery) that was originally clear or cleared by the treatment; patients with no absolute contraindications of balloon dilation for femoral artery and stent implantation. Criteria for exclusion: Patients with atherosclerotic lesions in other parts; patients with heart or lung diseases that could not tolerate the surgery; patients with active rheumatism or other kinds of acute inflammatory diseases, chronic liver disease, renal insufficiency, general immune disease, malignant tumors, acute myocardial infarction, or unstable angina pectoris.

Procedures of surgery

All surgeries were carried out in the same hemodynamics/arteriography room by the same team for all patients under local anesthesia in accordance with the guidance for the vascular intervention of Nanping First Hospital Affiliated to Fujian Medical University. Ipsilateral or bilateral puncture for the femoral arteries was performed for inserting the 6F or 7F sheathing canal, through which 5000 IU heparin was injected intravenously, followed by the infusion of hypotonic non-ionic contrast medium. A hydrophilic 0.035-inch guiding wire was guided through the lesion, and an appropriate balloon was placed prior to the implantation of the stent for pre-dilation. Restoration of blood flow in the vessels of lower extremities was performed via the angioplasty and placing an auto-dilation, the ePTFE-covered stent (diameter: 5-8 mm; length: 5, 10 or 15 cm) at the femoral-popliteal segment. After the implantation of the stent, dilation would be conducted for the residual stenosis > 30%. After the surgery, all patients would undergo antiplatelet therapy the medication of clopidogrel and aspirin.

Detection of inflammatory cytokines and NOS

Venous blood in the volume of 5 mL was drawn at 24 h before surgery and 24 h, 1, 3 and 6 months after surgery from the patients who were informed of keeping fasting for 8 h before sample collection. Samples were immediately placed at 4°C and centrifuged within 4 h at 3600 r/min for 5 min to collect the serum. The serum was then divided into three tubes, with 0.5 mL in each tube, stored at -70°C for detection in the central laboratory. Levels of IL-6, TNF-α and MMP-9 in serum were determined through the enzyme-linked immunosorbent assay (ELISA), ET-1 level in plasma through the non-balanced radioimmunity assay and activity of NOS through the chemical analysis. All protocols for determination were carried out according to the methods and steps of the manufacturers.

Follow-up

A 6-month follow-up was carried out for the patients at the clinic to analyze the incidence of restenosis, while at the end of 6 months, clinical evaluation, physical examination and color Doppler ultrasonic examination were performed for all patients.

Statistical analysis

SPSS 17.0 software was utilized to perform the statistical analysis. Measurement data in normal distribution were expressed in form of mean ± standard deviation (SD) and compared among groups via t-test. Measurement data not in normal distribution were expressed in form of [M (P25, P75)]. Count data were expressed in form of a ratio (%) and compared by chi-square test. $P < 0.05$ suggested that the difference had statistical significance.

Results

The results of the evaluation for 98 patients during 6 months showed that 15 patients reported restenosis (15.31%), while 83 patients had no restenosis. During the evaluation, no stent rupture was found. Except for the restenosis, no other obvious clinical deterioration was found in 15 patients. Besides, a comparison of the baseline characteristics (myocardial risk factors and medication) between the restenosis patients and non-restenosis patients showed no significant difference (Table 1). The baseline features of FP lesion, including the Rutherford grades and TASCII grades, initial stenosis or occlusion, and run-off arteries in the tibia and fibula (2 or 3 run-off arteries) are shown in Table 2. The ratio of TASC A lesions in patients with restenosis was much higher than that of patients with no restenosis ($P < 0.05$).

Firstly, we compared the levels of TNF-α, IL-6 and MMP-9 in the serum, ET-1level in plasma and NOS activity before and after surgery. Correspondingly, the results (Table 3) showed that the IL-6 level was doubled within 24 h but decreased after 6 months ($P < 0.05$). Comparison of TNF-α levels at different timepoints after surgery with the baseline levels showed no significant differences ($P > 0.05$). At postoperative 24 h and 3 months, levels of ET-1 were much higher than the baseline level ($P < 0.05$), but the difference between the level at postoperative 6 months and the baseline level showed no statistical significance ($P > 0.05$). An acute increase was found in the level of MMP-9 in the serum at postoperative 24 h ($P < 0.01$), but the level would return to normal at postoperative 1 month. After the implantation of the stent, the NOS level in serum decreased sharply, which was then rescued by the treatment of atorvastatin in a dose-dependent manner ($P < 0.05$).

