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ORIGINAL ARTICLE

The value of contrast-enhanced ultrasound in the diagnosis of microcirculatory perfusion abnormalities in diabetic foot

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Abstract

Background Diabetic foot is one of the most serious complications of type 2 diabetes mellitus (T2DM), and its incidence is increasing in China. Early detection of abnormal microcirculation in the foot is very important for the prevention and treatment of diabetic foot.

Objective To investigate the value of contrast-enhanced ultrasound (CEUS) in diagnosing microcirculatory alterations in the dorsum of the foot for patients with type 2 diabetes mellitus (T2DM).

Methods Eighty-eight T2DM patients were included, among them 30 patients sustained diabetes mellitus without complications (group A), 28 with lesions in the dorsum of the foot (no acute infection) that can be classified as Wagner grade 0 ~ 1 (group B), and 30 with lesions in the dorsum of the foot that can be classified as Wagner grade 2–5 (group C). Another 30 healthy adults were included as the control group. All subjects underwent CEUS to examine the dorsalis pedis arteries and blood perfusion to the underlying soft tissues. Parameters of the time-intensity curve (TIC), including rise time (RT), ascending slope (AS), time to peak (TTP), peak intensity (PI), area under the curve (AUC), and half of drop time (DT/2) were analyzed.

Results The analysis of TIC data of the dorsalis pedis arteries showed that group C had decreased AS, PI, and AUC and increased TTP, RT, and DT/2 compared with groups A, B, and the control group; the differences were statistically significant ($p < 0.05$). The analysis of TIC data of the perfusion to the underlying soft tissues showed that AS, PI, and AUC decreased from the control group through group A, B, and then C; the differences were all statistically significant ($p < 0.05$). The TIC data were correlated with the severity of microcirculatory impairment in the dorsum of the foot and among them the AUC, PI, and AS had higher predictive value.

Conclusions Microcirculatory impairment in the dorsum of the foot in T2DM patients presents itself as "delayed wash-in, delayed wash-out, and weak enhancement" on CEUS images. CEUS can provide quantification of the microcirculatory changes in the soft tissues in the dorsum of the foot and reflect the differences of microcirculatory perfusion across different grades of lesions.

Keywords Contrast-enhanced ultrasound · Diabetic foot · Microcirculatory perfusion

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Introduction

Diabetic foot is one of the serious chronic complications of type 2 diabetes mellitus (T2DM) with an increasing morbidity and high disability and mortality rates [1–5]. Microcirculatory dysfunction is an important pathological basis for its pathogenesis and an important factor in determining its prognosis [6–9]. Therefore, early detection and accurate assessment of microcirculatory perfusion abnormalities in the foot are essential for the prevention and treatment of diabetic foot. Contrast-enhanced ultrasound (CEUS) can provide quantitative assessment of the microcirculatory perfusion in tissues [10, 11] and has been widely used to characterize liver and kidney lesions [12–16]. However, few studies using CEUS to assess microcirculatory perfusion in diabetic foot have been reported. The study applied CEUS to assess soft tissue perfusion in the dorsum of the foot in order to provide more knowledge on the varied microcirculatory impairment across different grades of lesions in diabetic foot and to investigate the value of CEUS in diagnosing microcirculatory perfusion abnormalities.

