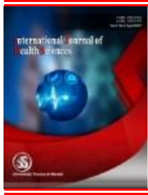

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Application of Contrast-Enhanced Ultrasound to Evaluate Skeletal Muscle Perfusion in Lower Extremity Arteriosclerotic Obliterans of Type 2 Diabetes Mellitus

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Keywords

contrast-enhanced ultrasound;
lower extremity arteriosclerosis obliterans;
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Abstract

To evaluate the value of contrast-enhanced ultrasound in evaluating skeletal muscle perfusion in Type 2 diabetic patients with lower extremity arteriosclerosis occlusion. 80 patients with type 2 diabetes were prospectively studied and divided into two groups: 40 patients with lower extremity arteriosclerosis obliterans(observation group)and 40 diabetic volunteers with normal lower extremity arteries(control group). All subjects were subjected to the same contrast-enhanced ultrasound (CEUS) technique before and after exercise to observe the changes in skeletal muscle blood perfusion in the calf, and the time to peak(TTP)of skeletal muscle blood perfusion parameters in the two groups were compared. The time-intensity curve established by the mathematical model showed that TTP in the observation group was significantly longer than TTP in the control group in the resting state and after exercise, with statistical significance(P<0.05). TTP had no significant correlation with age, hypertension, and other factors(P>0.05). TTP was correlated with ankle-brachial index (ABI)(P<0.05). In conclusion, CEUS can objectively reflect the changes in skeletal muscle perfusion in patients with lower extremity arteriosclerosis obliteration before and after exercise, and it is a new diagnostic method and evaluation index to observe the changes in skeletal muscle perfusion in patients with type 2 diabetes.

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Contents

1 Introduction

In recent years, with the continuous change of living standards and eating habits, the prevalence of type 2 diabetes is on the rise. There are many chronic complications in patients with type 2 diabetes, among which diabetic foot is the most common. One of the key factors is lower extremity arterial disease, among which the incidence of lower extremity arteriosclerosis obliterans is higher. Type 2 diabetes mellitus complicated with lower limb arteriosclerosis obliterans is a macrovascular complication. compared with non-diabetic patients, the rate of amputation is 5 times higher and the mortality rate is 2 times higher than that of non-diabetic patients (Xu et al., 2020). Therefore, it is very important to diagnose and evaluate the early lesions of T2DM lower extremity arteriosclerosis obliterans by an effective diagnostic method. On this basis, contrast-enhanced ultrasound was used to conduct a prospective study to observe and analyze the changes of blood perfusion parameters of calf skeletal muscle in patients with type 2 diabetes mellitus with normal lower limb artery and type 2 diabetic patients with lower limb arteriosclerosis occlusion. to explore the application value of this technique, which provides an objective basis for the effective prevention and treatment of lower limb arteriosclerosis obliterans in patients with type 2 diabetes mellitus.

2 Materials and Methods

2.1 General information

A prospective study was conducted on 80 patients with type 2 diabetes treated in our hospital. Inclusion criteria : (1) Meet the diagnostic criteria of type 2 diabetes; (2) All signed informed consent. Exclusion criteria: (1) type 1 diabetes; (2) Those who are unwilling to cooperate or have a disturbance of consciousness; (3) Severely impaired function of heart, brain and other important organs; (4) Patients who underwent lower extremity arterial surgery before enrollment. According to whether they were complicated with arteriosclerosis obliterans of lower extremities, they were divided into two groups: the observation group (n = 40) and the control group (n = 40). Observation group: 24 males and 16 females; 28 cases of hypertension; 24 cases of smoking; aged 46-90 years, mean (70.33±8.90 years); ABI ranged from 0.28 to 0.81, mean 0.57. inclusion criteria: (1) Lower extremity arterial stenosis (stenosis > 50 %) or occlusion was diagnosed by color ultrasonography. (2) Typical intermittent claudication. (3) According to the Fontaine classification (He et al., 2017), grade 2 or above. (4) Ankle brachial index ABI < 0.9. In the control group, there were 22 males and 18 females, 25 cases of hypertension, and 17 cases of smoking, with an average age of 67.78 ±10.03 years (43-84 years). ABI ranged from 1.00 to 1.30, with an average of 1.17. Inclusion criteria: (1) After a color ultrasound examination, lower extremity arterial disease was excluded. (2) No muscle ischemia symptoms such as intermittent claudication. (3) The ankle-brachial index (ABI) was all more than 1. 0.

