

Impact of the Post-Thrombotic Syndrome on the Arterial Wall of the Lower Limbs

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Abstract

Objective: Deep vein thrombosis of the lower limbs is a common disease in vascular surgery. Approximately 20–50% of deep vein thrombosis patients develop post-thrombotic syndrome, which can severely affect the patient's quality of life. However, the precise science of the pathophysiology of the progression of the post-thrombotic syndrome remains unclear. Studies have demonstrated that patients with post-thrombotic syndrome of the lower limbs have impaired arterial wall endothelial function. Nevertheless, there is little research on the different impacts of post-thrombotic syndrome on the arterial wall endothelial function between the affected limbs and the healthy limbs. This study aims to assess this difference.

Methods: A total of 60 patients treated for the post-thrombotic syndrome of the lower limbs were included. The flow-mediated dilation (FMD%) and nitroglycerin-mediated dilation (NMD%) were measured to assess the different endothelial function alterations of the common femoral arterial wall between the affected limb and the healthy limb.

Results: No significant differences in the common femoral artery diameter between the affected limbs and the healthy limbs were discovered (8.94 ± 0.92 mm vs 8.75 ± 1.0 mm, $P=0.710$). The flow-mediated dilation of the common femoral artery of the affected limbs were significantly lower compared to the healthy limbs (FMD%: $3.21 \pm 1.07\%$ vs $5.19 \pm 1.35\%$, $P=0.001$). However, there was no significant difference in the nitroglycerin-mediated dilation of the common femoral artery between the affected limbs and the healthy limbs (NMD%: $13.37 \pm 1.78\%$ versus $14.45 \pm 2.14\%$, $P=0.083$).

Conclusions: Our results demonstrated the association between post-thrombotic syndrome and deteriorated endothelial functional properties of the arterial wall of the lower limbs. Endothelial dysfunction of the arteries wall was more severe in the affected lower limbs with the post-thrombotic syndrome than in the healthy limbs. The mentioned findings may partly explain the pathophysiology of the progression post-thrombotic syndrome of the lower limbs.

Highlights: Studies have demonstrated that patients with post-thrombotic syndrome of the lower limbs have impaired arterial wall endothelial function. Our results demonstrated the endothelial dysfunction of the arteries wall was more severe in the affected lower limbs with the post-thrombotic syndrome than in the healthy limbs. Our findings may partly explain the pathophysiology of the progression post-thrombotic syndrome of the lower limbs.

Keywords

post-thrombotic syndrome, arterial wall endothelial function, flow-mediated dilation, nitroglycerin-mediated dilation

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Introduction

Deep vein thrombosis (DVT) of the lower limbs is a common disease in vascular surgery. More than one out of 1000 people were affected by DVT every year.¹ After a first episode of DVT, vessel wall damage and chronic venous occlusion accompanied by venous hypertension result in post-thrombotic syndrome (PTS). Approximately 20–50% of DVT patients develop PTS despite adequate anticoagulation, which is a chronic complication of DVT and a combination of signs and symptoms, such as lower limbs chronic edema, pain, telangiectasia, heaviness, hyperpigmentation, and ulcers. PTS can severely negatively affect the patient's quality of

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life.^{2,3} Nonetheless, the precise science of the pathophysiology of the progression of PTS has not been completely understood.

Just as the venous wall plays an important role in the pathogenesis of the PTS, the deterioration of arterial wall endothelial function might be related to PTS development. The arterial wall endothelial function can be non-invasively assessed by measurement of the flow-mediated dilation (FMD%) and nitroglycerin-mediated dilation (NMD%) with high-resolution ultrasound methods.⁴ Therefore, whether there is a different impact of PTS on the arterial wall endothelial function between the affected limb and the healthy limb was accessed in this study.

