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Analyses of transcutaneous oxygen pressure values stratified for foot angiosomes to predict diabetic foot ulcer healing

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ABSTRACT

Aims: Previous research suggested that diabetic foot ulcer (DFU) location could affect transcutaneous oxygen pressure ($TcPO_2$) values following the angiosome concept. Up to our knowledge no studies have yet analyzed if the location of a diabetic foot ulcer can be a confounding factor that modifies $TcPO_2$ values. The primary aim of this study was to compare the potential healing prognosis of $TcPO_2$ differentiated for diabetic foot ulcers in different angiosome locations.

Methods: a 2-years observational cohort prospective study was performed in 81 patients with diabetic foot ulcers. Transcutaneous oxygen pressure measurements were performed at baseline by placing the electrode on two different angiosomes: dorsal zone of the foot (dorsalis pedis angiosome) and between the navicular bone and the tibial malleolus (posterior tibial angiosome). The main outcome was establishing the effectiveness of $TcPO_2$ measurements (dorsalis pedis angiosome and posterior tibial angiosome) for predicting DFU healing.

Results: Transcutaneous oxygen pressure probe placed in the dorsum of the foot (dorsalis pedis angiosome) yielded a sensitivity (S) of 95 % and specificity (SP) of 73 %, and an area under the curve (AUC) of 0.902 ($p < 0.001$ [0.84–0.96]) for ulcers located in the forefoot and toes; while $TcPO_2$ placed in the posterior tibial angiosome yielded an S of 100 % and SP of 85 % and an AUC of 0.894 ($p < 0.001$ [0-822-0.966]) for DFU located in the midfoot and heel.

Conclusion: This study suggests that angiosome-guided $TcPO_2$ contributes to a prognosis of successful foot ulcer healing.

1. Introduction

Diabetic foot ulcers (DFU) have become one of the most prevalent complications related to diabetes [1]. Patients with foot complications related to diabetes have been demonstrated to suffer from a death event 2.5 times more in comparison with diabetes patients without foot complications [2]. People with diabetes are more prone to developing DFU due to the combination of nerve damage and reduced blood flow [2]. Peripheral artery disease (PAD) becomes a devastating complication of diabetes and microcirculatory disease; it has been estimated that patients with DFU and diabetes suffer from underlying PAD in 50 % of the cases [3,4]. This misdiagnosis occurs due to the lack of clinical symptoms of PAD, such as rest pain and/or claudication [5]. PAD affects not only the healing prognosis of DFU [6] but also increases minor and major amputation rates. Finally, it is associated with a worse prognosis than in patients with many common cancers [7,8]. Diabetic foot ulcer integral management is focused on the control of cardiometabolic status of the patient, vascular status, infection management and proper off-loading [9].

The literature suggests that microcirculatory status is believed to reflect the status of underlying vascularization of the skin [10,11]. Transcutaneous oxygen tension ($TcPO_2$) measurement is a non-invasive tool for diagnosing and assessing PAD, especially in cases with diabetes and foot complications [12,13].

The society of Vascular Surgery with the "Wound, Ischemia, and foot Infection (WIfI)" classification and the European Society for Vascular

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Surgery recommend that if arterial calcification precludes reliable ankle-brachial index (ABI) or toe pressure measurement, ischemia grade should be classified using $TcPO_2$ measurement [14].

A recent study reported a sensitivity ranging from 0.61 to 0.82 for the prognosis of DFU healing [6] and also reported that the $TcPO_2$ threshold values for detecting ischemia or non-healing DFUs differ significantly [6, 15–23]. Most studies analyze $TcPO_2$ values in the dorsum of the foot between the first and the second metatarsal bone [14]; despite this, DFU location could affect $TcPO_2$ values following the angiosome concept. First described by Taylor et al. [24], it divides the foot between different angiosomes, parts of tissue, each receiving blood from a separate arterial branch [25]. Previous systematic review and metanalysis demonstrated that $TcPO_2$ normal values may increase the preset probability of DFU healing up to 45 %; this percentage seems to be very low, it could be biased by probe location, as only a small number of studies evaluated probe and DFU location [6]. Izzo V et al. [26] demonstrated that when a heel lesion is present, the $TcPO_2$ recorded on the dorsum of the foot does not confirm the presence of critical limb ischemia; in these cases, a second $TcPO_2$ recorded on the rearfoot is useful to identify ischemia. Additionally, some authors suggested that the $TcPO_2$ parameter may be combined with the angiosome concept because it shows a connection between the location of the arterial occlusion and the location of the wound site and shows better results after hyperbaric oxygen therapy and low-intensity laser irradiation [27,28].

