

## DIAGNOSTIC VALUE OF ANKLE PEAK SYSTOLIC VELOCITY IN DIABETIC PATIENTS WITH CRITICAL LIMB ISCHEMIA

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**AIM:** To evaluate the diagnostic value of ankle peak systolic velocity (APSV) in diabetic patients diagnosed with critical limb ischaemia (CLI) and its resolution after percutaneous transluminal angioplasty (PTA).

**MATERIALS AND METHODS:** Forty-eight diabetic patients with CLI were included in this study. CLI was diagnosed according to the IWGDF 2015 criteria. Patients were examined before and 5–7 days after PTA with transcutaneous oxygen tension of the foot's soft tissues and APSV by duplex ultrasonography.

**RESULTS:** The median transcutaneous oxygen tensions before and after PTA were 14 [3; 20.5] and 30 [18.5, 39.0] mmHg, respectively ( $p < 0.001$ ). The median APSV in diabetic patients with CLI was 10 [7.4; 15.5] cm/s before PTA and 46 [33.5, 59] cm/s after PTA ( $p < 0.001$ ). The APSV cutoff point for diabetic patients with CLI is  $\leq 25.5$  cm/s with a sensitivity of 79.4% [95% CI 62.1–91.3] and a specificity of 96.4% [95% CI 81.7–99.9].

**CONCLUSIONS:** APSV may be considered as an additional method for CLI assessment. Lower limb artery calcification, soft tissue oedema or infection and foot ulcer and gangrene influence the results of routine ischaemia diagnostic methods such as the ankle–brachial index, toe–brachial index, transcutaneous oximetry but not APSV.

**KEYWORDS:** critical limb ischemia; diabetes mellitus; transcutaneous oximetry; ankle peak systolic velocity

## ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ ЛОДЫЖЕЧНОЙ ПИКОВОЙ СИСТОЛИЧЕСКОЙ СКОРОСТИ КРОВОТОКА У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ И КРИТИЧЕСКОЙ ИШЕМИЕЙ НИЖНИХ КОНЕЧНОСТЕЙ

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**ЦЕЛЬ.** Оценить диагностическое значение лодыжечной пиковой систолической скорости кровотока (ЛПССК) у лиц с сахарным диабетом (СД) при постановке диагноза критической ишемии нижних конечностей (КИНК) и ее разрешения после проведения чрескожной транслуминальной баллонной ангиопластики (ЧТБА).

**МЕТОДЫ.** Обследовано 48 пациентов с СД и КИНК. Диагноз КИНК устанавливался согласно критериям IWGDF, 2015 г. Перед ЧТБА и на 5–7 день после реваскуляризации всем пациентам проводилось диагностическое обследование: оценка транскутанного напряжения кислорода мягких тканей стопы, ЛПССК методом ультразвукового дуплексного сканирования (УЗДС) артерий нижних конечностей.

**РЕЗУЛЬТАТЫ.** По данным проведенного обследования, медиана транскутанного напряжения кислорода до и после ЧТБА составила 14 [3; 20,5] и 30 [18,5; 39] мм рт.ст. соответственно ( $p < 0,001$ ). Медиана ЛПССК составила 10 [7,4; 15,5] и 46 [33,5; 59] см/с соответственно ( $p < 0,001$ ). Отрезная точка для ЛПССК в отношении диагностики КИНК у пациентов с СД составила 25,5 см/с, значения ниже нее были свойственны пациентам с КИНК с чувствительностью метода 79,4% [95% ДИ 62,1–91,3], специфичностью – 96,4% [95% ДИ 81,7–99,9].

**ЗАКЛЮЧЕНИЕ.** ЛПССК можно рассматривать как дополнительный метод оценки КИНК. Кальциноз артерий нижних конечностей, наличие отека или инфекции мягких тканей, раневых дефектов или гангрены стопы не влияет на параметры измерения кровотока методом ЛПССК, что является его преимуществом перед рутинными методами диагностики ишемии, такими как лодыжечно-плечевой индекс (ЛПИ), пальце-плечевой индекс (ППИ), транскутанная оксиметрия.

**КЛЮЧЕВЫЕ СЛОВА:** критическая ишемия нижних конечностей; сахарный диабет; транскутанная оксиметрия; лодыжечная пиковая систолическая скорость кровотока

## BACKGROUND

Current methods for diagnosing critical lower limb ischaemia (CLLI) in patients with diabetes mellitus (DM) includes a comprehensive assessment of the symptoms and signs of lower limb artery disease (LLAD), as well as an objective instrumental examination of the patient. According to the recommendations of the 2015 International Working Group on Diabetic Foot [1], critical ischemia is defined by a systolic pressure reading of 50 mm Hg or less in the infragenicular arteries and a systolic blood pressure reading below 30 mm Hg in the first toe combined with a partial oxygen tension reading of less than 25 mm Hg in the dorsum of the foot. Currently, measuring the ankle-brachial index (ABI) and toe-brachial index (TBI) is used to detect symptoms of LLAD and diagnose CLLI. Transcutaneous oximetry ( $TsRO_2$ ) is used to determine the severity of limb ischaemia as well as the stage of CLLI. However, using non-invasive diagnostic methods to detect LLAD in patients with DM may produce variable results. Specifically, the interpretation of results from diagnostic tests may be affected by diabetic cardiovascular complications such as infectious inflammation in the foot, severe distal diabetic polyneuropathy, concomitant medial calcification of the distal flow arteries, trophic ulcers and oedema. Therefore, it is difficult for clinicians to objectively diagnose macrovascular and microcirculatory disorders in patients with DM [2–4].