To further clarify the interactions between indicators and ISR, we compared the indicators between the resteno-

Table 1. Baseline features of patients in the restenosis group and non-restenosis group.

	Total (n=98)	Restenosis group (n=15)	Non-restenosis group (n=83)	P
Age (years)	65.2±10.4	67.6±9.2	65.7±11.6	0.85
Males	69 (70.4%)	11 (73.3%)	58 (69.8%)	0.99
Hypertension	72 (73.4%)	10 (66.7%)	60 (72.3%)	0.96
Diabetes mellitus	26 (26.5%)	4 (26.7%)	22 (26.5%)	0.83
Dyslipidemia	14 (14.2%)	2 (13.3%)	12 (14.5%)	0.86
Smoking	76 (77.6%)	12 (80.0%)	64 (77.1%)	0.68
ACE inhibitor	42 (42.9%)	6 (40.0%)	36 (43.3%)	0.99
Angiotensin receptor blocker	14 (14.2%)	0	14 (16.8%)	0.99
β adrenergic receptor	18 (18.4%)	5 (33.3%)	13 (15.6%)	0.99
Diuretic	36 (36.7%)	4 (26.7%)	32 (38.6%)	0.99
Statins	26 (26.5%)	5 (33.3%)	20 (24.1%)	0.26
Insulin	25 (25.5%)	8 (53.3%)	17 (20.5%)	0.14
Melbine	15 (15.3%)	3 (20.0%)	12 (14.5%)	0.20

Table 2. Rutherford grades and features of lesion and implanted stents in patients of the restenosis group and the non-restenosis group.

	Total (n=98)	Restenosis group (n=15)	Non-restenosis group (n=83)	P
Rutherford Grades				
Rutherford 3	41 (41.8%)	5 (33.3%)	36 (43.4%)	0.99
Rutherford 4	11 (11.2%)	3 (20.0%)	8 (9.7%)	0.99
Rutherford 5	46 (47.0%)	7 (46.7%)	39 (46.9%)	0.99
TASC II Grades				
TASC A	22 (22.4%)	58 (53.3%)	14 (16.8%)	0.02
TASC B	34 (34.6%)	2 (13.3%)	32 (38.5%)	0.26
TASC C	44 (44.9%)	5 (33.3%)	36 (43.3%)	0.63
Features of the initial lesion				
Stenosis	14 (14.3%)	0	14 (16.8%)	0.99
Occlusion	84 (85.7%)	15 (100%)	69 (83.1%)	0.99
Run-off arteries in the tibia and fibula				
2 – run-off arteries	62 (63.3%)	15 (100%)	47 (56.6%)	0.26
3 – run-off arteries	36 (36.7%)	0	36 (43.3%)	0.26

Table 3. Changes in the levels of TNF-α, IL-6, MMP-9, ET-1 and NOS before and after surgery.

Item	Baseline level	Postoperative 24 h	Postoperative 1 month	Postoperative 3 months	Postoperative 6 months
IL-6 (pg/mL)	15.08±16.69	26.32±14.21**	18.08±13.53*	16.08±11.26	15.12±8.31
TNF-α (pg/mL)	177.47±87.12	172.42±80.34	175.43±83.18	167.73±75.21	171.26±80.53
MMP-9 (ng/mL)	84. 37±21. 37	151.21±31.15**	85. 45±42. 3	83. 45±23. 38	82. 25±12. 45
ET-1 (ng/L)	72.14±85.64	77.32±6.65**	72.29±85.42	74.91±86.73*	72.64±86.82
NOS (μg/mL)	177.06±29.86	87.21±23.45**	117.11±23.88*	139.30±27.15*	164.36±32.60

Note: * $P < 0.05$, ** $P < 0.01$ *vs.* the levels before surgery.

