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Original Article

The relationship between vascular endothelial function and carotid ultrasound examination in different disease populations

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Abstract: Objective: This study aims to investigate the relationship between vascular endothelial function and carotid ultrasound examination in different disease populations. Methods: A total of 405 patients were selected as the study object. These patients were divided into six groups: hypertension group, hyperlipidemia group, diabetes mellitus group, hypertension-hyperlipidemia group, hypertension-hyperlipidemia-hyperglycemia group, and non-above-mentioned disease group. Patients in these groups were evaluated through vascular endothelial function and carotid ultrasound examinations, respectively. Results: Brachial artery blood flow mediated diastolic function was consistent with carotid atherosclerosis together with plaques, as detected by carotid ultrasound examinations. Furthermore, flow-mediated dilation results were inconsistent with the carotid atherosclerosis detected by carotid ultrasound examinations, especially in the hypertension and hypertension-hyperlipidemia groups. Conclusion: Patients with metabolic diseases can select either vascular endothelium or ultrasound examination to detect lesions in the arteries. These two methods are recommended for patients with hypertension.

Keywords: FMD, vascular endothelial function, carotid artery ultrasound, hypertensions, metabolic diseases

Introduction

Vascular endothelial dysfunction is correlated with arteriosclerosis caused by hypertension, diabetes mellitus and dyslipidemia; which represents the early changes of arteriosclerosis [1-3]. Brachial artery flow-mediated dilation (FMD) is used to evaluate vascular endothelial function via ultrasound examination, which can detect endothelial diastolic function impairment in the early stage of arteriosclerosis function changes, with accurate positioning and no injuries [4, 5]. This study aims to completely understand vascular injuries through detecting FMD changes in patients with metabolic diseases and hypertension in combination with ultrasound examination for cervical blood vessels; thus, providing support for the early intervention of diseases.

Material and methods

Study object

A total of 405 patients, who underwent physical examination in our hospital from August 2014 to April 2015, were included into this study. The age of patients ranged between 27-79 years old (mean: 50 ± 5 years old), and 211 male and 194 female patients were included. These patients were divided into six groups, according to the history of their previous illness: hypertension group, hyperlipidemia group, diabetes mellitus group, hypertension-hyperlipidemia group, hypertension-hyperlipidemia-hyperglycemia group, and non-above-mentioned disease group (**Table 1**). The diagnostic criteria of the above diseases were determined according to existing uniform standards in China.

Methods

Vascular endothelial detection was carried out using a UNEX EF FMD endothelial function detector. Subjects were refrained from smoking and drinking coffee within 12 hours prior to the examination and were instructed to relax (excluding menstrual cycles and other influence factors). The examination was performed by professional technicians. Subjects were in a

Table 1. Grouping of patients

	Number	Sex	
		Male	Female
Total	405	211	194
Hypertension group	37	22	15
Hyperlipidemia group	56	34	22
Diabetes mellitus group	12	10	2
Hypertension-hyperlipidemia group	29	23	6
Hypertension-hyperlipidemia-hyperglycemia group	6	5	1
Non-above-mentioned disease group	232	91	141

quiet state (in the spinal position and at rest for 10 minutes), and the probe was placed on the right elbow and kept parallel to the artery to detect the inner diameter of the upper arm blood vessels. Then, hemostasis was carried out for five minutes by systolic pressure (detected ahead) plus 50 mmHg; and the probe was kept parallel to the artery. Approximately 45-60 seconds after releasing the wristband, the maximum expanded inner diameter was observed; and the detection was carried out continuously. FMD (%) = maximum vascular diameter (mm)-vascular diameter in the quiet state (mm)/vascular diameter in the quiet state × 100. The normal value was 6% and above. If the value was less than 5%, vascular endothelial dysfunction was diagnosed [6].

The color Doppler ultrasonic diagnostic instrument iU2 (Philips) was used for carotid ultrasound examination, and the frequency of the probe was 7.5 MHz. Subjects were placed in the spinal position, and the distance between the internal surface of the inner membrane and the outer surface of the tunica media of the proximal end, distal end and crotch of the common carotid artery and the posterior wall of the start of the internal carotid (intima-media thickness, IMT) was measured. Measurements were performed three times to obtain the mean. Furthermore, the location, number and nature of the carotid atherosclerotic plaque were measured. Standards for the carotid plaque: The partial vascular wall was thickened to reach any of the following standards: (1) IMT ≥1.0 mm; (2) circumscribed apophysis and protrusion into the lumen ≥2.5 mm; (3) IMT exceeded ≥50% of peripheral IMT [7].