Materials and methods

Eighty-eight patients with T2DM admitted to the Department of Endocrinology of the Hospital of Chengdu University of TCM from October 2021 to March 2023 were included, all of whom met the diagnostic criteria of diabetes mellitus by the American Diabetes Association (2021 edition). Among them, 30 patients sustained T2DM alone without peripheral vasculopathy and neuropathy (group A); 28 patients were with lesions in the dorsum of the foot that were classified as Wagner grade 0–1 (group B); 30 patients were with lesions in the dorsum of the foot that were classified as Wagner grade 2–5 (group C) (see Table 1 for the composition); 30 adults without T2DM and with normal body mass index (BMI) were included in the control group. The included patients with diabetic ulcer all have the ulcer located on areas that are supplied by the dorsalis pedis artery. Patients with lower extremity vascular diseases from other etiologies, malignant tumors, severe heart conditions, acute diabetic foot infections, severe stenosis and/or occlusion of the posterior tibial and peroneal arteries, and patients with contraindications for CEUS were excluded. All subjects received echocardiography, lower limb arterial color Doppler ultrasound, and transcutaneous partial pressure of oxygen ($TcPO_2$) tests. During $TcPO_2$ tests, electrodes were all placed on the same dorsal areas of the foot as examined on CEUS. The general data and laboratory findings of the four groups are shown in Table 2. CEUS was performed on the dorsal area unilaterally, and for those with bilateral lesions, the more severe side was selected. All patients signed informed consent form for this procedure. Time intensity curves (TIC) of the ROIs were obtained, and the correlation between TIC parameters and foot microcirculation perfusion abnormalities was analyzed. Then, the optimal cut-off value of the parameters such as AUC, PI, and AS for diagnosing foot microcirculation perfusion abnormalities was determined with receiver operating characteristic curve (ROC) and Youden's index.

Table 1 Composition of the cohort

Grade	0	1	2	3	4	5
Case	14	16	8	8	9	5

Instrument and contrast agent

A Philips EPIQ7C ultrasound diagnostic instrument equipped with quantitative ultrasonography analysis software and its L12-3 probe were used. The contrast agent was SonoVue (Bracco, Italy). Each vial of the contrast agent contained 59 mg of phospholipid-coated sulfur hexafluoride lyophilized powder, which was shaken for 30 s in 5 ml

Table 2 Comparison of general data of the three groups to the control group

	Group A/30 cases	Group B/28 cases	Group C/30cases	Control group/30 cases	*p*
Male/female	18/12	16/12	19/11	15/15	0.186
Age (years)	61.45 ± 10.80	63.05 ± 6.30	69.88 ± 11.70	63.51 ± 11.08	0.698
LVEF (%)	64.68 ± 7.02	67.43 ± 5.24	66.38 ± 3.29	66.68 ± 5.12	0.804
Disease course (years)	3.8 ± 1.12	13.91 ± 6.23*	20.05 ± 9.68$^{*\&}$	/	< 0.001
HbA1c (%)	7.11 ± 1.4$^{\#}$	8.81 ± 2.2$^{\#*}$	9.81 ± 1.64$^{\#*\&}$	5.24 ± 0.73	0.001
FBG (mmol/l)	9.8 ± 1.57$^{\#}$	11.28 ± 2.20$^{\#*}$	12.40 ± 4.29$^{\#*\&}$	5.0 ± 0.93	< 0.001

Note: $^{\#}p < 0.05$ when the experiment group was compared with the control group

$^{*}p < 0.05$ when the group was compared with group A

$^{\&}p < 0.05$ when the group was compared with group B

FBG fasting blood glucose

of normal saline to form a microbubble suspension with phospholipid as the shell enveloping the sulfur hexafluoride bubble inside.

The CEUS procedure

The patient lay supine with the knee at 90 degrees of flexion and kept the lower extremity stationary and fully relaxed. The probe was placed in the ankle fossa to show both the dorsalis pedis artery and the underlying soft tissues that were directly in front of the ankle capsule, then CEUS was performed with mechanical index (MI) set at 0.07. As shown in Fig. 1, 2.0 ml of contrast agent was injected through the median cubital vein and flushed with 5 ml of normal saline; upon this, a 4-min real-time observation of the dorsalis pedis artery and its underlying soft tissues was performed and the images recorded. The sample gate was set as 4 mm × 2 mm and placed on the dorsalis pedis artery and its underlying soft tissues, respectively. TIC were obtained and the CEUS perfusion data of this area analyzed. A goodness of fit index (GFI) > 0.75 was used as the criterion for successful quantitative analysis. The main parameters included the ascending slope (AS), time to peak (TTP), peak intensity (PI), area under the curve (AUC), rise time (RT), and half of drop time (DT/2).