sis group and non-restenosis group and found that levels of TNF-α, IL-6 and MMP-9 in serum, level of ET-1 in plasma and NOS activity before surgery were similar between two groups (P > 0.05). However, when it came to 24 h after surgery, the level of IL-6 in the restenosis group was much higher than that in the non-restenosis group (P < 0.05), but the difference in TNF-α at all timepoints after surgery between the two groups had no statistical significance (P > 0.05). At 24 h after surgery, patients had a higher level of MMP-9 in the restenosis group than that in the non-restenosis group (P < 0.05). The level of ET-1 in patients of the two groups increased at 24 h after surgery when compared to the baseline data (P < 0.05). In the non-restenosis group, the average level of ET-1 at postoperative 1, 3 and 6 months was all higher than the baseline level (P < 0.05). Besides, the average levels of ET-1 in the restenosis group at postoperative 24 h, 1, 3 and 6 months were all higher than those in the non-restenosis group (P < 0.05). No significant difference was shown in the comparison of the NOS levels in the serum of patients in the non-restenosis group (P > 0.05); after the implantation of the stent, patients had an obvious decline in the level of NOS in serum, which was then reversed by the treatment of atorvastatin in a dose-dependent manner (P < 0.05); the difference in the level of NOS in serum between two groups had statistical significance (P < 0.05) (Table 4).

Table 4. Changes in the levels of TNF-α, IL-6 and MMP-9 in serum and the level of ET-1 in plasma and NOS activity of patients in two groups.

Item	Group	Baseline	Postoperative			
			24 h	1 month	3 months	6 months
IL-6 (pg/mL)	Non-restenosis	15.08±16.69	18.32±12.15*	16.08±13.53*	15.86±11.26	15.59±10.31
	Restenosis	15.08±16.69	30.46±18.32**,o	22.08±14.32*, o	16.54±13.86	15.67±12.52
TNF-α (pg/mL)	Non-restenosis	175.31±86.42	172.51±83.45	170.35±82.16	172.74±80.22	173.28±81.52
	Restenosis	176.34±85.56	173.54±82.51	172.25±82.83	170.63±79.24	174.43±82.78
MMP-9 (ng/mL)	Non-restenosis	84. 37±21. 37	90.36±25.37*	84.35±32. 63	84. 47±28. 34	85. 25±20. 83
	Restenosis	85. 16±20. 85	163.34±38.57**,o	86. 45±25. 31	83. 86±29. 44	84.53±18. 61
ET-1 (ng/L)	Non-restenosis	71.91±85.64	76.35±86.44	73.92±85.74	72.26±85.17	73.83±85.89
	Restenosis	72.82±85.81	80.99±87.12**, o	77.51±85.96*, o	75.62±86.93*, o	78.43±87.02*, o
NOS (μg/mL)	Non-restenosis	175.34±25.75	166.08±27.36	168.05±27.92	164.26±25.38	172.21±28.86
	Restenosis	177.06±29.86	87.21±23.45**, o	126.32±26.75*, o	142.35±26.45*, o	166.34±30.63

Note: $^{o}P < 0.05$ *vs.* the non-restenosis group; * $P < 0.05$, ** $P < 0.01$ *vs.* the baseline data in the same group.

Discussion

ISR is the most common risk for patients after PTA (12). As for the fragility of the artery and endothelial regeneration after stent implantation, neointima hyperplasia emerges usually at the site of the stent which could further result in the dysfunction and ectopic proliferation of endothelial cells and migration of vascular smooth muscle cells (13). A study by Guimaraes et al. reported that the restenosis rate is 15% during the 6-month follow-up for the patients with atherosclerosis-induced peripheral arterial diseases who accepted the implantation of the membrane-covered stent (14), which is similar to our findings in this study (15.31%). Besides, exploring the valuable biomarkers in predicting the incidence of restenosis is quite important for optimizing the treatment protocols for PTA and improving the prognosis.