2.2 Method

All subjects were told to lie down for 15 minutes before radiography, and an intravenous indwelling needle (with a three-way tube) was placed in the anterior vein of the left elbow. Contrast-enhanced ultrasound: The subjects were placed in a supine or lateral position, the calf was flexed, and the calf gastrocnemius muscle below the knee joint was exposed. The L12-3 linear array probe on the EPIQ5 instrument of PHILIPS was placed in the central part of the gastrocnemius muscle, avoiding the large blood vessels and opening the contrast mode. During the entire procedure, the probe remains fixed and the 2D image remains unchanged. The 2.4ml SonoVue suspension was quickly injected, and then 5ml of 0.9 % sodium chloride solution was used to flush the tube at the same speed. The timing began before the tube was flushed, and the dynamic angiographic images were taken for 4 minutes. After the first contrast agent clearance, rest for 15 minutes, let the research object hold the fixed rod with both hands and feet tiptoe for a total of 30 times, and then conduct the second contrast-enhanced ultrasound technique in the same method and measurement. The two contrast-enhanced ultrasounds were performed by the same attending physician.

2.3 Image analysis

Using QLAB on-machine analysis software, the $1cm^2$ square of calf gastrocnemius muscle was taken as the ROI region of interest, the microbubble echo curve in ROI was obtained, and the curve was fitted (LDRW WIWO formula). The time-intensity curve TIC and peak time TTP were obtained, and the morphology of TIC was observed and analyzed.

2.4 Statistical analysis

SPSS 24.0 software was used. The measurement data were expressed as（$\bar{x}$±s）, and the Mann-Whitney U test was used to compare the parameters; Sperman correlation analysis was used to analyze the correlation between ankle-brachial index, age, and other factors and TTP; according to the test level $P<0.05$, the difference was statistically significant.

3 Results and Discussions

3.1 Analysis of time-intensity TIC curves of two groups of subjects

The horizontal axis represents time; the vertical axis represents intensity; the peak of the curve is the time to peak TTP. Both groups of subjects showed an ascending branch and a descending branch at rest and after exercise. In the resting state, the TIC curve of the observation group showed low blunt ascending and descending branches, while the TIC curve of the control group showed steep ascending and descending branches; After exercise, the TIC curves of the two groups showed that both the ascending and descending branches were steeper than those in the resting state, and the apex moved forward. See Figure 1 a, b, c, d.