Qualitative and statistical analyses

SPSS 26.0 (the statistical Package for Social Sciences, version 26; IBM Corp., Armonk, NY, USA) was used. Numerical variables were expressed as ($\overline{x} \pm s$), *t*-test was used for comparison between two groups, one-way ANOVA was used for multiple group comparisons, and Tukey's multiple comparisons test was used for further two-by-two comparisons. Count data were expressed as (*n*%), and Fisher's exact test was used for comparison between rates. Correlation analysis was performed using Spearman's analysis. The predictive value of each parameter on abnormal microcirculatory perfusion in the soft tissues of the foot dorsum was analyzed with the receiver operating characteristic curve (ROC), and the values of the area under the ROC curve (AUROC) were obtained. The value of AUROC above 0.7 indicates a fair predictive performance of a variable and above 0.9, an excellent predictive performance. In our study, the criteria used to determine the best cut-off value of each parameter was Youden's index (*J*):

$$J = \text{sensitivity} + \text{specificity} - 1$$

The index indicates the overall diagnostic capability of a variable in a test and the best cut-off value can be determined by the maximum value of *J*. [17, 18] $p < 0.05$ was considered a statistically significant difference.

Results

Comparison of general data and laboratory test results

There were no significant differences in terms of age, gender, and left ventricle ejection fraction (LVEF) when the three experimental groups were compared with the control group respectively. The years of disease course, glycated hemoglobin (HbA1c), and fasting blood sugar (FBS) levels were compared, and they were on a decreasing trend from Group

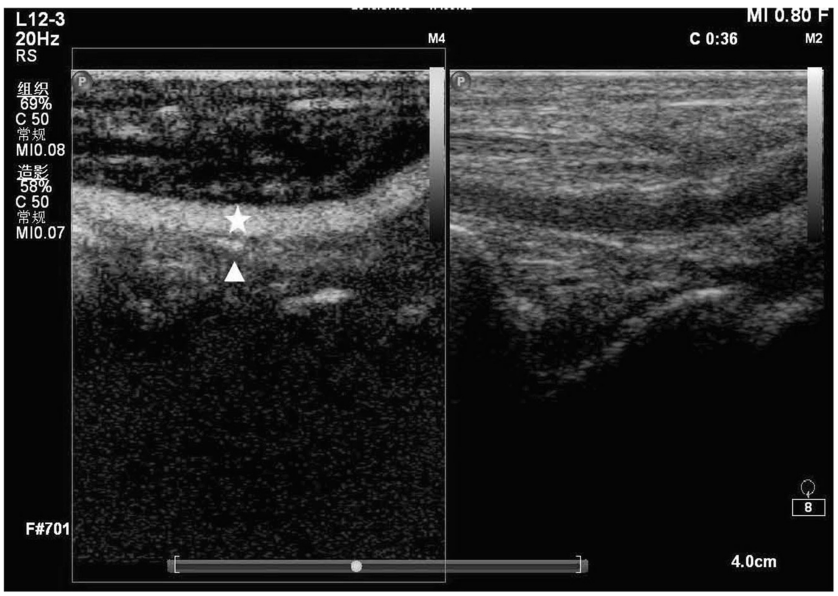

Fig. 1 ☆ indicates the dorsalis pedis artery and △ the underlying tissues

C, to Group B, and then Group A. The differences were all statistically significant ($p < 0.05$), see Table 2.

Three patients from group C showed bimodal TICs for the dorsalis pedis artery and the soft tissues and their results were excluded before curve fitting. The rest of the patients all showed unimodal parabolic TICs.

Comparison of TIC data of the dorsalis pedis artery

There were no statistically significant differences in each parameter between the control group and groups A and B ($p > 0.05$). Group C showed reduced AS, PI, and AUC and prolonged TTP, RT, and DT/2 compared with the other three groups; the differences were statistically significant ($p < 0.05$), see Table 3 and Fig. 2.