As previously stated, measuring the ABI is used as a screening method for detecting LLAD [1]. However, in individuals who have chronic struggles with DM, the calculation of ABI has a low sensitivity and specificity in assessing the severity of ischaemia, especially if the patient is diagnosed with CLLI [2, 5]. This is because significant arterial calcification in the lower limb makes it very difficult to assess the rate of blood flow due to incomplete compression of the vessels, even when pressure in the cuff exceeds 200 mm Hg. According to L. Mills, ABI is overevaluated or not detected in 30% of patients with DM and patients with ulcerative defects of the feet [6]. Complete occlusion of the artery in question and wound defects in the area where the cuff is applied are also potential limiting factors for this test [7]. Therefore, it is important to calculate the ABI during the initial examination of DM patients with suspected LLAD.

$TsRO_2$  is performed to assess microcirculatory function in the soft tissues of the foot and is a standard method to assess the severity of CLLI. This method provides several key advantages over other non-invasive methods, such as its lack of dependence on medial calcification and its ability to predict defects in wound healing and ability to predict the level of amputation needed in the case of irreversible necrosis of the foot. There are several factors that determine the results of  $TsRO_2$ , including the thickness of the skin in the location where the sensor is applied and the ambient room temperature [8]. Despite optimal levels of revascularisation,  $TsRO_2$  indices may be reduced in case of infectious inflammation and post-reperfusion oedema in the soft tissues of the foot. As a result, it is necessary to re-measure the percutaneous tension of oxygen after a course of antibiotic therapy, surgical treatment of an infected plantar wound and the resolution of oedema. The significant clinical factors associated with hypoxia also include anaemia, arterial hypertension, ischaemic heart disease and

creatinine blood levels. To obtain an accurate assessment of abnormal arterial blood flow using  $TsRO_2$ , consider systemic and local factors that influence the interpretation of results [4]. Therefore, there is a crucial need for alternative methods for the diagnosis of CLLI in patients with DM.

## AIM

We aimed to evaluate the value of ankle peak systolic blood flow velocity (APSBV) as a tool for diagnosing CLLI in patients with DM and evaluating the resolution of CLLI after transcutaneous balloon dilatation angioplasty (TBDA).

## METHODS

### Study design

This study was a single-center, unblinded pilot study with a full-design interventional prospective.

### Inclusion criteria

The study included patients with DM who met the following criteria for CLLI diagnosis:

1. constant pain at rest, requiring regular intake of analgesics for 2 weeks or more;
2. trophic ulcer or gangrene of the toes or feet that arises from chronic arterial insufficiency (CAI) and
3. percutaneous foot oxygen tension measurement that is less than 25 mm Hg.

### Study conditions

The study was conducted in the Endocrinology Research Centre with unselected enrolment of patients who were previously hospitalised in the Diabetic Foot Department. All patients were required to meet the inclusion criteria and provide informed consent to participate in the experiment.

### Study duration

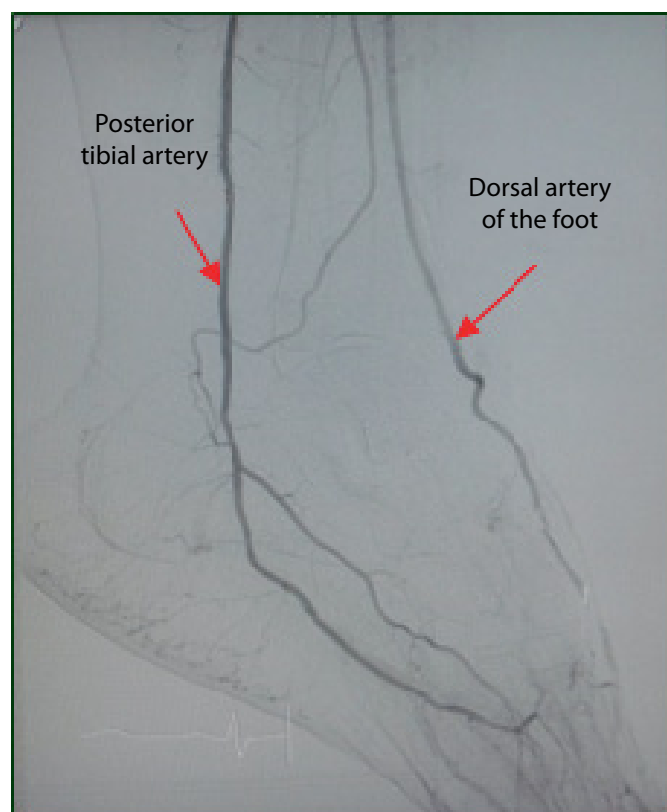
The study was conducted in 2015 with a follow-up period of up to 8 months.