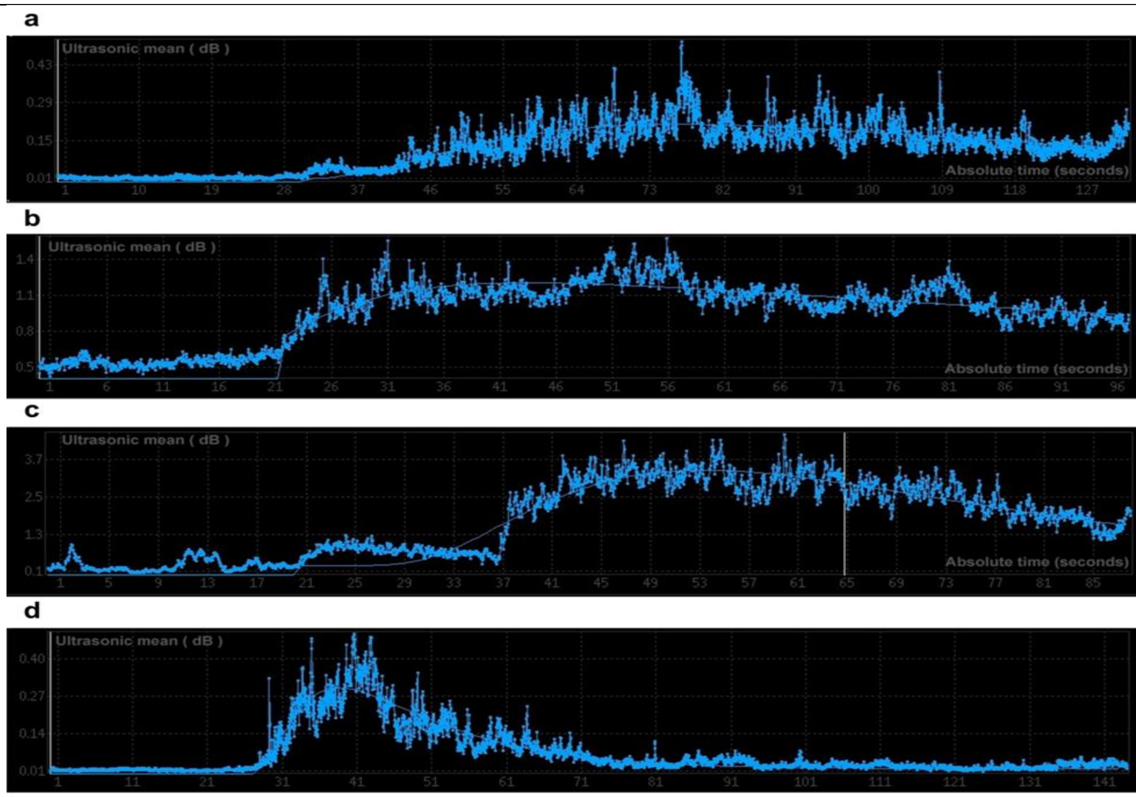

Figure 1. The horizontal axis represents the time; the vertical axis represents the strength； the peak of the curve is the time to peak TTP. In the observation group, TTP76.38s in resting state (a) and TTP43.86s after exercise (b); in the control group, TTP53.29s in resting state (c) and TTP35.64s after exercise (d).

3.2 Comparison of TTP between two groups

In Table 1, TTP in the observation group was significantly longer than that in the control group ($P< 0.05$). After exercise, the TTP of the observation group was significantly longer than that of the control group ($P < 0.05$).

Table 1
Comparison of resting state and TTP after exercise between observation group and control group （$\bar{x}\pm s$, s）

Group	Case	resting state TTP	TTP after exercise
observation group	40	81.78±17.04	57.78±15.26
control group	40	43.03±11.47	15.85±4.98
Z value		-7.259	-7.703
P value		<0.05	<0.05

3.3 Analysis of the correlation between TTP and basic factors in the two groups

In Table 2 There was no significant correlation between TTP and post-exercise TTP in the two groups of subjects with age, gender, hypertension, hyperlipidemia, and smoking factors ($P> 0.05$). TTP in resting state and TTP after exercise were correlated with ABI in both groups ($P< 0.05$).

Table 2
Analysis of the correlation between resting state, TTP after exercise, and age, sex, and other factors in the two groups

Time	*R*-value	*P* value
Resting-state TTP		
Age	0.192	0.089
Gender	0.096	0.396
Smoking	0.142	0.209
hypertension	-0.067	0.555
hyperlipidemia	-0.086	0.4467
ABI	-0.804	<0.05
TTP after exercise		
Age	0.198	0.078
Gender	0.081	0.476
Smoking	0.131	0.246
hypertension	-0.121	0.286
hyperlipidemia	-0.159	0.16
ABI	-0.842	<0.05