Comparison of TIC data of the underlying soft tissues

AS, AUC, and PI were on a decreasing trend from the control group, to Group A, to Group B, and then Group C; the differences were all statistically significant ($p < 0.05$).

Comparison among the groups A, B, and C demonstrated an increasing trend of TTP, RT, and DT/2 with no statistically significant differences between groups A and B (TTP 32.68 ± 4.38 vs. 38.31 ± 3.76, $p = 0.294$; RT 8.64 ± 4.32 vs. 9.41 ± 3.46, $p = 0.374$; DT/2 21.88 ± 2.43 vs. 22.17 ± 2.74; $p = 0.608$) and statistically significant difference between groups B and C was (TTP 38.31 ± 3.76 vs. 56.00 ± 3.20, $p = 0.004$, RT 9.41 ± 3.46 vs. 19.09 ± 1.73, $p = 0.001$, DT/2 22.17 ± 2.74 vs. 33.68 ± 3.88, $p = 0.002$), see Table 4 and Fig. 2.

Diagnostic value of CEUS for microcirculatory perfusion abnormalities in the dorsum of a diabetic foot

Spearman correlation analysis showed a correlation between the severity of the abnormalities and the data obtained for each parameter, with r values of AS, PI, AUC, TTP, DT/2, and RT being − 0.784, − 0.897, − 0.8 77, 0.518, 0.476, and 0.105, respectively. Further analysis with ROC on the predictive value of each parameter of TIC for microcirculatory perfusion abnormalities in the dorsum of the foot found that AUC, PI, and AS of

Table 3 Comparison of TIC data of the dorsalis pedis artery

	AS (dB/s)	TTP (s)	PI (dB)	AUC (dB*s)	RT (s)	DT/2 (s)
Group A	7.21 ± 1.89	33.12 ± 3.02	37.16 ± 3.41	1198.26 ± 143.52	7.96 ± 0.84	18.21 ± 2.64
Group B	6.98 ± 0.16	35.50 ± 1.60	36.62 ± 2.89	1100.95 ± 110.97	8.06 ± 0.54	18.4 ± 3.07
Group C	$1.14 \pm 0.11^{\#*\&}$	$48.29 \pm 2.36^{\#*\&}$	$20.65 \pm 2.37^{\#*\&}$	$423.37 \pm 94.56^{\#*\&}$	$10.44 \pm 0.88^{\#*\&}$	$26.7 \pm 4.97^{\#*\&}$
Control	7.33 ± 1.26	32.00 ± 2.1	37.32 ± 5.88	1314.52 ± 159.34	8.09 ± 0.77	17.33 ± 4.64
p (control vs. group C)	< 0.001	0.001	< 0.001	< 0.001	0.001	0.005

Note: $^{\#}p < 0.05$ when the experiment group was compared with the control group

$^{*}p < 0.05$ when the group was compared with group A

$^{\&}p < 0.05$ when the group was compared with group B

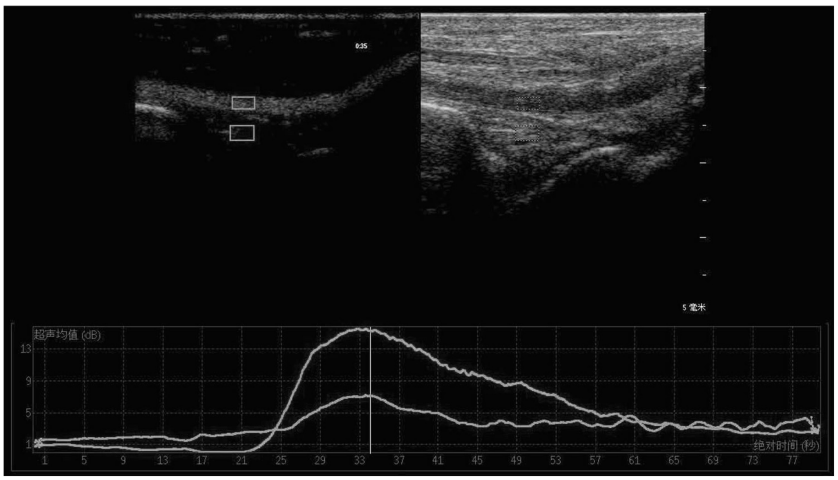

Fig. 2 The blue curve represents the TIC for the dorsalis pedis artery; the yellow is for the underlying soft tissues