### Description of medical intervention

The study provides clinical and demographic characteristics of patients with DM and CLLI including the patients' gender, age, type of DM (type I or II), time elapsed since initial diagnosis of DM, the level of glycated haemoglobin, type of hypoglycaemic therapy, type of cardiovascular complications (microvascular or macrovascular), blood lipid levels and the presence of comorbidities (arterial hypertension, cardiac arrhythmias and anaemia).

The object of the study was to determine the severity of CAI and the severity of morphological lesions in the lower limbs of patients with DM and CLLI.

Two researchers were responsible for measuring the percutaneous oxygen tension in the soft tissues of the lower limb. During the study, the patient was required to rest in a supine position. The ambient temperature in the room where  $TsRO_2$  was measured stayed between 21 °C and 23 °C. Before the examination, the electrodes were calibrated with atmospheric air. After the skin was cleaned with an alcohol solution, a fixing ring was installed within the first interdigital gap of the foot dorsum or 1–2 cm from



**Fig. 1.** The level of measurement of the spectral characteristics of the blood flow in the dorsal artery of the foot and the posterior tibial artery (angiogram of the right foot).

the edge of the wound defect. The cavity was filled with an electrolyte solution, and the electrodes were placed in the fixing ring. Within a few minutes, the electrodes were used to heat the application site to a temperature of 43 °C. The TsRO<sub>2</sub> indicators were registered when they were stabilised approximately 20 min after the start of the study.

APSBV measurements were performed by a single researcher. The patient was placed in a room with an ambient temperature between 21 °C and 23 °C, asked to lay in a supine position and allowed to rest for 10–15 min. After the 10–15 min period, the APSBV was changed. To register the APSBV, the ultrasound device sensor was installed at the level of the dorsal artery of the foot (DAF) and the posterior tibial artery (PTA) distal to the medial ankle (Fig. 1).

The APSBV for each artery under study was determined using spectral Doppler mode (Fig. 2).

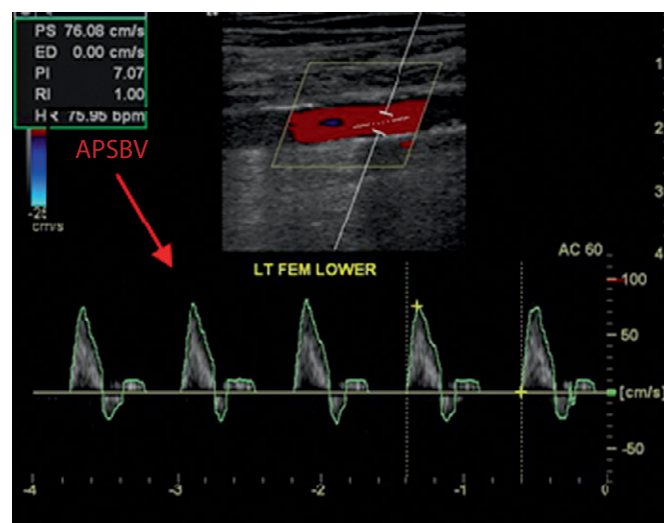
The average value of APSBV was calculated by taking the sum of APSBV measurements for the DAF and PTA and dividing by 2:

$$\text{APSBVav} = \frac{\text{APSBV (DAF)} + \text{APSBV (PTA)}}{2}$$

For example, APSBV (DAF) = 0 cm/s, APSBV (PTA) = 40 cm/s, APSBVav = (0 + 40)/2 = 20 cm/s.

If there was less than 50% stenosis of the arteries in the lower extremities, the main type of blood flow was registered. If there was more than 50% stenosis, the main-modified type of blood flow was registered. If the main arteries were occluded, the collateral blood flow in the arterial segments distal to the occlusion was determined. The APSBV was evaluated in another artery if the occlusion of an artery was too severe.

All patients with DM and CLI underwent balloon angioplasty in the affected arteries.



**Fig. 2.** Measurement of the ankle peak systolic blood flow velocity in the spectral Doppler mode. The arrow indicates the Doppler wave, the peak of which forms the blood flow velocity (cm/s).

### Primary study outcome

The main end point of the study was to determine the dynamic changes in TsRO<sub>2</sub> and APSBV measurements before and after endovascular treatment in patients with DM and CLI.

### Additional study outcomes

1. Use duplex ultrasound (DU) to assess the level and degree of occlusive lesions of the arteries of patients with DM and CLI.
2. Use the classification system designed by R.B. Rutherford to assess the severity of CAI, and use the Graziani classification to determine the severity of morphological lesions of the arterial bed of the lower extremities.
3. Assess of the technical success of endovascular treatment in lower limb arteries of DM patients.
4. Determine the haemodynamically significant complications of revascularised arteries during the early postoperative period (within 5–7 days after revascularisation), and detect re-occlusion of arteries during the immediate postoperative period (up to 1 month post-procedure) using DU.
5. Assess clinical resolution for cases of CLI as well as cases of CLI relapse.