Despite the previous advances and individualization of vascular treatments, up to our knowledge no studies have yet analyzed if the location of a diabetic foot ulcer can be a confounding factor that modifies $TcPO_2$ values, thus no previous research has still evaluated the power of $TcPO_2$ probe in different angiosome locations depending on ulcer location. Understanding the $TcPo_2$ values in different angiosome locations could provide valuable insights into the healing potential of DFUs. Therefore, this study primarily aimed to compare the potential healing prognosis of $TcPO_2$ differentiated for DFU in different angiosome locations.

2. Material and methods

2.1. Participants

Eighty-one patients with active DFUs participated in this 2-years prospective study in a specialized diabetic foot unit between December 2018 and January 2020. To be eligible, patients should meet all inclusion and no exclusion criteria. Patients came to our outpatient clinic whose reason for the visit were a first consultation with a diabetic foot ulcer. Inclusion criteria included patients older than 18 years presenting with type 1 or 2 diabetes and the presence of DFU in the presence of diabetic polyneuropathy (DPN). Additional inclusion criteria were the location of the ulcer on the toe or the lateral, dorsal, or plantar aspect of the foot with a wound surface area between 1 and 30 cm^2 after debridement. Exclusion criteria included heart failure, previous stroke, end-stage renal disease, critical limb ischemia as defined by the International Working Group Diabetic Foot (IWGDF) [23], or any other disease that could affect wound healing, such as antineoplastic treatment. Poor glycemic control patients were also excluded from the research due to the worse related outcomes; good glycemic control was confirmed by a glycosylated hemoglobin (HbA1c) value of 10 % (85.8 mmol/mol) or lower in the 3 months before enrollment or during screening.

Diabetic foot ulcers included in the study were lesions with a break of the skin of the foot that involved as a minimum the epidermis and part of the dermis secondary to DPN and foot deformity; presence of deep foot ulcers, ulcers that extends deeper than the dermis, that may include abscess, septic arthritis, osteomyelitis, septic teno-synovitis or necrotizing soft tissue infection, were excluded from the research. Diabetic foot osteomyelitis (DFO) was defined as an infection of the bone, with involvement of the bone marrow. For the diagnosis of DFO, combination of probe-to-bone test (PTB) and X-rays was performed at baseline and classified as pathologic or non-pathologic. The PTB test was positive when the researcher felt a hard or gritty surface through the ulcer using metal forceps (Halsted mosquito forceps). Two standard views of X-ray were performed, and we considered the X-ray positive when the research could visualize the following radiological signs in X-ray: focal loss of trabecular pattern or marrow radiolucency (demineralization); periosteal reaction or elevation; the presence of sequestrum (devitalized bone with radio dense appearance separated from normal bone); loss of bone cortex, with bony erosion or demineralization; and other types of signs (bone sclerosis, with or without erosion; the presence of involucrum (layer of new bone growth outside previously existing bone resulting and originating from stripping off the periosteum), and the presence of cloacae (opening in the involucrum or cortex through which sequestrum or granulation tissue may discharge) [9].

After institutional review board approval was obtained, patients' medical records and clinicopathologic conditions were recorded in a prospective basis for two years.

2.2. Clinical evaluation

At baseline, clinical characteristics were assessed after the patient signed informed consent on day 0. Clinicopathologic data were collected, including diabetes type, mean duration of diabetes, hypertension, smoking history, and HbA1c (%) values over the previous 3 months. The patient's renal, cardiac, and retinopathy statuses and previous minor amputations were recorded in the case report form from the patient's clinical histories. Systolic toe and ankle pressures were registered; additionally, ankle-brachial index (ABI) and toe-brachial index (TBI) values were calculated for the ulcerated limb. According to the IWGDF guidelines, critical limb ischemia is defined as the absence of both distal pulses and a brachial ankle index of less than 0.39, a systolic ankle pressure of less than 50 mm Hg, and a toe pressure of less than 30 mm Hg [23]. Critical limb ischemia patients, previously revascularized, could be included in the research if vascular status remained normal after three months of vascular procedure was performed. Diabetic polyneuropathy was diagnosed according to the inability to sense the pressure of a 10-*g* Semmes-Weinstein monofilament at three plantar foot sites and/or a vibration perception threshold of greater than 25 V as assessed using a biothesiometer (Me·Te.Da. s. r.l., San Benedetto del Tronto, Italy) [29]. Foot deformities were evaluated at baseline, claw toe, hammer toe, hallux valgus, and bony prominence were included. To assess wound improvement, wound surface area was measured at inclusion and then weekly via Visitrak electronic mapping until wound healing was achieved. Ulcers were classified according to the Site, Ischemia, Neuropathy, Bacterial Infection, and Depth (SINBAD) classification system at inclusion. The SINBAD system uses six parameters (ulcer site, ischemia, neuropathy, bacterial infection, area, and depth), scored with a 0 or 1 point to create a SINBAD score of 0–6 [30]. Additionally, the Wound, Ischemia and foot infection (WIfI) classification was used to stratify patients at risk for foot amputation [31]. The WIfI stage was calculated using a freely available download as a calculator tool to create a WIfI clinical stage from 0 to 4 [32]. Finally, Wagner classification, University of Texas and PEDIS (Perfusion, Extent, Depth, Infection and Sensation) classification systems were used to classify the severity of DFUs [33].