Table 4 Comparison of TIC data of the underlying soft tissues in the foot

	AS (dB/s)	TTP (s)	PI (dB)	AUC (dB*s)	RT (s)	DT/2 (s)
Group A	$1.26 \pm 0.39^{\#}$	32.68 ± 4.38	$8.66 \pm 2.02^{\#}$	$243.92 \pm 46.57^{\#}$	8.64 ± 4.32	21.88 ± 2.43
Group B	$0.85 \pm 0.24^{\#*}$	38.31 ± 3.76	$6.38 \pm 1.95^{\#*}$	$180.49 \pm 51.96^{\#*}$	$9.41 \pm 3.46^{\#}$	22.17 ± 2.74
Group C	$0.35 \pm 0.08^{\#*\&}$	$56 \pm 3.20^{\#*\&}$	$4.53 \pm 1.01^{\#*\&}$	$79.31 \pm 24.27^{\#*\&}$	$19.09 \pm 1.73^{\#*\&}$	$33.68 \pm 3.88^{\#*\&}$
Control	1.32 ± 0.06	34.34 ± 2.58	12 ± 1.85	348.57 ± 50.81	7.27 ± 3.28	21.76 ± 1.82
p (Control vs Group C)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Note: $^{\#}$ indicates $p < 0.05$ when the experiment group was compared with the control group

* indicates $p < 0.05$ when the group was compared with group A

$^{\&}$ indicates $p < 0.05$ when the group was compared with group B

the TIC had higher predictive value for microcirculatory perfusion abnormalities (AUROC > 0.7). The best cut-off values of the three parameters of the TIC determined with Youden's index were as follows: the best cut-off value of AUC of the TIC, 290.23 (AUROC, 0.984; sensitivity 93.8%; specificity 89.9%); the best cut-off value of PI of the TIC, 10.17 (AUROC, 0.911; sensitivity 87.5%, specificity 86.9%); the best cut-off value of AS of the TIC, 1.05 (AUROC, 0.954; sensitivity 87.5%, specificity 92.3%) as shown in Table 5 and Fig. 3.

Comparison of the performance of CEUS and $TcPO_2$ in detecting microcirculatory impairment in the dorsum of a diabetic foot

Generally, a foot can be diagnosed with microcirculatory impairment if the oxygen tension is < 40 mmHg in a $TcPO_2$ test [19] and if two or more of the TIC parameters, i.e., AS, PI, and AUC, are abnormal on CEUS.

For group A, the positive rate was 33.33% with CEUS and 10% with $TcPO_2$; the difference was statistically significant ($p < 0.05$). For group B, the positive rate was 100% with CEUS and 75% with $TcPO_2$; the difference was statistically significant ($p < 0.05$). For group C, both CEUS and $TcPO_2$ registered a positive rate of 100%, see Table 6.

Discussion

That microcirculatory dysfunction causes ischemia and hypoxia in local tissues plays a critical role in the pathogenesis of diabetic foot [20], hence the importance of an accurate evaluation of microcirculatory function. Currently, various techniques can be used to evaluate the microcirculatory perfusion in diabetic foot. Among them, percutaneous partial pressure of oxygen monitoring, dynamic capillary microscopy, laser Doppler perfusion imaging, etc. can only evaluate the microcirculation of the capillaries in the skin due to their limited penetration capabilities; iontophoresis measures red blood cell flow by nourishing the subpapillary vascular plexus, but only indirectly reflects microcirculation to the tissue [21–23]. Magnetic resonance imaging (MRI) can offer quantitative analysis of perfusion to the underlying soft tissue, but being time-consuming and expensive with various contraindication have made it unfeasible to be a routine diagnostic work-up [24–26].