Statistical analysis

Enumeration data were expressed as the mean ± standard deviation, and data were processed by the SPSS 20.0 software package. Intergroup comparison of enumeration data adopted the X^2-test. α=0.05 was the inspection level.

Results

General data

According to the history of previous illness, subjects were divided into six groups, as shown in **Table 1**. Male/female ratio was basically similar, and patients without the above diseases accounted for over half of patients (1.34:1). Patients in the hyperlipidemia group, hypertension group, and hyperlipidemia-hypertension group accounted for 30% of the total number of patients, respectively.

Statistical analysis for FMD and ultrasound examination results in all groups

FMD results were compared with carotid ultrasound examination results in the different disease groups, respectively. Carotid ultrasound examination results were divided into two categories: carotid atherosclerosis and carotid atherosclerosis accompanied by plaques. Differences were observed between the vascular endothelium and carotid atherosclerosis, as detected by carotid ultrasound examination in the hypertension group, hypertension-hyperlipidemia group and non-above-mentioned group ($P<0.05$). No differences were observed in the hyperlipidemia, diabetes mellitus and hypertension-hyperlipidemia-hyperglycemia groups. FMD was compared with carotid atherosclerosis accompanied by plaques, and no differences were observed among the six groups, as shown in **Table 2**.

Discussion

The main function of vascular endothelial cells is to regulate vascular contraction and relaxation. Nitric oxide, angiotensin II, endothelin and prostacyclin and other vasoactive substances participate in this process [8, 9]. Many factors can cause vascular endothelial dysfunction; for example, increased serum triglyceride level, decreased high-density lipoprotein cholesterol, increased low-density lipoprotein, hypertension, hyperglycemia, smoking and vitamin deficiency [10]. The mechanism of body

Table 2. Results of FMD and carotid ultrasound examination

	FMD positive	Carotid atherosclerosis	*P* value	Carotid atherosclerosis accompanied by plaques	*P* value
Hypertension group	27.03% (10)	8.11% (3)	0.032	48.65% (18)	0.055
Hyperlipidemia group	10.71% (6)	10.71% (6)	1.000	21.43% (12)	0.123
Diabetes mellitus group	33.33% (4)	8.33% (1)	0.132	33.33% (4)	1.000
Hypertension-hyperlipidemia group	37.93% (11)	13.79% (4)	0.036	34.48% (10)	0.785
Hypertension-hyperlipidemia-hyperglycemia group	66.67% (4)	16.67% (1)	0.079	33.33% (2)	0.248
Non-above-mentioned disease group	14.22% (33)	4.74% (11)	0.000	14.22% (33)	1.000

FMD was compared with carotid atherosclerosis and carotid atherosclerosis accompanied by plaques, having statistically significant when *P* value less than 0.05.

dysfunction caused by endothelial dysfunction is mainly impaired vascular diastolic ability and barrier function, abnormal hemodynamics, and injured fibrinolysis ability. A large quantity of growth factors is generated to lead to increased oxidative stress and increased expression of inflammatory genes of adhesion molecules, and consequently, pathological changes are formed; for example, atherosclerosis, vasospasm, thrombogenesis and vascular stenosis [11]. Generally, vascular endothelial function is impaired earlier than the morphological changes of vascular arteriosclerosis [12, 13].

Currently, there are two means of detecting vascular endothelial function: FMD and nitrate-mediated dilatation (NMD). FMD means vascular endothelial cells release endothelium-derived relax factors under physiological stimulation caused by compression actions that lead to vascular relaxation, in order to reflect the situation of vascular endothelial function. For this method, the vascular endothelial structure shall be complete and its function would be normal. NMD is the direct vascular diastole caused by nitroglycerin and other drugs. This method does not need the vascular endothelium to release nitric oxide and other diastolic factors. In recent years, FMD has been used as a non-invasive examination technology, which can accurately reflect the distance between the inner surface of the internal membrane and the outer surface of the tunica media of the carotid artery, vascular plaques and endothelial diastolic function of brachial artery; which is extensively used for clinical practices [14]. This study determined that FMD results were inconsistent with carotid atherosclerosis detected by the carotid ultrasound examination in the hypertension group, which indicates that such patients shall select two detection methods to determine the vascular atherosclerosis situation at an earlier period. Patients in the hypertension group can aggravate vascular endothelial dysfunction in combination with significant FMD disorders and vascular endothelial endocrine function impairment. Iiyama et al [15] found that vascular endothelial dysfunction was the main mechanism of hypertension, and one of important onset links. For patients with hypertension, vascular pulsatile blood flow was increased, changes in shear stress of the vascular wall, and vascular contraction and spasm leas to hypoxia and ischemia; thus, causing vascular endothelial cell impairment. The generation and decreased release of endothelial nitric oxide together with decreased activity presents with reduced vasodilator response and endothelial function impairment. In addition, vascular endothelial dysfunction leads to nitric oxide and endothelin imbalance in the blood circulation, and plays an important role in the occurrence and progress of hypertension [16, 17]. Therefore, this study indicates that FMD detection has significant for patients with hypertension.