2.3. Diabetic foot ulcers management

All patients in the study received standard care consisting of ulcer debridement twice a week and proper offloading following the IWGDF guideline recommendations [9]. Patients were subjected to full DFU debridement including edges and wound bed with sharp debridement prior wound irrigation with saline solution. The offloading device consisted in a removable knee-high offloading device. During the follow-up period, all sample received the same neutral dressing [17] (atraumatic dressings with a silicone-ulcer interface without silver) twice per week,

all the dressings were covered with triple layer vendage consisting in gauze, cotton, and elastic bandage without any occlusion.

Additionally, minor and major amputation events, revascularization, and deaths were documented until the 2-years follow-up period. Despite exclusion of critical limb ischemia patients from the study, non-healing patients at 24-weeks could be evaluated by the same vascular surgeon to consider revascularization, irrespective of the results of bedside tests, following IWGDF guidance recommendations [23].

2.4. Transcutaneous oxygen pressure assessment

Transcutaneous oxygen pressure measurements were performed at baseline using the TCM400 measuring device (Radiometer, Copenhagen, 2700, Denmark) by placing the electrode on the dorsal zone of the foot between the first and the second metatarsal bones (dorsalis pedis angiosome) and between the navicular bone and the tibial malleolus (posterior tibial angiosome) (Fig. 1), and recording the values in millimeters of mercury after a calibrating time of 10 min and maintaining a temperature of 44 °C in the electrode. Patients were placed supine during the examination and asked not to move or speak [14].

2.5. Outcome measures

The main outcome was establishing the effectiveness of $TcPO_2$ measurements (dorsalis pedis angiosome and posterior tibial angiosome) for predicting DFU healing. The entire population was analyzed together for primary outcome measure (healing) and stratified into two patient groups for analyses: (1) healing or (2) non-healing. Wound healing was defined as complete epithelialization without any drainage confirmed for at least 10 days after closure and was first documented at 24 weeks [34]. If a patient underwent a minor amputation that healed, was considered a wound healing failure. A senior healthcare provider (MLM) followed all patients for their care in the service and applied the dressing twice per week until the study completion. Additionally, the same clinician performed the monthly follow-up to record study variables. Secondary outcomes were evaluated until the 2 years to assess late complications, such as amputation, revascularization, and death.

2.6. Statistical analysis

The assumption of normality of all the continuous variables was verified using the Shapiro–Wilk test. The normally distributed variables (Shapiro–Wilk test with $p \geq 0.05$) were reported as mean and standard deviations. The categorical variables were reported as a frequency and percentage, while the continuous variables were reported as the mean ± standard deviation (SD; parametric distribution) or the median and interquartile range (IQR; non-parametric distribution). For the univariate analyses and to explore differences in clinical features between patients with and without ulcer healing, the x^2 test for categorical variables and the Student's t-test for continuous variables were performed. For selecting the optimal predictive model, a threshold of 30 mmHg for transcutaneous oxygen pressure, as recommended by international guidelines [23,31], was used as a cut-off point for both angiosomes models depending on DFU location.

To respond the main outcome measure, Receiver operating characteristic (ROC) curves were used. This method is a graphical way of representing sensitivity and specificity for a given test, formal testing for the optimum cut point was performed by Youden's test. In addition, positive predictive values (PPV) and negative predictive values (NPV) and positive (PLR) and negative likelihood ratios (NLR) were calculated for vascular tests. For the multivariate analysis we analyzed clinical factors affecting wound closure by 24 weeks in the study groups were assessed with logistic regression. The independent variables consisted of $TcPO_2$ located in the dorsalis pedis angiosome and $TcPO_2$ located in the posterior tibial angiosome, and covariates with P values of 0.1 or less in the univariate analyses were included in the model. P values of less than 0.05 were considered statistically significant with confidence intervals (CI) of 95 %. All statistical analyses were performed using SPSS statistics version 27.0 for Mac OS (SPSS, Chicago, Ill).