### Methods of registration of the outcomes

The clinical and demographic characteristics of the patients were obtained via patient records and examinations conducted in the clinic of the Endocrinology Research Centre.

The R.B. Rutherford classification was used to clinically assess the degree of CAI [9]. The Graziani classification was used to determine the severity of the morphological lesions of the arterial bed. This method involves identifying the number of arteries in the lower extremities that have steno-occlusive lesions [10].

The Russian language version of the QUADAS questionnaire was used to assess the risk of systematic errors in this study, the diagnostic test used in this study, and the verification of lower limb ischaemia [11].

Therefore, this method of TsRO<sub>2</sub> was adopted as

a reference test that met the pre-established criteria for assessing the severity of lower limb ischaemia. TsRO<sub>2</sub> was performed using a RADIOMETER transcutaneous oximeter (Copenhagen).

Measurement of APSBV was used to diagnose CLLI. APSBV was measured in the PTA and DAF using DU. The following modes were used for these measurements: colour and energy mapping modes, B-mode, and spectral analysis criteria (Voluson 730<sup>®</sup> Expert ultrasound system (GE Medical Systems Kretztechnik GmbH & Co OHG, Austria). The DU method was also applied to determine the number and severity of occlusive lesions in the arteries of the affected lower limb, as well as the presence of postoperative complications in revascularised arteries of the lower limb.

Measurements for TsRO<sub>2</sub> and APSBV were conducted 5–7 days before and after endovascular treatment.

The reference test was conducted in the entire sample of patients. Evaluation of the results for the reference test and studied method (APSBV) was conducted within 1–3 days for most of the patients. The patients were examined using the same reference test regardless of the results obtained from the studied method. The studied method was not a component of the reference test. In some cases, the operator who conducted the test under study knew the results of the reference test. To interpret the results of the reference and the studied tests, all clinical information was available to researchers in accordance with pre-established criteria. In the study, the number of interpreted tests was equal to the number of patients. There were no withdrawals during this study.

#### Ethical considerations

The study was approved by the local ethical committee of the Endocrinological Research Centre. Extract from protocol No. 9a of the meeting of the local ethics committee of 9.12.2013.

#### Statistical analysis

A preliminary calculation of the sample size required for this study was not performed. Quantitative data were presented as the median with interquartile range as follows: Me [Q1; Q3]. Qualitative sampling data were presented as the absolute and relative frequencies of a certain characteristic. The relative frequency of the characteristic was expressed as a percentage in the form of integers for samples with an *n* between 20 and 100.

The Kolmogorov–Smirnov criterion was used to determine the distribution of quantitative data. Non-parametric statistical methods were performed because of the non-normal distribution of data and small sample sizes. The Wilcoxon test was used to compare measurements between dependent groups. The critical level of significance was set at 0.05. Data analysis was performed using Statistica 13.2 En application programmes (StatSoftInc., USA).

The creation of a receiver operating characteristic (ROC) curve was used to determine the cutoff point for CLLI diagnosis using the APSBV assessment. This method was performed to determine the sensitivity and specificity of this method. Statistical data processing was conducted using the MedCalc statistical software program. The optimal cutoff point was the level of the indicator that corresponded to the maximum value of the sum of sensitivity (proportion

of true-positive results, confirmed by the test method, in relation to the gold standard) and specificity of the method (proportion of true-negative results, confirmed by the test method, in relation to the gold standard) obtained during the ROC analysis [12].

APSBV indicators that did not indicate the presence of CLLI were taken as APSBV indicators after endovascular treatment of lower limb arteries in patients with DM. APSBV values that corresponded to TsRO<sub>2</sub> readings greater than 25 mm Hg were said to not indicate the presence of CLLI.

However, when APSBV values corresponded to TsRO<sub>2</sub> readings that were lower or equal to 25 mm Hg, they were said to indicate the presence of CLLI.

## RESULTS

### Study participants

Clinical and demographic characteristics of patients with DM and CLLI are presented in Table 1.

Endovascular treatment of arteries was performed on 51 lower limbs in 48 patients with DM and CLLI.

### Primary results of the study

In order to diagnose CLLI and assess the clinical outcome of revascularisation, percutaneous oxygen tension in the foot tissues and APSBV were measured during the perioperative period (Figs. 3 and 4).

The cutoff point for APSBV with respect to diagnosis of CLLI in patients with DM amounted to 25.5 cm/s, whereas the values below it are typical for patients with CLLI. The sensitivity of the method was 79.4% [95% CI 62.1–91.3], whereas the specificity of the method was 96.4% [95% CI 81.7–99.9] (Fig. 5).