CEUS has been widely used to evaluate microcirculatory perfusion in the heart and kidneys of patients with T2DM [27, 28]. And in the peripheral vasculature, CEUS has been reported to be mainly used in the evaluation of the arterial patency in the lower extremities, the stability of arterial plaque, the extent of ischemia in foot ulcers, and the microcirculatory function in the calf muscle [29–31], whereas studies on its usage in evaluating microcirculatory perfusion

Table 5 The best cut-offs of TIC parameters

TIC parameters	AUROC	95% CI	Best cut-off	Sensitivity	Specificity	Maximum J
AUC	0.984	0.959–1.000	290.23	93.8%	89.9%	0.837
PI	0.911	0.834–0.988	10.17	87.5%	86.9%	0.744
AS	0.954	0.899–1.000	1.05	87.5%	92.3%	0.798

AUROC the area under the ROC curve; AUROC value > 0.9, excellent test; 0.8–0.9, good test; 0.7–0.8, fair test

CI confidence interval;

J the Youden index = sensitivity + specificity − 1

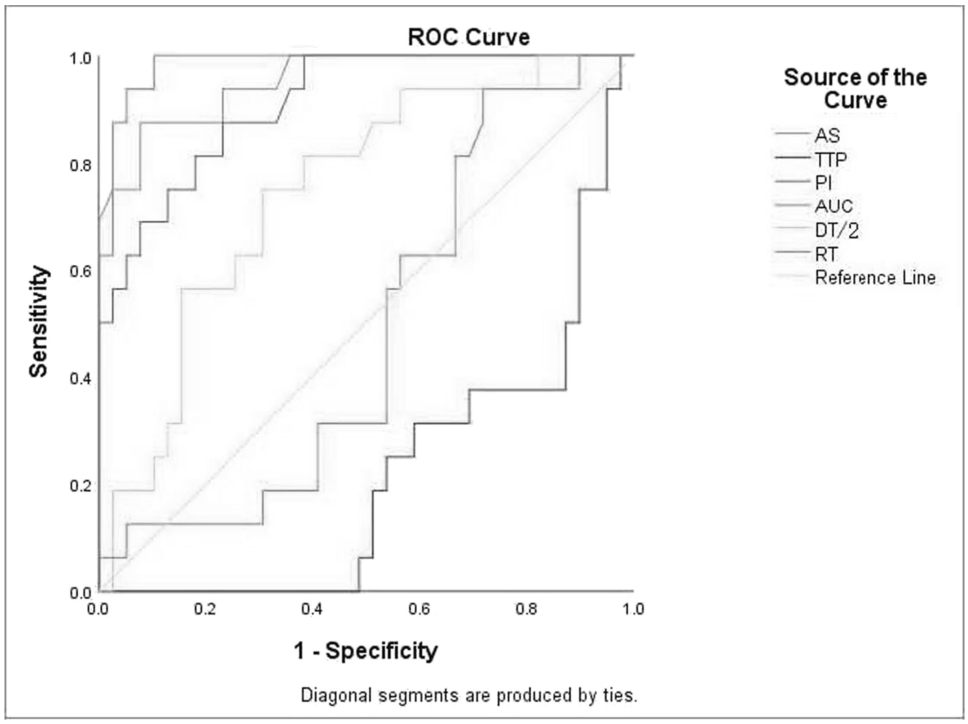

Fig. 3 ROCs of different TIC parameters

Table 6 performance of CEUS and $TcPO_2$ in detecting microcirculatory impairment in the dorsum of a diabetic foot

Group	CEUS Positive rate (%)	$TcPO_2$ Positive rate (%)	*p* value
Group A	33.33	10	0.029
Group B	100	75	0.005
Group C	100	100	/

Positive rate number of patients with microcirculatory perfusion impairment/total number of patients

in diabetic foot are still lacking. Li et al. [32] reported that CEUS could distinguish the differences of microcirculatory perfusion to the phalangeal area in the foot between patients with impaired glucose tolerance (IGT) and patients with diabetes (without complications), but to date no studies addressing diabetic foot microcirculatory perfusion in female patients and across different disease courses have been reported. Therefore, this study included both male and female patients with diabetic foot in equal proportions across Wagner's 0–5 grades to investigate the value of CEUS in evaluating microcirculatory perfusion to the foot of T2DM patients in a wider patient population.