For the sample calculation, a 1-year follow-up study of patients with diabetic foot ulcers [15] showed that 30 mmHg $TcPO_2$ cut-off value predicted wound healing efficiently. As a relevant risk reduction, we assumed a difference in the 15 % healing rate in patients after screening $TcPO_2$ values in the ulcerated angiosome in comparison with patients who did not. We intended to include 81 patients based on a 0.05 setting (two-sided), a power of 0.80 in an x^2 analysis, and an anticipated loss to follow-up of 20 %.

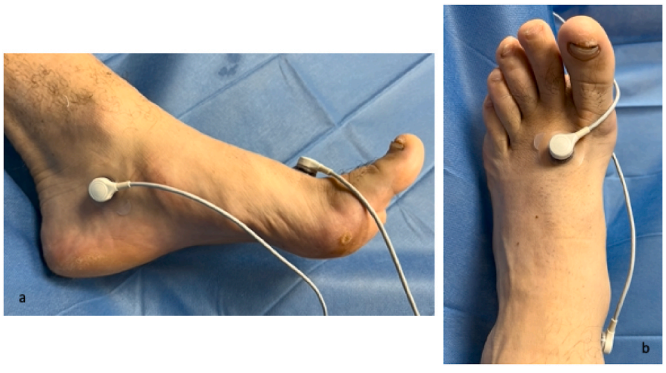

Fig. 1. Location of $TcPO_2$ electrodes by dorsalis pedis or posterior tibial angiosomes.
Fig. 1 Legend. a. electrode on the dorsal zone of the foot between the first and the second metatarsal bone (dorsalis pedis angiosome); b. Electrode between the navicular bone and the tibial malleolus (posterior tibial angiosome).

3. Results

3.1. Demographic and wound characteristics

The study included 81 patients with type 1 or 2 diabetes and an active DFU (72 males and 9 females). Table 1 shows the baseline data on demographic characteristics and diabetes complications. As expected, healing patients (n = 50, 61.72 %) at 24 weeks showed higher $TcPO_2$ values in both the dorsalis pedis and posterior tibial angiosomes than non-healing patients. A total of 62 patients (76.5 %) were included in the dorsalis pedis angiosome (forefoot ulcers) group, and 19 patients (23.5 %) in the posterior tibial angiosome (midfoot and rearfoot ulcers) group.

Wound characteristics differed between healing and non-healing patients, with most hallux ulcers in the interphalangeal joint (IPJ) resulting in non-healing patients, while patients with metatarsal head DFUs resulted in healing. Additionally, most patients with a WIfI stage of 1 healed, and most non-healing patients had DFUs with a WIfI stage of 3. No differences were found in the SINBAD score and wound surface area. The results of the current research suggest that there was a trend toward a lower likelihood of healing with increasing age. The median healing time was 14 weeks (interquartile range (IQR), 11–17 weeks). The healing time for DFUs located in the dorsalis pedis angiosome was 11.5 weeks (IQR, 7.25–15 weeks), and that for DFUs located in the posterior tibial angiosome was 14 weeks (IQR, 7–21 weeks). Regarding Wagner, Texas and PEDIS classification we did not find any difference between patients who achieved healing at 24-weeks and patients who did not. Wound characteristics are shown in Table 2.

3.2. Main outcome measure

We observed that when placing the $TcPO_2$ electrode in the specific ulcerated region (the dorsalis pedis or posterior tibial angiosome), it resulted in better prognostic values with a balance of sensitivity (S) and specificity (SP) (Fig. 2). Fig. 2 shows the ROC curves for all DFU

Table 1
Patients' baseline characteristics and diabetes complications (N = 81).