Vasculitis after the intravascular surgery has now been curtained as the cornerstone in the process of restenosis, and some inflammatory markers have been considered as the potential predictors for the mid-term outcomes. IL-6, as a cytokine possessing multiple effects generated spontaneously or in response to stimuli from a variety of cells, is generally involved in the pathophysiological process of atherosclerosis (15), and the protein and gene expression of IL-6 in human atherosclerotic diseases has been confirmed. A study by Songlin Guo et al. (16) has confirmed that after the intervention, IL-6 level is a key predictor for the midterm ISR. Our work demonstrated that at 24 h after the operation, the level of IL-6 in the restenosis group was much higher than that in the non-restenosis group ($P < 0.05$). The baseline of IL-6 is more sensitive in prediction, so it could reflect the vasculitis and endothelial injury in the development and progression of atherosclerosis directly. TNF-α, as a pleiotropic pro-inflammatory cytokine, is generated and secreted by a variety of cells, including macrophages, natural killer cells, T cells, endothelial cells, vascular smooth muscle cells and adipose tissue (17). It has been suggested that in the stable phase after myocardial infarction, the increase of TNF-α is related to the augmentation of the risk of recurrent coronary artery events (18). But in our study, we did not find any direct correlation between TNF-α and the incidence of ISR. Moreover, TNF-α could also enhance the expression of matrix metalloproteinases, including MMP-9, thereby attenuating the atherosclerotic plaques and increasing the instability (19).

MMP-9, as a type IV collagen, is mainly expressed in macrophages and is able to enhance the instability of plaques. Related data have shown that after implantation of the stent, activity and expression of MMP-9 at the site of ISR increased significantly (20). Likewise, in our study, the level of MMP-9 at 24 h after surgery in the restenosis group was much higher than that in the non-restenosis group ($P < 0.05$). This may attribute to the excessive repair of vessels at the site of injury after stent implantation, and essentially, the process of restenosis is believed to be the neointima hyperplasia and vascular remodeling after vascular injury, during which MMP-9 plays a pivotal role that could regulate the degradation and deposition of extracellular matrix to induce the migration and proliferation of vascular smooth muscle cells (21).

ET-1 is a major vasoconstrictor, and increasing the release of ET-1 could promote the proliferation of vascular smooth muscle cells and accelerate thrombosis (22). It has already been proved that the ET-1 receptor system is pivotal to the pathogenesis of neointimal hyperplasia after endothelium injury (23). Thus, antagonizing the endothelin-receptor system may be a potential strategy to prevent restenosis after angioplasty. In this study, we found that all patients had an increase in the level of ET-1 in the plasma within 24 h after PTA. In the restenosis group, the ET-1 level in plasma was kept higher than the baseline. At 6 months after PTA, the average level of ET-1 in the restenosis group was also higher than that in the non-restenosis group. Hence, the increase of ET-1 6 months after PTA may correlate with the ISR.

NO is synthesized by NO synthases, of which NOS is the one that is constitutively expressed in the endothelium. Endothelium-derived NO possesses multiple biological effects, including dilating the vessels, inhibiting the growth of vascular smooth muscle cells, antagonizing atherosclerosis, preventing the aggregation of platelet and suppressing the adhesion of white blood cells on the vascular wall (24). Besides, NO is already known to inhibit the generation of endothelin, a kind of vasoconstrictor, and angiotensin II, which may further induce the proliferation of vascular smooth muscle cells (25). The results of this study also indicated that after implantation of a stent, the NOS level in the serum of patients in the restenosis group decreased evidently, which could be rescued by the treatment of atorvastatin in a dose-dependent manner ($P < 0.05$); dif-

ferences in NOS levels between two groups showed no statistical significance ($P < 0.05$). Hence, due to the reduction of NOS synthesis, decreased or damaged NO generation could promote the proliferation of vascular smooth muscle cells, thereby inducing neointimal hyperplasia and eventually triggering the ISR.

Overall, at postoperative 24 h, the levels of IL-6 and MMP-9 increased, while the level of NOS decreased, and the level of ET-1 in the plasma of restenosis patients keeps higher than the baseline. Regretfully, we, in this study, did not find any correlation between the peripheral artery and the indicators above, so whether these indicators could be used to predict the ISR should be further investigated in future work.

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