In this study, group C with the most severe conditions of diabetic foot had the longest disease course and the highest HbAlc and blood sugar, indicating that the length of disease course; the fluctuation range of blood sugar were directly proportional to the severity of impairment in the foot of diabetic patients; the longer the disease course and the poorer the blood sugar control, the severe the impairment in the foot.

This study compared the TIC data of the dorsalis pedis artery obtained from CEUS for all groups. PI and AUC values reflected the volume of blood flow in the region of interest and larger values indicated better perfusion, while RT, AS, TTP, and DT/2 values reflected the blood flow velocity in the region of interest and would indicate a fast or slow perfusion. The results showed that the differences of the TIC data of the dorsalis pedis artery were statistically significant between the control group and group C only, which might indicate that long-term abnormal glucose metabolism had led to the severest atherosclerosis in group C where the narrowed or even occluded lumen impeded the passage of the contrast agent, resulting in a lowered blood flow velocity at the distal end of the stenosis, a delayed enhancement of the dorsalis pedis artery, and a reduced amount of contrast agent to the artery, whereas there were no statistically significant difference in the TIC data between the other two experimental groups and the control group, which might indicate that less severe atherosclerosis in the other groups allowed for a smoother passage of the contrast agent.

The intergroup comparison of TIC data of the underlying soft tissue in the dorsal region of the foot of all groups showed that as the condition of diabetic foot worsened, parameters reflecting the rapidity of perfusion such as TTP, RT, and DT/2 prolonged and AS decreased; among them, TTP, RT, and AS reflected the rapidity of wash-in while

DT/2 reflected the rapidity of the return of blood flow; and parameters reflecting the intensity of perfusion such as PI and AUC decreased. These signs demonstrated an enhancement pattern of "delayed wash-in, delayed wash-out and weak enhancement" for microcirculatory impairment in the dorsum of the foot on CEUS. This may be due to the thickening of microvascular basement membrane, the microvascular distortion, and the narrowing or even occlusion of the lumen following microvascular impairment under the influence of hyperglycemia, which resulted in the prolonged passage time and the decreased passed amount of the contrast agent. Meanwhile, due to the insufficient perfusion, the distal venules were in a diastolic state, which slowed down the return of the contrast agent, further reducing effective perfusion and aggravating ischemia, hypoxia, and undermining the vitality of local tissues, thereby resulting in local "weak enhancement."

The comparison of TIC data of the underlying soft tissue showed that compared with the control group, AUC and PI decreased and AS increased in group A, and the difference was statistically significant, indicating the existence of microcirculatory perfusion abnormalities in the dorsum of the foot of patients with diabetes mellitus alone (without diabetic foot). The intergroup comparison among the three experimental groups showed that AUC and PI decreased and AS increased from group A to group B and then group C, suggesting the differentiated microcirculatory impairment between different grades of diabetes. Moreover, as the condition of diabetic foot worsened, the soft tissue perfusion intensity decreased, the perfusion time extended, and the microcirculation became worse. AS, RT, and AUC of groups A and B were statistically different from the control group, whereas DT/2 reflecting the rapidity of the return of blood flow between them was without statistically significant difference, suggesting that the microcirculatory impairment mainly involve the arterioles and metarterioles and relatively less impact the venules.