Baseline Characteristics	All Patients (N = 81)	Patients with healed ulcers at 24 weeks (n = 50)	Patients with not healed ulcers at 24 weeks (n = 31)	*P*-value (95 % CI)
Male, n (%)	72 (88.9 %)	45 (90 %)	27 (87.1 %)	.691
Female n, (%)	9 (11.1 %)	5 (10 %)	4 (12.9 %)	
Type 2 Diabetes, n (%)	54 (66.7 %)	33 (66 %)	21 (67.7 %)	.874
Type 1 Diabetes, n (%)	27 (33.3 %)	17 (34 %)	10 (32.3 %)	
Caucasian race, n (%)	81 (100 %)	81 (100 %)	81 (100 %)	–
Retinopathy, n (%)	48 (59.3 %)	26 (52 %)	19 (61.3 %)	.607
Renal disease, n (%)	16 (19.8 %)	7 (14 %)	9 (29 %)	.108
Hypertension, n (%)	62 (76.5 %)	37 (73.5 %)	26 (83.9 %)	.284
Neuropathy, n (%)	79 (97.5 %)	48 (96 %)	31 (100 %)	.159
Previous Ulceration, n (%)	58 (71.6 %)	39 (78 %)	19 (61.3 %)	.108
Body Mass Index, mean ± SD	28.12 ± 4.12	27.69 ± 3.84	28.83 ± 4.51	.151
Mean age ± SD (years)	66.88 ± 11.4	63.84 ± 10.34	71.8 ± 11.45	.091
Current smoker, n (%)	13 (16 %)	10 (20 %)	3 (9.7 %)	.219
Glycated hemoglobin mmol/mol (%), mean ± SD	7.74 ± 1.4	7.68 ± 1.49	7.85 ± 1.34	.053
Diabetes mellitus (years), mean ± SD	22.49 ± 10.41	21.64 ± 10.6	23.87 ± 10.12	.07
Foot deformity, n (%)	71 (87.6 %)	42 (84 %)	29 (93.5 %)	.204
Presence of dorsalis pedis pulse, n (%)	35 (43.2 %)	21 (42 %)	14 (45.2 %)	.783
Presence of posterior tibial pulse, n (%)	27 (33.3 %)	19 (38 %)	8 (25.8 %)	.263
Ankle Systolic Pressure (mmHg), mean ± SD	131.9 ± 53.32	135.79 ± 50.82	125.9 ± 57.68	.205
Toe Systolic Pressure (mmHg), mean ± SD	79.85 ± 31.06	81.51 ± 30.83	66.04 ± 27.18	.238
Ankle Brachial Pressure Index, mean ± SD	0.99 ± 0.33	1.01 ± 0.29	0.95 ± 0.38	.053
Toe Brachial Pressure Index, mean ± SD	0.63 ± 0.28	0.67 ± 0.31	0.54 ± 0.19	.549
$TcPO_2$ (mmHg) dorsalis pedis angiosome, mean ± SD	31.11 ± 16.11	38.94 ± 12.63	18.48 ± 12.83	**<.001***
$TcPO_2$ (mmHg) posterior tibial angiosome, mean ± SD	33.77 ± 13.22	35.5 ± 12.2	31 ± 14.5	**.008***

Table 1 legend. SD, standard deviation; CI, confidence interval. *P < 0.05 indicates statistical significance.

locations and $TcPO_2$ measurements. When the $TcPO_2$ was placed in the dorsum of the foot, it yielded an S of 95 %, SP of 73 %, and area under the curve (AUC) of 0.902 (p-value <0.001 [0.84–0.96]) for ulcers located in the forefoot and toes. When it was placed in the posterior tibial angiosome, it yielded an S of 100 %, SP of 85 %, and AUC of 0.894 (p-value <0.001 [0-822-0.966]) for ulcers located in the midfoot and heel. The transcutaneous oxygen pressure showed worse results in predicting DFU healing when the probe location was evaluated irrespective

Table 2
Baseline characteristics of wounds.

Baseline Characteristics	Patients (N = 81)	Patients with healed ulcers at 24 weeks (N = 50)	Patients with not healed ulcers at 24 weeks (N = 31)	*P*-value (95 % CI)
Location				
Hallux, n (%)	19 (23.5 %)	6 (12 %)	13 (41.9 %)	**.002***
Minor Toe, n (%)	15 (18.5 %)	8 (16 %)	7 (22.6 %)	.459
Metatarsal head, n (%)	19 (23.5 %)	17 (34 %)	2 (6.5 %)	**.004***
Dorsum, n (%)	9 (11 %)	5 (10 %)	4 (12.9 %)	.686
Midfoot, n (%)	10 (12.3 %)	8 (16 %)	2 (6.5 %)	.204
Heel, n (%)	9 (11.1 %)	6 (12 %)	3 (9.7 %)	.746
SINBAD Score System, mean ± SD	2.56 ± 1.4	2.52 ± 1.35	2.64 ± 1.49	.699
WIfI stage				
Stage 1	29 (35.8 %)	23 (46 %)	6 (19.4 %)	**.015***
Stage 2	23 (28.4 %)	15 (30 %)	8 (25.8 %)	.684
Stage 3	29 (35.8 %)	12 (24 %)	17 (54.8 %)	**.005***
Stage 4	–	–	–	–
University of Texas classification, mean ± SD				
Grade 1 A	81 (100 %)	50 (61.7%)	31 (38.3 %)	.362
Wagner classification, mean ± SD				
Wagner 1	41 (50.6 %)	23 (46 %)	18 (58.1 %)	.442
Wagner 2	40 (49.4 %)	27 (54 %)	13 (41.4 %)	.395
PEDIS classification, mean ± SD				
Grade 1	81 (100 %)	50 (61.7 %)	31 (38.3 %)	.362
Wound Area Surface (cm^2), median [Q1-Q3], outliner	1.8 [1–2.6], 7.2	1.8 [1–2.7], 5.1	1.6 [1–2.6], 7.2	.694