Patients and Methods

This study was conducted in the Department of Vascular Surgery, Jinan City People's Hospital Affiliated to Shandong First Medical University, Shandong Province, China, from January first 2019 to June 30th 2021. The study protocol and informed consent were approved by the medical ethics committee of the Jinan People's Hospital Affiliated with Shandong First Medical University. Every participant included in the study signed informed consent.

In this study, 60 consecutive patients aged 45-75 diagnosed with and treated for PTS of one lower limb were included. All participants had a history of deep vein thrombosis of lower limbs for more than one year and were treated with anticoagulation and compression therapy following the guidelines.⁵ After the acute stage of DVT, the follow-up examination of patients was performed 12-24 months. Besides, the Villalta scale was employed to evaluate signs and symptoms of PTS. Patients were diagnosed with PTS if they scored five or more points on the Villalta scale,^{6,7} while patients with scores below five were considered to have no PTS. Exclusion criteria were: patients with prior limb surgery, history and clinical signs of peripheral arterial disease, diabetes, hypercholesterolemia, high blood pressure, leg trauma, clinical signs of lymphedema, active cancer, history of chronic obstructive pulmonary disease, as well as other cardiovascular comorbidity and patients do not want to participate in this study. According to the protocol, participants should provide a medical history and undergo a clinical examination to exclude these diseases.

The Flow-mediated dilation (FMD%) and nitroglycerin-mediated dilation (NMD%) of the common femoral artery (CFA) of the affected limb and the healthy limb were measured using ultrasound to assess the endothelial function of the arterial wall of lower limbs. They were calculated by the rate of change of the arterial diameter before and after the pressure of the cuff.

The measurements in the morning were conducted using ultrasound Doppler by SonoScape (China) portable ultrasound equipment, with a SonoScape 4-16 MHz transducer. The measurements were performed by experienced vascular physicians from the same team. They all learned the measurement standard before the study. The participants were in the resting supine position for 20 min in a quiet, temperature-controlled room at 21°C between 9:00 and 11:00 AM. The participants were requested to fast overnight before testing and avoid exercise at least 12 h before the test, so as to empty their bladder before the examination.

Moreover, they refrained from taking drugs with known vascular effects for example alcohol, caffeine, nicotine.

Common femoral artery (CFA) was measured just below the inguinal ligament 2 cm proximal of the bifurcation in the deep and superficial femoral artery (SFA). The diameter of CFA was measured at the end of the diastolic phase, as confirmed by the R-wave on the synchronized electrocardiogram monitoring. The diameters of CFA were measured in three cardiac cycles, and the values were averaged. First, the resting mean arterial diameter of CFA of the affected limb and the healthy limb were measured, forming the baseline arterial diameter of CFA.

A large blood pressure cuff was first placed around the upper thigh of the affected limb, 10 cm distally from the greater trochanter. Thereafter, the blood pressure cuff was inflated to 50 mm Hg above systolic pressure to block arterial inflow for 10 min. CFA diameter was measured after the cuff deflation of 60 s. The same procedure was performed for the CFA of the healthy limb.

After a 10-min rest, participants were administered a spray of sublingual nitroglycerine (NTG) 400µg. Five minutes later, the CFA diameter of the affected limb and the healthy limb were measured. Flow-mediated dilation (FMD%) and nitroglycerin-mediated dilation (NMD%) were defined as the percentage increase in the CFA diameter one minute after cuff deflation and five minutes after administration of nitroglycerin compared with the baseline arterial diameter of CFA, respectively.

Statistical Analysis

Data are expressed as mean \pm standard deviations and analyzed with the Paired-sample t-test for the comparison between the affected limbs and the healthy limbs. Additionally, all data were analyzed with SPSS software (SPSS Inc, Chicago, IL). $P \leq 0.05$ indicated significance.

Results

A total of 60 patients treated for PTS of the lower limbs were included in the present study. At baseline, the mean age of the patients was 55 years, 28 patients were female, 32 patients were male, 33 patients had a history of iliofemoral DVT, and 27 patients had a history of femoropopliteal DVT. The mean disease course was 16 months, the mean BMI was 29 kg/m², and the mean Villalta score was 10. Further details are listed in Table 1.