### Additional results of the study

According to the results of DU, haemodynamically significant stenoses and occlusions of the tibial arteries were detected at baseline among patients with DM and CLLI. In 47% of cases (24 lower extremities), there were multi-level occlusive lesions of the femoral–popliteal and pedial–foot segments with relatively intact iliac arteries. The prevalence of extended occlusions of the arteries of the lower extremities (more than 10 cm) relative to stenosis was noted (Fig. 6). The severity of morphological lesions in the arteries of the lower extremities was also evaluated according to the classification of L. Graziani when performing intraoperative X-ray contrast angiography. Most patients had occlusive changes of 2–3 tibial arteries in combination with multiple stenoses and occlusions within the femoral–popliteal segment. These symptoms characterise a severe course of LLAD in patients with DM. Total occlusions in all three arteries of the lower leg, corresponding to class seven lesions, were present in 3.8% of patients. The distribution of patients with CAI, according to the R.B. Rutherford classification, is presented in Fig. 7.

Among patients with DM and CLLI, 48 (94%) showed restored blood flow in at least one tibial artery following revascularisation of the lower limbs.

According to DU readings, postoperative haemodynamically significant complications of the operated arterial segments were revealed between 3 and 5 days after operation. These complications included over 50% residual stenosis in 30 (59%) lower limbs. Out of these

Table 1. Clinical and demographic characteristics of patients with DM and CLLI.

Characteristic	N = 48 patients	%
Men/women	29/19	61/39
Age, Me [Q <sub>1</sub> ; Q <sub>3</sub> ], years	66.7[56.8; 76.6]	
DM type 1/type 2	3/45	6/94
DM duration course, Me [Q <sub>1</sub> ; Q <sub>3</sub> ], years	16.9[8;25.8]	
Antihyperglycaemic therapy:		
Oral antihyperglycaemic drug / insulin/combination therapy	7/19/22	14.6/39.6/45.8
HbA1c, Me [Q <sub>1</sub> ; Q <sub>3</sub> ], %	8.25±1.53	
Arterial hypertension	45	93.75
Constant antihypertensive therapy	33	68.75
Heart rhythm disorder	10	20.8
Ischaemic heart disease	36	75
History of myocardial infarction	9	18.75
Cerebrovascular disease	24	50
History of acute cerebrovascular disease	8	16.6
History of smoking	27	56.25
Dyslipidaemia	34	70.8
Chronic kidney disease C1, C2	35	73
Chronic kidney disease C3-C5	13	27
Renal replacement therapy (programme haemodialysis)	3	6.3
Anaemia of various origin	17	35.4
Diabetic retinopathy: proliferative/terminal stage	14/3	29.1/6.25

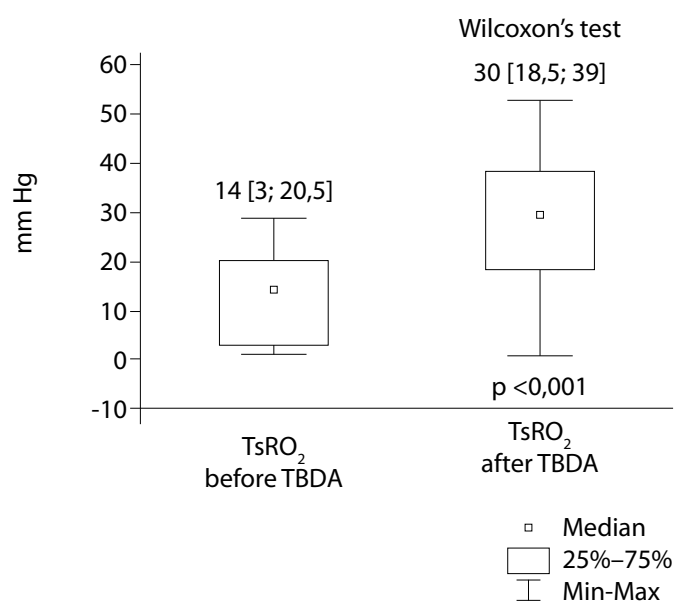


Fig. 3. Percutaneous oxygen tension in the soft tissues of the foot among patients with DM and CLLI before and after transcutaneous balloon dilatation angioplasty.

30 cases of residual stenosis, 18 (35%) had critical residual stenosis, 12 (23%) had extended intimal dissection (more than 3–4 cm) and 1 (2%) had acute thrombosis. Despite the high prevalence of haemodynamically significant adverse outcomes following TBDA, the resolution of CLLI was noted in the majority of patients (93.75%). Resolution of CLLI was determined by the following criteria: reduced limb pain

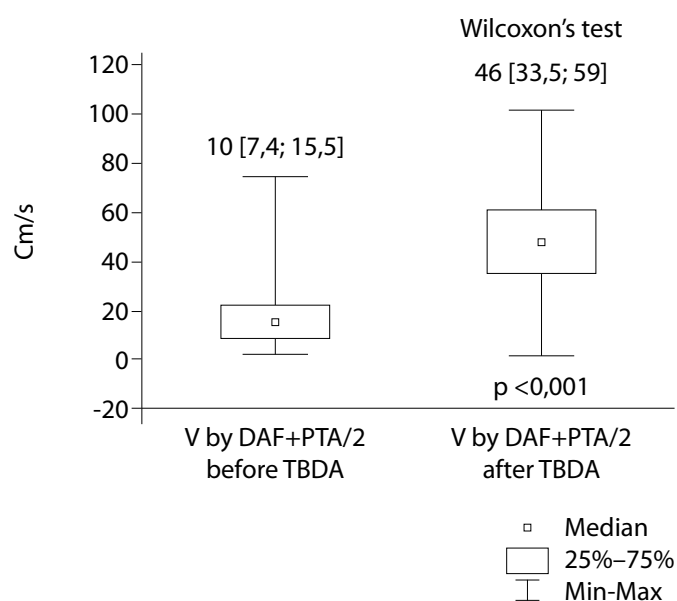


Fig. 4. Results of APSBV in patients with DM and critical lower limb ischaemia before and after transcutaneous balloon dilatation angioplasty.

and positive changes in the condition of the wound defect. Clinically significant complications of the intervention of the early follow-up period were noted in four lower limbs (8.3%) of four patients.