Table 2 legend. SINBAD; Site, Ischemia, Neuropathy, Bacterial Infection and Depth; CI: confidence Interval. WIfI; Wound, Ischemia, foot Infection. Q; Quartile. University of Texas Grade 1 A, superficial ulcer without infection and ischemia; Wagner 1, superficial ulcer; Wagner 2, Deep full thickness extension ulcer; PEDIS, Perfusion, Extent, Depth, Infection and Sensation; PEDIS Grade 1, superficial full thickness ulcer, not penetrating any structure deeper than the dermis in absence of symptoms or signs of infection; *P < 0.05 indicates statistical significance.

of foot angiosomes (Table 3).

Logistic regression analyses were performed using variables with a p-value of less than 0.1 in the univariate analyses (glycated hemoglobin, age, evolution time of DM, TBI, DFU location, WIfI stage 3, $TcPO_2$ in the dorsalis pedis angiosome, and $TcPO_2$ in the posterior tibial angiosome). $TcPO_2$ performed in the dorsalis pedis angiosome was the only variable associated with wound healing at 24 weeks in patients with a DFU located in the dorsalis pedis angiosome (forefoot and dorsum of the foot) (P < 0.001; 95 % CI, 1.11–1.46). $TcPO_2$ performed in the posterior tibial angiosome was the only variable associated with wound healing at 24 weeks in patients with a DFU located in the posterior tibial angiosome (midfoot and rearfoot) (P = 0.003; 95 % CI, 1.06–1.32).

3.3. Secondary outcomes

In the group of non-healing DFU patients (N = 31), 15 patients (48.4 %) healed after the 24-week period (IQR, 30–41 weeks), 16 patients (51.6 %) required a minor amputation, 11 patients (35.5 %) healed following previous endovascular revascularization. These patients who

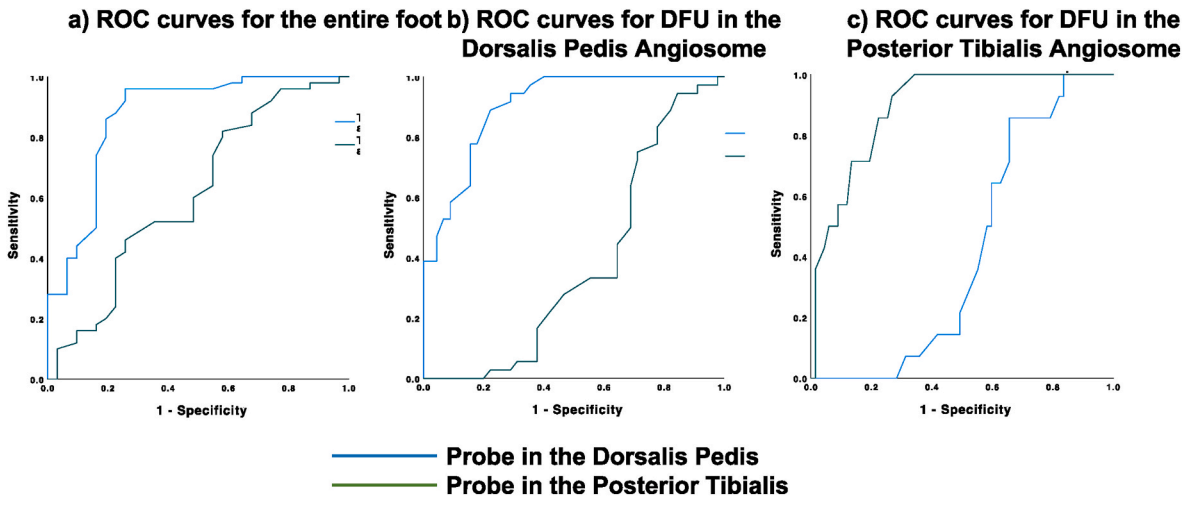

Fig. 2. Receiver operating characteristic (ROC) curves for TcPO2 regarding different electrode locations and angiosomes.
Fig. 2 Legend. Receiver operating characteristic (ROC) curves for TcPO2 (mmHg); a) ROC curves for the entire foot; b) ROC curves for DFU located in the dorsalis pedis angiosome; c) ROC curves for DFU in the posterior tibial angiosome.