Lower limb arteriosclerosis obliterans is a kind of disease of lower limb ischemia and microcirculatory disturbance. It is a chronic disease of the lower limb artery caused by atherosclerotic plaque of the lower limb artery, resulting in stenosis or occlusion. Type 2 diabetes is an important risk factor for lower extremity arteriosclerosis obliterans (Zheng et al., 2020), which is unique. Because most patients with type 2 diabetes are asymptomatic or atypical at the initial stage, it is difficult to make a real diagnosis of arteriosclerosis obliterans of the lower extremities. By the time the symptoms such as intermittent claudication appear, the disease has developed to a late stage, when the vascular sclerosis is serious, with poor blood circulation, and even gangrene and eventually amputation, which not only greatly increases the difficulty of treatment, but also recovers extremely poorly.

There are many techniques for the examination of lower extremity arteries, such as Doppler ultrasound, DSA, CTA MRA, etc. Quantitative skeletal muscle perfusion disorders, such as CE-MRI ; There are also non-invasive methods for evaluating lower extremity arteriosclerosis obliterans such as ankle brachial index ABI. However, the examination that reflects the anatomy is not comprehensive. CE-MRI is expensive and should not be used as a conventional method. When ABI is calcified in the arterial intima, the compressibility of the ankle artery is poor, which can be greater than 1.3. It is more common in patients with type 2 diabetes. False-negative results are prone to occur, with poor sensitivity and unreliable results. Therefore, another examination method is needed to evaluate the skeletal muscle perfusion of the lower extremities. Contrast-enhanced ultrasound is a technique that uses the scattered echo after contrast microbubble enhancement to compare the effects. It has the advantages of non-invasive, real-time, repeatability, and contrast enhancement, and can quantify the microperfusion of skeletal muscle microcirculation functionally. As a new technology in the history of ultrasound development, CEUS has a short history of development, but it has been widely used in the abdomen, nail breast, blood vessels, and gynecology (Chen & Zhang, 2021; Wang, 2021; Zheng, 2020). Therefore, in recent years, scholars at home and abroad have made the assessment of skeletal muscle microperfusion changes by contrast-enhanced ultrasound as one of the research hotspots. Foreign scholar Naehle (Naehle et al., 2015) used contrast-enhanced ultrasound to observe the skeletal muscle perfusion of the lower extremity arteriosclerosis obliterans observation group and normal volunteers. The results showed that the TTP of the observation group was longer than that of the normal group at rest, and the TTP of the same subject at rest was longer than that after exercise, indicating that exercise can promote the improvement of calf skeletal muscle perfusion. The domestic scholars Song Ye and Wu Dongmei (Song et al., 2014; Wu & Huang, 2016), used contrast-enhanced ultrasound to observe the calf skeletal muscle of lower limb arteriosclerosis obliterans and analyze the disturbance of skeletal muscle perfusion, which opened up a new direction of contrast-enhanced perfusion imaging for the early study of arteriosclerosis obliterans of lower extremities in China. It can be seen that CEUS, as a new technology, can objectively reflect the perfusion disorder of calf skeletal muscle in patients with lower extremity arteriosclerosis obliterans, and provide a certain scientific basis for the study of type 2 diabetes mellitus complicated with lower extremity arteriosclerosis obliterans.

The purpose of this study was to observe and analyze the changes of skeletal muscle perfusion in patients with type 2 diabetes mellitus before and after the occurrence of lower limb arteriosclerosis occlusion. to provide a clinical basis for timely diagnosis and treatment of type 2 diabetes mellitus. In this study, 2.4ml of SonoVue suspension was injected into the group, and ROI (1cm2 square area in the central part of the calf gastrocnemius muscle) was selected for analysis to obtain the blood perfusion parameter TTP. The results were more reliable, because the calf gastrocnemius muscle was superficial and constant, with a rich capillary network, and according to the study, TTP was the most reliable blood perfusion parameter in contrast-enhanced ultrasound (Song et al., 2014). This study analyzed the correlation between TTP and age, sex, smoking, hypertension, hyperlipidemia, and other basic factors before and after exercise. The results showed that TTP was not affected by it. The results of correlation analysis between TTP and ABI before and after exercise showed that there was a negative correlation between them, that is, when there was stenosis or occlusion of the lower limb artery, the blood flow through the ankle artery decreased, the systolic blood pressure of the ankle artery decreased, and the ABI was small, while the skeletal muscle perfusion was poor, and the peak time TTP was prolonged when the contrast medium reached the maximum strength of the skeletal muscle (Johnson et al., 1993; Duerschmied et al., 2008; Virally et al., 2007).