From the results of correlation analysis and ROC curve analysis, TIC parameters were found to be correlated with microcirculatory perfusion abnormalities in the dorsal area of a diabetic foot and could be used to predict the severity of lesions, particularly, AUC, PI, and AS of the TIC had higher diagnostic efficacy for microvascular lesions in the dorsal area of a diabetic foot. Further, the study used Youden's index to determine the best cut-off values of the three parameters. By this way, the obtained best cut-off values of AUC, PI, and AS of the TIC for diagnosing microcirculatory perfusion impairment in diabetic feet were 290.23, 1.05, and 10.17, respectively. The presence of anomalies of at least two of the three parameters was used as the criteria for diagnosing diabetic foot microvascular impairment, and the results were compared with that of $TcPO_2$. The results showed that CEUS and $TcPO_2$ had the same efficacy in detecting microcirculatory perfusion impairment for patients in group C with severe diabetic foot, while for patients with milder microcirculatory perfusion impairment in group A and group B, the positive rate with CEUS was significantly higher than that with $TcPO_2$. This indicated a higher sensitivity of CEUS in detecting milder microcirculatory perfusion impairment than $TcPO_2$. It might be due to the limited performance of electrodes which were deployed on the skin surface to detect oxygen partial pressure on in $TcPO_2$ and cannot detect microcirculatory perfusion in deep underlying soft tissues. And since its results are influenced by various factors such as environmental temperature, skin thickness, edema degree, and patient preparation, the $TcPO_2$ test is often considered for screening. In contrast, CEUS utilizes a contrast agent that has a similar diameter to red blood cells and can enter the microvasculature to directly display the microcirculation status of the region of interest (ROI), without being impeded by the ROI's depth. Meanwhile, the TIC quantitative assessment with CEUS better overcomes the aforementioned interference and provide more scientific details of the microcirculation status of soft tissue. It is arguable that CEUS may be reliable and superior to $TcPO_2$ in detecting microcirculatory perfusion impairment in the dorsal area of the foot.

In this study, three patients from group C showed bimodal changes in sync in their TIC curves of the dorsalis pedis artery and the underlying soft tissue, with the first peak higher than the second. The medical records of the three patients showed that they all received digital subtraction angiography (DSA), and all were confirmed to have severe stenosis of the anterior tibial artery with collateral angiogenesis. The collateral vessels resulted by atherosclerosis now first allowed the majority of the contrast agent to pass and reach the dorsalis pedis artery to form the first main peak of the TIC curve, while the rest small portion of the contrast agent reached the artery through the narrowed lower extremity arteries and its delay resulted a secondary peak lower than the previous one. The above perfusion patterns suggested that collateral circulation in the lower extremity of diabetic foot might be assessed and quantified through TIC curves obtained from CEUS.

Atherosclerosis of all pedal vessels, either the dorsalis pedis artery or its distal extensions and arterioles, affect the microcirculatory perfusion in the soft tissues of the foot. However, an effective tool to detect calcification in the distal arterioles are still absent. The study chose the dorsalis pedis artery because it is superficially located and relatively larger in diameter, making it easily detectable. And since the superficial soft tissue above the dorsalis pedis artery is located in the near field of ultrasound which has a poorer image resolution, this study chose the deep underlying soft tissue as the ROI. All patients were examined with the same instrument by the same radiologist, the size and location

of the ROI were kept the same for quantitative analysis to ensure the reliability of the acquired data. The limitation to our study is that it is a single-center study, so additional centers and patients are needed for further study.

Conclusion

Microcirculatory impairment in the dorsum of a diabetic foot presents a characteristic enhancement pattern of "delayed wash-in, delayed wash-out and weak enhancement" on CEUS. With the capability to quantify microcirculatory alterations in the soft tissues of the foot and reflect the variability of microcirculatory perfusion across different grades of diabetic foot lesions, CEUS can be expected to be an effective tool for assessing microvascular lesions in diabetic foot.

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Author contribution LFH, HYY, and JK conceived the original ideas, designed the study, and drafted the manuscript. YY analyzed the data and revise the manuscript. YK and DL supervised the drafting of the manuscript. All authors reviewed and approved the final manuscript.

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Data availability Data supporting the finding of this study are available within the article text and tables.

Declarations

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Written informed consent was obtained from all the patients who participated in the study.

Conflict of interest The authors declare no competing interests.

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