During the immediate postoperative period (up to 1 month after the procedure), re-occlusion of the operated arteries was observed in 12 revascularised lower limbs (23%)



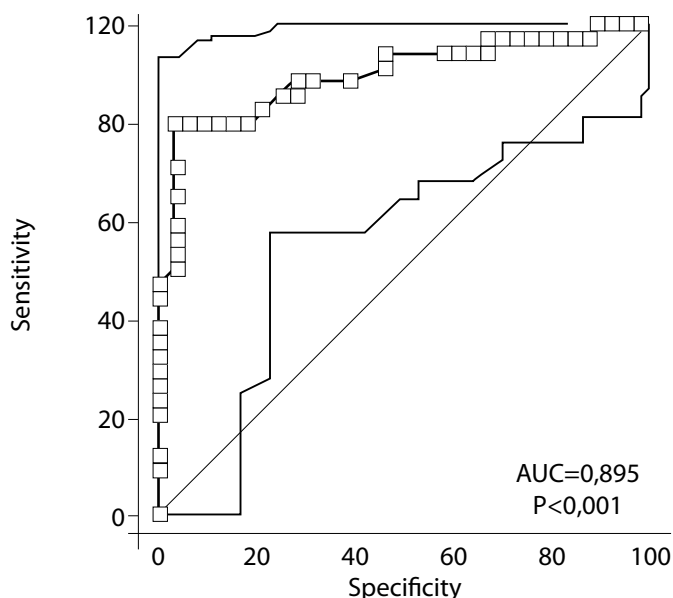


Fig. 5. ROC analysis for cutoff points of the APSBV in critical lower limb ischaemia in patients with DM.

and 12 total patients (25%). Among 8 (16.7%) patients, a primary patency disorder was accompanied by CLLI recurrence, which required subsequent revascularisation of the limb.

Among 20 patients (39.2%), surgical treatment was performed on 20 lower limbs after revascularisation. These procedures involved surgical debridement of wound defects on five lower limbs (9.8%) from five patients (10.4%), amputation of one or several toes on 11 lower limbs (21.5%) belonging to 11 patients (23%) or transmetatarsal resection of the foot in four lower limbs (7.8%) from four patients (8.3%). In 55% of cases, surgery on the lower limbs was not required. In these cases, patients were given a comprehensive but conservative treatment regimen. This treatment regimen involved statin administration, antiplatelet drug administration, limb unloading, antibiotic therapy and treatment of local wounds. High-level amputation of three limbs (5.8%) at the level of the upper third of the lower leg was conducted in three patients (6.25%) due to the failure of revascularisation, the development of extensive purulent and necrotic wounds and the impossibility of preserving the function of the foot.

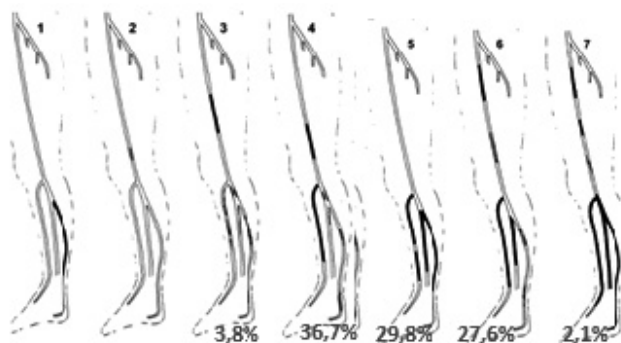


Fig. 6 Morphological lesions of lower limb arteries in patients with DM and CLLI according to the L. Graziani classification: severe lesions of lower limb arteries with occlusions of the distal bed (tibial arteries), and in some cases of the proximal bed, are found in most cases (categories 4–7).

Table 2. Diagnostic indices for APSBV study in patients with DM to identify CLLI.

Indicator	95% CI
Cutoff point, cm/s	25.5
Sensitivity, %	79.4 [95% CI 62.1–91.3]
Specificity, %	96.4 [95% CI 81.7–99.9].

#### Adverse events

No adverse events associated with the diagnostic methods used were recorded during this study.

## DISCUSSION

### Summary of primary result

According to the results of the study, a statistically significant increase in the level of  $TsRO_2$  was revealed among patients with DM and CLLI from level 14 [3; 20.5] mm Hg to level 30 [18.5; 39] mm Hg at similar measurement points on days 5–7 after endovascular treatment. Similarly, APSBV measurements revealed a statistically significant increase from level 10 [7.4; 15.5] cm/s in patients with DM during the CLLI stage up to 46 [33.5; 59] cm/s during the postoperative period.