The results showed that the evaluation of skeletal muscle perfusion disturbance in type 2 diabetic patients with lower extremity arteriosclerosis obliterans by TTP was consistent with the evaluation of the degree of lower extremity arteriosclerosis obliterans by ABI to some extent. However, the detection of ABI is subjective and can not objectively reflect the quantification of skeletal muscle perfusion, which also reflects that contrast-enhanced ultrasound is an evaluation technique that can objectively reflect and energize lower limb skeletal muscle perfusion. According to the time-intensity curve TIC, there was one ascending branch and one descending branch before and after exercise in both the normal group and the observation group. The ascending branch represents the process of angiographic microbubbles entering the artery and diffusing in the skeletal muscle. The descending branch indicates the dissipation of angiographic microbubbles in the skeletal muscle. The peak indicates that the amount of contrast microbubbles in the skeletal muscle reaches the maximum intensity, which is the time to peak TTP. The TIC curve of the observation group showed low blunt ascending and descending branches, while the TIC curve of the control group showed steep ascending and descending branches (Bertoldi et al., 2008; Mancini et al., 1987; Mustika et al., 2017). The TIC curves of the two groups of subjects after exercise showed that the ascending and descending branches were steeper than those in the resting state, and the apex moved forward. Analysis of TTP parameters: In the resting state, the TTP of the observation group was significantly longer than that of the control group, $P < 0.05$, the difference was statistically significant, indicating that the blood perfusion of the calf skeletal muscle in the observation group was blocked, and the perfusion was significantly damaged compared with the control group. After exercise, the TTP of the two groups of subjects was shorter than that in the resting state, indicating that the microvascular microperfusion of skeletal muscle in both groups increased after exercise, and exercise improved the perfusion of calf skeletal muscle. In the control group, the muscle contraction of calf skeletal muscle, the increase of arterial blood flow and capillary permeability, the increase of microcirculation and microperfusion of skeletal muscle and the shortening of TTP after exercise in the control group were compared with those in the rest state. In the observation group, due to lower limb arteriosclerosis occlusion, lower limb macrovascular blood flow decreased, after exercise, the change of arterial vascular resistance and the opening of collateral vessels may lead to the increase of skeletal muscle microcirculation microperfusion and the shortening of TTP compared with the resting state. The results show that contrast-enhanced ultrasound observation of skeletal muscle perfusion changes can objectively, quantitatively, and visually evaluate the microcirculation microperfusion state of type 2 diabetic patients with lower extremity arteriosclerosis obliterans (Stolar, 2010; Ejtahed et al., 2012; Ovalle & Azziz, 2002; Suryasa et al., 2021).

In summary, contrast-enhanced ultrasound, as a non-invasive imaging method, can be used to monitor the changes of skeletal muscle perfusion in lower extremity arteriosclerosis obliterans in type 2 diabetes. to provide a clinical basis for the prevention and treatment of arteriosclerosis obliterans of lower extremities (Phielix & Mensink, 2008; Febbraio et al., 2003).

4 Conclusion

In conclusion, CEUS can objectively reflect the changes in skeletal muscle perfusion in patients with lower extremity arteriosclerosis obliteration before and after exercise, and it is a new diagnostic method and evaluation index to observe the changes in skeletal muscle perfusion in patients with type 2 diabetes.

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