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ORIGINAL RESEARCH

Association Between the Effectiveness and Magnitude of Foot Microcirculation Assessed by Radionuclide Angiography and One Year Limb Outcomes in Patients with Chronic Limb Threatening Ischaemia

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Objective: Microcirculation focused evaluations may provide physiological insights that complement those of the established clinical criteria for patients with chronic limb threatening ischaemia (CLTI), since complex treatments are needed in this high risk population. However, current methods for quantitatively assessing foot microcirculation are limited. Thus, in this study, the aim was to demonstrate a proof of concept non-invasive method with novel parameters for assessing foot microcirculation.

Methods: This was a single centre prospective cohort pilot study. The lower limbs of 13 patients diagnosed with CLTI were evaluated by radionuclide (RN) angiography with ^{99m}Tc-tetrofosmin two weeks after revascularisation or non-revascularisation procedures. Novel parameters (pedal transit time and peak pedal count) were derived by processing the time–activity curves of the detected tracers in each region of interest in the limbs. The Mann–Whitney *U* test was used for the analysis of associations between these two parameters and limb fate at one year, and Pearson and Spearman tests were used to analyse associations with transcutaneous partial oxygen pressure ($tcPO_2$), a conventional perfusion test result.

Results: The mean pedal transit time of the affected limbs in the non-healing group was longer than that in the healing group (19.1 ± 18.6 *vs*. 2.9 ± 2.1 seconds, $p = .001$). The mean peak pedal count of nucleotides in the non-healing group was lower than that in the healing group (24.4 ± 19.0 *vs*. 72.0 ± 36.1 counts/sec/GBq, $p = .008$). The pedal transit time and peak pedal count showed little to no correlation with the conventional $tcPO_2$ at the midfoot ($r = 0.26$ for pedal transit time; $r = -0.11$ for peak pedal count).

Conclusion: Two novel microcirculation parameters derived from RN angiography were associated with one year limb outcomes in patients with CLTI. Non-invasive radiotracer imaging derived parameters may provide an additional dimension to indices of pathophysiological microcirculation in CLTI.

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INTRODUCTION

Chronic limb threatening ischaemia (CLTI) is caused by critical insufficiency of blood flow to the soft tissues of the foot due to atherosclerotic obstruction of the limb arteries. Patients with CLTI suffer from intractable rest pain and or forms of pedal tissue loss, such as ulcers or gangrene, leading to reduced health related quality of life (QOL).[1,2] The prognosis of CLTI in terms of outcomes involving both the limb and survival is known to be poor, as CLTI represents end stage cardiovascular disease. Providing sustained care for these high risk patients strains healthcare systems owing to the chronic and progressive nature of CLTI.[2]

Surgical and endovascular revascularisation have been the mainstay approaches for salvaging ischaemic limbs alongside optimal medical and wound therapy. However, wound healing is often delayed or not achieved in the affected foot despite successful revascularisation and haemodynamic restoration by angiography,[3] thus negatively impacting patient QOL; up to 30% of patients with CLTI experience delayed or incomplete wound healing, with tissues remaining unhealed even six months after revascularisation.[3] Thus, despite recent advances in revascularisation and wound therapy, managing CLTI remains

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challenging, as many patients have poor post-treatment limb outcomes. While there are multiple factors contributing to these outcomes, such as ongoing infection or systemic metabolic impairments,[4–6] delayed healing can be attributed to impaired peripheral microcirculation in the soft tissues of the diseased foot. This underscores the importance of developing approaches to quantify and evaluate microvascular perfusion patterns, which this study aimed to address.

Assessing foot microcirculation is critical; however, current methods have vital limitations, and few imaging methods can be used to accurately identify insufficient foot microcirculation spatially and quantitatively.[2,7] Among them, digital subtraction angiography (DSA) and computed tomography angiography (CTA) can be used to visualise macrovascular anatomy effectively but cannot be used to evaluate microvascular perfusion patterns within tissue beds that directly influence pedal wound healing. Indeed, prior studies have shown a poor correlation between angiographic findings and skin perfusion pressure (SPP), a surrogate marker of microcirculation.[8] On the other hand, conventional microcirculatory metrics such as the SPP itself depend heavily on macrovascular inflow. Transcutaneous oxygen partial pressure ($tcPO_2$) detection provides a measure of skin perfusion alone and does not enable the evaluation of subcutaneous tissues critical to healing. Thus, there is an unmet need for better microcirculatory evaluation methods to help guide clinical management decisions.