Vascular endothelium has an important relationship with blood lipid. Zhu et al [18] found that FMD is negatively correlated with the concentration of plasma cholesterol, which indicates that increased concentration of cholesterol in blood is related with reduced vasodilation ability and endothelial function impairment. When patients with hypertension are complicated with mixed hyperlipidemia, endothelial dysfunction basically occurs. Decreased endothelial function can promote lipid infiltration in the wall of arteries, especially for patients with hypercholesterolemia. When hypercholesteremia is complicated with hypertension, risk factors of arteriosclerosis are overlapped. This infiltration is aggravated, endothelium-dependent vasodilatation is reduced, and

consequently, the endothelium is impaired to impair vascular endothelial function, promote inflammatory cell chemotaxis and filtration, and blood platelet aggregation to form a thrombus. Furthermore, the thrombus further damages vascular endothelial function and forms a vicious circle; and vascular endothelial function is deteriorated. This study found that the FMD result was consistent with carotid atherosclerosis accompanied by plaques detected by carotid ultrasound examination in the hyperlipidemia and hypertension-hyperlipidemia group. This indicates that vascular endothelial function is abnormal when carotid atherosclerosis accompanied by plaques is detected by ultrasound examination. Similarly, positive FMD indicates that arteriosclerosis may exist together with plaques. Furthermore, in the diabetes mellitus group, the FMD result was consistent with sclerosis or plaques detected by carotid ultrasound examination. The vascular complication of diabetes mellitus has an important relationship with vascular endothelial dysfunction, and changes in vascular endothelial function are important factors of other onset mechanisms for diabetes mellitus; which mainly present with insulin resistance, insulin secretion impairment and lipotoxicity [19]. The excessive release of adipose tissues and decrease in skeletal muscle intake leads to increased concentration of free fatty acids for patients with diabetes mellitus [20]. The lipotoxicity of free fatty acids damages endothelial function in several channels, including increased mitochondrial reactive oxygen species (ROS), increased glycosylation end products, and the activation of protein kinase C and hexosamine signaling pathways. Some diabetes mellitus patients with no vascular chronic complications present with a significant decrease in vascular endothelial function. Endothelial function impairment is the main pathophysiological basis and initiating factor of diabetic angiopathies. Therefore, FMD detection can detect vascular complications at an early stage for patients with diabetes mellitus.

The mechanism of the endothelial dysfunction is different for different types of diabetes mellitus. For type-1 diabetes mellitus, endothelial dysfunction is caused by metabolic changes due to hyperglycemia; and microvascular complications occur gradually with increasing age. Type-2 diabetes mellitus presents with increased thickness in the wall of the great vessels and endothelial dysfunction, which may be related with the following factors: (1) as blood glucose is fully used by body tissues, endothelial cells are basically damaged, and consequently, vascular dysfunction is caused, affecting the secretion of vasoactive substances and leading to vasomotor dysfunction; (2) the high sugar state in blood promotes the generation of protein glycosylated end products that accumulate in tissues, and consequently leads to vascular smooth muscle cell proliferation and increased thickness and roughness of the vascular wall; (3) this is often accompanied by lipid metabolism disorders due to insulin biological regulation action disorders, and lipidosis or filtration and platelet aggregation occurs in the vascular wall, leading to increased thickness or plaques in the vascular wall. Suzuki et al [21] indicated that if blood glucose was controlled, vascular endothelial function can be improved and atherosclerosis can be delayed for patients with diabetes mellitus. Hence, to some extent, FMD can help to understand the management of blood glucose in patients with diabetes mellitus.

FMD technology for detecting vascular endothelial function can detect endothelial diastolic dysfunction impairment at an early stage, with its noninvasive feature, convenient characteristics, and good repeatability and accuracy. In combination with carotid ultrasound examinations, FMD technology can comprehensively and accurately understand the relationship between risk factors and vascular injuries for patients with metabolic diseases. This would assist in predicting the risk of complications, discovering the disease at an early stage, and allowing early prevention and treatment. In this study, due to the small number of cases in the hypertension-hyperlipidemia and hyperglycemia groups, the clinical significance was not obvious. Hence, it is necessary to accumulate cases for further studies.

Disclosure of conflict of interest

None.

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