### Discussion of the primary result of the study

The assessment of the percutaneous oxygen tension of the lower limb tissues is considered the 'gold standard' for assessing the severity of lower limb ischaemia in patients with DM and arterial diseases of the lower limb. Thus,  $TsRO_2$  is used as the reference method in this study.

The study showed a statistically significant increase in  $TsRO_2$  values from the level of CLLI, which is defined as less than 25 mm Hg, to optimal levels of percutaneous oxygen tension in the soft tissues of the foot during the early postoperative period (5–7 days). This increases the likelihood of a positive outcome after revascularisation of the affected limb.

Because of concomitant severe infection and oedema of the foot and a delayed increase in  $TsRO_2$ , indices were noted on average after 4 weeks among eight patients, which was due to local factors affecting the results of the study. Nevertheless, these results indicating the important role of

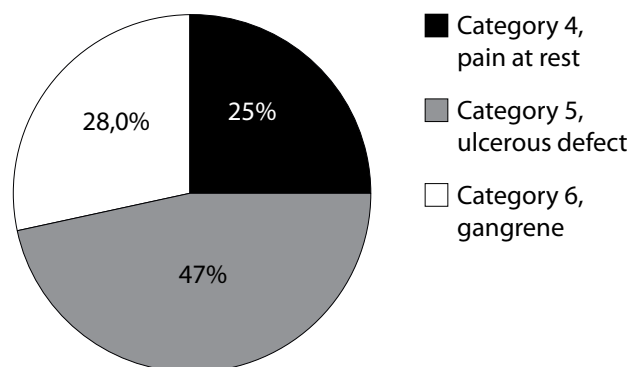


Fig. 7. Distribution of patients with chronic arterial insufficiency according to R.B. Rutherford classification. n = 51 lower limbs.

TsRO<sub>2</sub> in managing patients with DM and CLLI are consistent with findings in the literature [2, 4, 6, 7].

The advantages of this test, in comparison with other non-invasive methods include its lack of dependence on medial calcification, its ability to predict wound healing defects and the likelihood of high-level amputation during the development of irreversible purulent-necrotic changes in the foot. *Ankle peak systolic velocity* is a diagnostic method that is currently under investigation and may be considered as an additional tool for assessing the blood flow in the lower limbs. APSBV is defined as the systolic blood flow velocity in the tibial arteries at the ankle level, which is measured using DU in the lower limb arteries.

Haemodynamics studies the movement of blood throughout the vascular system. This process occurs continuously in the body due to the difference in pressure between blood vessels of various sizes. Therefore, blood moves through the vessels from areas of high pressure to areas of low pressure. The linear velocity of blood flow decreases as the total cross-sectional area of parallel vessels increases. Therefore, the highest blood flow velocity is observed in the aorta, whereas the lowest blood flow velocity is observed in the capillaries because the total area of the capillaries is higher than that of the aortic lumen [13].

The estimation of the velocity of blood flow in the arteries is based on the Doppler principle, which states that an ultrasonic wave undergoes a frequency shift proportional to the speed of a moving object. Therefore, speed waves provide information about the speed of red blood cells.

When arteries are occluded, an adaptation mechanism (arteriogenesis) is triggered, which leads to dilation of existing collateral vessels (Fig. 8). The driving forces behind collateral artery formation [14] include arterial pressure, the pressure gradient proximal and distal to the occlusion level and the force of shear stress on the walls of the new vessel. The outcome of arteriogenesis is a 20- to 50-fold increase in the preceding arteries [15], which may partially compensate for the occluded arteries and reduce the severity of lower limb ischaemia.

The progression of steno-occlusive lesions of arteries may impair the compensatory capabilities of arteriogenesis. For instance, ischaemic pain in the lower limbs often leads to limited physical activity and subsequent loss of muscle mass. This decreases the shear stress in the new vessel and impairs the stimulation of arteriogenesis. As a result, the newly formed arteries degenerate and the tissue becomes ischaemic/hypoxic.

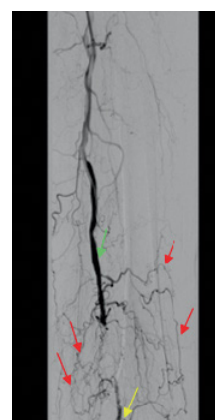
From a physical point of view, the blood flow velocity in collateral vessels is reduced, and APSBV is decreased [14]. Furthermore, changes in the speed of red blood cells are directly correlated with the degree of stenosis [6, 7].

According to the study results, a statistically significant increase in the level of APSBV was observed from the CLLI stage (median of 10 cm/s) to 46 cm/s during the postoperative period. The mean value of APSBV was calculated by taking the sum of APSBV measurements for the DAF and PTA and dividing by 2. This calculation of APSBV was based on the assumption that the resolution of CLLI requires blood flow in at least one tibial artery to the foot. In a study conducted by Bishara et al. [16, 17],

researchers showed that APSBV was significantly correlated with the levels of ABI and TBI, as well as with the indicators of ischaemia identified by the Rutherford classification in patients with DM and CLLI.