Table 3
Performance characteristics of TcPO2 measurements stratified by ulcer location.

Pooled data	DFU in the entire foot (N = 81)		DFU in the dorsalis pedis angiosome region (n = 62)		DFU in the posterior tibial angiosome region (n = 19)	
	Probe in the dorsalis pedis angiosome	Probe in the posterior tibial angiosome	Probe in the dorsalis pedis angiosome	Probe in the posterior tibial angiosome	Probe in the dorsalis pedis angiosome	Probe in the posterior tibial angiosome
AUC (P value [95 % CI]	.871 (<0.001 [0.784–0.958])	.612 (0.092 [0.481–0.743])	.902 (<0.001 [0.84–0.96])	.379 (0.06 [0.256–0.502])	0.418 (0.336 [0.295–0.541])	.894 (<0.001 [0-822-0.966])
Sensitivity	86 %	82 %	95 %	48 %	50	100 %
Specificity	74 %	42 %	73 %	34 %	42 %	81 %
PPV	84.4 %	67.3 %	57.28 %	59.65 %	55.35 %	55.96 %
NPV	76.4 %	58.26 %	89.95 %	28.61 %	34 %	100 %
PLR	3.3	1.4	3.5	0.72	0.9	5.26
NLR	0.2	0.4	0.06	1.52	1.2	0

Table 3 legend. $TcPO_2$, transcutaneous oxygen pressure; DFU, diabetic foot ulcer; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; NLR, negative likelihood ratio; PLR, positive likelihood ratio.

healed after 24 weeks were not included as healed for analyses. All the patients subjected to revascularization underwent endovascular procedures below the knee after the 24-week study period. Balloon angioplasty of the anterior tibial artery was performed in 10 patients (90.9 %) with a DFU located in the forefoot, and one (9.1 %) balloon angioplasty of the posterior tibial artery was performed for one patient with a DFU located in the heel. Minor amputations included 7 partial phalangectomies of the hallux, 5 partial phalangectomies of minor toes, 2 metatarsal head resections, 1 cuboid exostectomy, and 1 partial calcanectomy. In the group of patients that required minor amputation, 14 (45.2 %) patients finally healed in a median time of 35 weeks (IQR, 29–45 weeks), and 2 patients (12.9 %) required a major amputation (one below the knee and one above). Two (6.45 %) patients died for causes other than the ulcer (one of them due to stroke and the other due to COVID-19).

4. Discussion

Here we identified $TcPO_2$ measurements – separated for ulcer location depending on the angiosome theory – as the best predictor of ulcer healing after the 24-week follow-up period. Previous meta-analyses have reported that $TcPO_2$ is the best available predictive test for predicting both DFU healing and limb amputation [6]. Furthermore, a recent systematic review (evaluating 29 studies) reported that in 24 (67 %), probes were placed on specific anatomical locations. These locations were on the dorsum of the foot (n = 20, 54 %), ankle (n = 3, 8 %) and calf (n = 1, 3 %). The specific location was not reported in five (14 %) studies [14]. None of these studies evaluated if there existed any relationship between ulcer location and $TcPO_2$ healing prognosis. Studies in the literature regarding $TcPO_2$ values and healing prognosis are heterogeneous; it has been suggested that heterogeneity in method (probe location and temperature, study type and participants included) alters $TcPO_2$ values. The current research proposes a new assessment method based on the personalization of $TcPO_2$ probe location depending on ulcer location and patients' characteristics. Related to these results, vascular procedures and direct revascularization of the ischemic angiosome may improve wound healing of diabetic foot ulcers and subsequent limb salvage. Applying the angiosome-targeted concept of perfusion has been reported to improve outcomes for both wound healing time and limb salvage [35,36]. Previous research have proposed that $TcPO_2$ parameter may be combined with the angiosome concept because it shows a connection between the location of the arterial occlusion and the location of the wound site and shows better results after focused treatment [37,38]. If direct revascularization to the affected angiosome plays a key role in ulcer healing, clinicians should assess the affected angiosome of the foot regarding ulcer location.

Izzo et al. [26] conducted the first study on critical limb ischemia patients; they demonstrated that rearfoot DFU patients with dorsal $TcPO_2 > 30$ mmHg received a diagnosis of critical ischemia when $TcPO_2$ was performed on the rearfoot; despite this, the retrospective nature of the research does not allow to confirm the results and additionally, they did not find any prediction model for ulcer healing. In our research

hallux IPJ ulcer patients resulted in worse outcomes, 13 (41.9 %) not healed ulcers; it could be explained due to the implication of the first ray in gait.