As the Table 2 was showed, the results demonstrated no significant differences in CFA diameter between the affected limbs and the healthy limbs (8.94 ± 0.92 mm vs 8.75 ± 1.0 mm, $P = 0.710$). The flow-mediated dilation of the common femoral artery of the affected limbs were significantly lower compared to the healthy limbs (FMD%: $3.21 \pm 1.07\%$ vs $5.19 \pm 1.35\%$, $P = 0.001$). However, there was no significant difference in the nitroglycerin-mediated dilation of the common femoral artery between the affected limbs and the healthy limbs (NMD%: $13.37 \pm 1.78\%$ versus $14.45 \pm 2.14\%$, $P = 0.083$).

Table 1. Baseline Characteristics (n = 60)

Characteristic	Mean \pm SD or No
Age, years	55 \pm 14
Sex	
Female	28
Male	32
BMI, kg/m ²	29 \pm 5.6
disease course, months	16 \pm 5
DVT extent	
Iliofemoral DVT	33
Femoropopliteal DVT	27
Villalta score.	10 \pm 3
Type of anticoagulant	
rivaroxaban	60
TT(s)	16.25 \pm 2.14
PT(s)	12.35 \pm 1.17
APTT(s)	26.88 \pm 3.49
D-dimer levels(μ g/mL)	3.03 \pm 1.47
FB(g/L)	4.65 \pm 0.34

Abbreviations: TT, thrombin time; PT, prothrombin time; APTT, activated partial thromboplastin time; FB, fibrinogen.

Table 2. Flow-mediated Dilation (FMD%) and Nitroglycerin-mediated Dilation (NMD%) of the Common Femoral Artery of the Affected Limb and the Healthy Limb in Post-thrombotic Syndrome (PTS) Patients.

	Affected Limb	Healthy Limb	p
CFA diameter (mm)	8.94 \pm 0.92	8.75 \pm 1.01	0.710
FMD (%)	3.21 \pm 1.07	5.19 \pm 1.35	0.001
NMD (%)	13.37 \pm 1.78	14.45 \pm 2.14	0.083

Discussions

Deep vein thrombosis is a common disease in vascular surgery. Approximately 20–50% of the DVT patients will develop post-thrombotic syndrome (PTS), which is a chronic complication and can negatively severely affect the quality of patients' life of quality.^{1,2} There are several pathophysiological mechanisms linked with the progression of DVT to PTS formation. Venous obstruction and reflux after DVT can induce venous hypertension, which initiates a cascade of complex cellular and immune events magnified by genetic predisposition. Venous hypertension leads to leukocytes activated, and then leukocytes adhere to venous endothelium and migrate through the vein wall. Venous hypertension also causes shear stress on the endothelial cells altered, and then the endothelial cells release inflammatory mediators, prothrombotic precursors, express adhesion molecules, chemokines, and vasoactive agents.^{8,9} These events result in the initiation of inflammatory cascades in patients with DVT. Changes in shear stress and inflammation can injure glycocalyx, alter nitric oxide production, increase expression of monocyte chemoattractant protein-1, and promote the production of cytokines and MMPs.^{10,11} All of these events have contributed to the development of DVT towards PTS. Nevertheless, the exact pathophysiology mechanisms of PTS are not completely understood.

Besides, previous studies have revealed the association between DVT and deteriorated functional capability of the arterial wall including endothelial dysfunction of macro- and microcirculation. Jeraj L et al discovered that the function of the brachial arterial wall in patients with DVT was changed, and the patients with DVT deteriorated endothelium-dependent and independent dilation of the brachial artery.¹² Additionally, patients with a family history of myocardial infarction have a higher incidence of DVT,^{13,14} reflecting a certain relationship between arterial and venous disease. Carotid and femoral arterial intima-media thickness increased in patients with DVT compared with healthy controls; endothelial dysfunction of the brachial artery was also revealed in patients with unprovoked DVT.^{15–17} These studies suggested that arterial stiffness increased in DVT patients, and there is an interrelationship between venous thromboembolic disease and arterial disease. However, the different impacts of PTS on the arterial wall endothelial function between the affected limbs and the healthy limbs have not been studied.