A similar approach was applied in the work of Gamzatov et al. [18], which focused on 30 patients with CAI as determined by the classification system developed by A.V. Pokrovsky and 10 patients without clinical signs of ischaemia. It should be noted that this group of examined patients did not include DM patients with lesions of the lower limb arteries. Thus, on the basis of the assessment of CAI by the Pokrovsky classification, the following APSBV diagnostic criteria were developed: measurements lower than 20 cm/s for patients with CLLI, 20–40 cm/s for CAI IIA–IIB and 50 cm/s or greater in the group of healthy individuals without CAI. The sensitivity and specificity of the selected criteria ranged from 87.5% to 100%.

Despite the high sensitivity and specificity for assessing APSBV using the above method, the authors modified the blood flow assessment method using APSBV [19]. Gamzatov et al. suggested that the absolute values of APSBV, which were measured in the main arteries of the extremities, are influenced by the parameters of systemic haemodynamics (blood pressure, heart rate and ventricular ejection). It was also suggested that the APSBV values depend on the technical characteristics of the dopplerograph (duplex scanner), which does not enable the use of this parameter for objectively determining the deficiency of blood flow to the lower extremities. Thus, a new approach to APSBV estimation was proposed, which was the ratio of the sum of APSBV on the radial and ulnar arteries to the sum of APSBV on the dorsal and posterior tibial arteries of the foot. Thus, APSBV values between 1.0 and 1.3 correspond to the normal regional blood circulation, 0.80 and 0.99 correspond to mild ischaemia and 0.50 and 0.79 correspond to moderate ischaemia, and the value lower than 0.50 corresponds to severe ischaemia. On the basis of our ROC analysis, various intervention points were obtained, from which the optimal ones were selected (the maximum amount of sensitivity and specificity). The cutoff point for APSBV with respect to diagnostics of CLLI in DM patients was 25.5 cm/s; values below it are typical for patients with CLLI. The sensitivity of



**Fig. 8.** Angiogram of the arteries of the lower limb of a patient with DM and CLLI. The green arrow indicates the normal blood flow in the superficial femoral artery, the red arrows indicate the collateral vessels and the yellow arrow indicates the blood flow in the distal segment of the artery.

the method was 79.4% [95% CI 62.1–91.3], and the specificity was 96.4% [95% CI 81.7–99.9].

### Discussion of additional results of the study

Patients with DM at the CLLI stage had severe morphological lesions in the arteries of the lower limb, which is consistent with findings in the literature [6, 10]. The severity of clinical lesions of the lower limbs in patients with DM and CLLI also made medical intervention absolutely necessary. In most cases, endovascular treatment resolved symptoms of CLLI, despite the presence of haemodynamically significant complications following TBDA. For some patients, concomitant severe infection and oedema of the foot caused a delayed increase in  $TsRO_2$  indices after an average of 4 weeks (no data presented), which was due to local factors affecting the results of the study. However, during follow-up, the cases of CLLI relapses were revealed, which were accompanied by exacerbation of clinical symptoms, a decrease in  $TsRO_2$  and re-occlusion of the arterial segments that previously underwent endovascular treatment. These cases required subsequent revascularisation of the limb. Within the complex treatment of CLLI, patients with DM received a conservative treatment regimen. In other cases, surgery was required to preserve the support function of the limb.

### Study limitations

1. A small sample of patients.
2. The study did not determine whether different equipment or sensor sensitivity affected the reproducibility of APSBV measurements.
3. The study did not assess the reproducibility of APSBV as performed by different operators. It is necessary to follow the methodology of APSBV measurements, since its level may depend on the position of the ultrasonic sensor, etc.
4. This study did not examine trophic changes in the affected foot tissues of patients following revascularisation of the lower limb arteries.

## CONCLUSIONS

According to the data obtained during the study, the determination of APSBV in the tibial arteries with the calculation of the average value of the indicator may represent an additional method for diagnosing CLLI in patients with DM. This proposed for assessing the deficiency of arterial blood flow in the lower extremities has several advantages in comparison with currently used non-invasive diagnostic procedures for detecting CLLI. For instance, calcification of the tibial arteries, oedema, infection of soft tissues and extensive wound defects of the forefoot do not affect the results of the study [16, 17]. This method is affordable, economical, highly reproducible and can be applied in both inpatient and outpatient healthcare settings. In the absence of expensive equipment used to measure transcutaneous oxygen stress, measuring APSBV using a dopplerograph can serve as an alternative method for diagnosing CLLI and evaluating the success of revascularisation procedures.

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**Contribution of authors.** Z.N. Jemilova was involved in enrolment of patients, creation of the concept and design of the article, analysis of the literature, statistical processing of the study results, interpretation of the results and writing of the article. O.N. Bondarenko performed enrolment of patients, created the concept and design of the article, conducted analysis of the literature, performed the text editing and conducted approval of the final version of the manuscript text. G.R. Galstyan performed the text editing, conducted approval of the final version of the manuscript text.

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