The combined sensitivity and specificity previously found for $TcPO_2$ for ulcer healing were 0.72 and 0.86, respectively [6]. Our results show higher prognostic values when separated for dorsalis pedis angiosome in forefoot ulcers (S = 0.95; SP = 0.75) and posterior tibial angiosome in midfoot and rearfoot ulcers (S = 1; SP = 0.81). This model improves the diagnostic accuracy of $TcPO_2$ only by stratifying ulcer and probe location.

Previous authors have suggested that tissue oxygenation saturation foot-mapping can successfully and non-invasively detect ischemic areas in the peripheral tissue of the foot and is also more appropriate than the assessment provided by the angiosome model [39]. In the literature, alternative techniques to assess microcirculation are used, including stimulation $TcPO_2$ testing [40], fluorescence angiography [41], capillaroscopy, laser doppler [42] and hyperspectral imaging [6,10]. With the limited number of the available studies, more work is needed to understand the differences in the structure and function of the microcirculation between people with healed and non-healed DFU. Up to date, $TcPO_2$ becomes the most widely test to screen microcirculation in the literature [6].

Further studies should investigate $TcPO_2$ for the selection of diabetes and ulcer patients for revascularization, or for additive treatment such as hyperbaric oxygenation. This study could help to understand why direct endovascular revascularization of the ischemic area (to the angiosome containing the area of tissue loss) result in superior outcome compared with indirect revascularization [36]. Additionally, more work is needed regarding the risk stratification to determine possible various cut-off values related to the use of $TcPO_2$ through foot angiosomes.

Patients' clinical characteristics and treatment methods (wound care and debridement, offloading, blood sugar control and vascular interventions) employed in the current research were standardized for all the studied patients; despite this, the external validity of the research could be limited, as we managed all the patients in a controlled setting into a specialized diabetic foot unit; actual results may differ between the primary care and specialized settings.

Patients included in the research were WIfI stage 1–3, and further research should confirm our findings in critical limb ischemia patients (WIfI stage 4), the results found in the research suggest that ulcers with higher WIfI stage (WIfI 3) showed worse healing prognosis and it was not surprising, as WIfI stage system becomes one of the best prognostic tools in the clinical bedside to evaluate foot ulcers in persons with diabetes [43], it could bias the results of the $TcPO_2$. In our study, SINBAD score, University of Texas, Wagner and PEDIS classifications did not differ in patients' healing prognosis; further research should evaluate together $TcPO_2$ and DFU classifications to improve the predictive prognostic model.

Our results should be interpreted with caution owing to some study-related limitations; first, non-healing patients showed $TcPO_2$ mean results of 18.48 ± 12.83 mmHg in the dorsalis pedis angiosome location. Patients included in the research could be underdiagnosed for critical limb ischemia. As a result, all non-healing patients at 24 weeks were referred to vascular surgery. Second, patients' mobility status was not evaluated in the current research; it could influence clinical results as physical activity has previously been described as a factor of non-healing ulcers and worse outcomes [44].

Additionally, further research should confirm our results based on a larger study cohort, including frailty and activity data, and evaluating different assessment methods (hyperbaric oxygen chambers, laser doppler or hyperspectral imaging).

This prospective study is the first to investigate the potential healing prognosis of $TcPO_2$ stratified by foot angiosomes, clinicians should separately assess ulcer and $TcPO_2$ probe location to better predict DFU healing.

5. Conclusion

The angiosome concept applied to $TcPO_2$ measurement was shown to be effective in the prognosis of DFU healing compared with standard measurements. Diabetic foot ulcers located in the forefoot must be assessed with the $TcPO_2$ probe in the dorsalis pedis angiosome, while DFU located in the rearfoot and midfoot must be assessed with $TcPO_2$ probe in the posterior tibial angiosome. Angiosome-guided $TcPO_2$ contributes to a prognosis of successful foot ulcer healing. $TcPO_2$ probe location is essential to assess the real angiosome of the foot.

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Authors' contribution statement

MLM, MGM and JLLM designed the study. MLM, MGM, RJMB, YGA, ATG, and JLLM conducted the study. MLM, MGM, RJMB, YGA, ATG, JLLM were involved in sample processing and analysis. MLM performed the statistical analyses. MLM drafted the manuscript and MGM and JLLM critically reviewed the manuscript for important intellectual content and approved the final version to be published. MLM, MGM and JLLM are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of competing interest

There are no relevant conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtv.2023.10.003.

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