Arterial endothelial cells play a key role in regulating vascular tension by releasing endothelial-derived relaxation factors and endothelial-derived contraction factors. Impaired vascular endothelial function is an early marker of atherosclerosis that can occur before the formation of atherosclerotic lesions. There are two forms of vasodilation. One is endothelium-dependent vasodilation, which means that endothelial cells release endothelium-derived diastolic factors under drugs (such as acetylcholine) or physiological stimuli (for example, reactive congestion), which cause vasodilation, which depends on a structurally intact and functional endothelium.¹⁸ The other is non-endothelial-dependent vasodilation, which refers vasodilation caused by releasing nitric oxide directly by nitroglycerin, independent of the vascular endothelium. Arteries with normal endothelial function expand at the release of endothelial-derived relaxation factors with increased flow, while arteries with abnormal endothelial function lose this response upon increased blood flow.

The flow-mediated dilation (FMD%) test is a standard non-invasive clinical tool for assessing arterial wall endothelial function. In the test, rapid release of the tourniquet causes the increased blood flow in hypoxic muscles (reactive hyperemia), followed by increased flow through the upstream artery and vasodilation induced by increased shear stress.¹⁹ Nitroglycerin-mediated dilation (NMD%) was used to quantify the endothelium-independent maximal vascular dilatation following exogenous NTG supplementation and to determine whether impairments in vasodilatation are caused by a loss in smooth-muscle cell integrity or the inability of endothelial cells to release nitric oxide.²⁰ FMD and NMD are typically expressed as the percentage increase in the artery diameter above baseline. Our study is the first to evaluate the arterial wall endothelial function of the limbs in patients developing PTS by FMD and NMD test. Our results demonstrated that the flow-mediated dilation of the common femoral artery of the affected limbs were significantly lower compared to the healthy limbs (FMD%: 3.21 \pm 1.07% vs 5.19 \pm 1.35%, P = 0.001). However, there was no significant difference in the nitroglycerin-mediated dilation of the common femoral artery

between the affected limbs and the healthy limbs (NMD%: $13.37 \pm 1.78\%$ versus $14.45 \pm 2.14\%$, $P = 0.083$). In order to prevent the occurrence of post-thrombotic syndrome of lower extremities, for patients with acute lower extremity deep vein thrombosis, in addition to standard anticoagulation therapy, early thrombus removal and elastic support are also crucial. Wear some loose pants every day. If you sit for a long time, it is best to move around when you stand up for half an hour. You should also control your weight every day, and pay attention to quitting smoking and drinking. This finding suggests a worse arterial wall endothelial function of the affected limbs than the healthy limbs in patients who develop PTS. Limbs with PTS have an increased stiffness of peripheral arteries owing to the functional incapability of the venous system. In the pathophysiological study of PTS formation, more attention should be paid to the altered arterial wall endothelial function of the affected limbs.

Conclusions

This is the first study to demonstrate that the endothelial dysfunction of the arterial wall was worse in the affected lower limbs with PTS than in the healthy limbs. The findings would partly explain the pathophysiology of the progression of PTS of the lower limbs.

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Author Contributions

Mingshu Lu researched data and outlined the article. Xiangbin Qi researched data for the article and wrote the manuscript. Yunhui Li and Jingpeng Bi reviewed/edited the manuscript before submission.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The research project were approved by the institutional review board (Committee of Medical Ethics of the People's Hospital Affiliated to Shandong First Medical University).


Informed Consent

All participants in this study have signed an informed consent and agreed to be enrolled into the clinical trial.

Trial Registration

The study has been registered in the Chinese Clinical Trials Registry.

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