A technetium 99m (^{99m}Tc)-tetrofosmin blood flow tracer can be used to assess myocardial perfusion, and radionuclide (RN) imaging enables anatomical and functional assessments of tissue perfusion. Here, the aim was to expand the application of this non-invasive imaging method to include the microcirculation of the foot. ^{99m}Tc-tetrofosmin is taken up into cells via passive diffusion mediated by the cell membrane and mitochondrial membrane potential in proportion to capillary blood flow. This allows a direct assessment of microvascular perfusion integrity beyond delivery. Furthermore, most existing approaches are invasive, provide only qualitative data, or are limited to small regions. In contrast, RN imaging can enable direct, non-invasive, quantitative assessment of the microcirculation of the entire foot.

In this study, the aim was to develop a non-invasive method to quantify haemodynamic parameters and foot microcirculation by using planar RN angiography imaging with a ^{99m}Tc-tetrofosmin blood flow tracer because this method provides dynamic perfusion information and is a potentially suitable candidate for assessing microcirculation. It was hypothesised that novel parameters derived from the time–activity curves (TACs) of the detected RNs could be used to predict one year wound healing outcomes after initial treatment. The objectives of this study were to introduce novel imaging markers of microcirculatory status to address the limitations of prior assessments and to test the associations between these novel markers and limb fate one year after assessment.

MATERIALS AND METHODS

Study design

This was a single centre, prospective cohort study performed with an exploratory purpose.

Patients and ethics approval

From April 2019 to October 2021, 13 of 285 patients diagnosed with pedal tissue loss due to CLTI were included. The patients had chronic foot ulcers or gangrene with proven ischaemia, as assessed by objective haemodynamic tests ($tcPO_2 < 60$ mmHg).[2] All these patients underwent a procedure for the treatment of CLTI (revascularisation, minor amputation, or angiogenesis). In addition to the diagnosis of CLTI, the presence or suspicion of coronary artery disease was an inclusion criterion for since RN imaging data were obtained from the foot during myocardial perfusion tests that are covered by medical insurance in Japan. Although patients were randomly selected due to the nature of this proof of concept pilot study, patients with large amounts of tissue loss were included, which is easy to detect via single photon emission computed tomography (SPECT), despite its relatively limited spatial resolution. The study protocol followed the principles outlined in the Declaration of Helsinki. The Saitama Medical Centre Institutional Review Board approved this study (no. 2261); all the participants provided written informed consent.

Clinical assessment of limb severity

Limb severity was assessed via the Wound, Ischaemia, Foot Infection (WIfI) classification system.[9] Briefly, the system enables a structured assessment of the degree of a wound, ischaemia, and foot infection in CLTI; the resulting integrated stage, ranging from 1 to 4 in order of increasing severity, was initially designed to assess the risk of lower limb amputation.

Clinical imaging protocol

In addition to a standard assessment of the diseased vasculature by transarterial DSA and CTA with an iodinated contrast agent,[10] the participants underwent the following radiotracer imaging study within a month after revascularisation or supportive therapy procedures, including primary minor amputation or therapeutic angiogenesis.

Radiotracer imaging and processing

Scanning protocol. The lower limbs of the patients were comfortably immobilised. Nuclear imaging (128 × 128 matrix) was performed with a two detector SPECT camera (Discovery NM630, GE Healthcare, Chicago, IL, USA). Low energy, high resolution, parallel beam collimators and a 15% energy window on the ^{99m}Tc photopeak (140.5 keV) were used. Dynamic planar scans (360 × 1 second) were started immediately after a bolus injection of ^{99m}Tc-tetrofosmin

(approximately 740 MBq). The estimated whole body radiation exposure per test was 0.074 mGy.

Processing and quantification of radionuclide angiography in the limbs. To quantify the TAC obtained from RN angiography at a region of interest (ROI) of the affected and contralateral unaffected limbs, the bolus arrival time was calculated with Origin Pro 2020b (OriginLab Corporation, MA, USA). The TAC of the detected RN (time frame, 0—120 seconds) was fitted to a sigmoid function, and the time of the inflection point ($\times 0$), when the increasing rate of detection reached its maximum, was recorded as the bolus arrival time at the index ROI (Fig. 2A and B). Next, the pedal transit time was obtained by subtracting the bolus arrival time at the ROI of the midfoot from that of the mid to lower thigh, representing the time needed for the radiolabelled tracer in the artery to transit from the mid-lower thigh to the midfoot. The peak RN count detected at the midfoot was recorded as A2, the plateau phase of the sigmoid curve, and then normalised to the injected dose of ^{99m}Tc-tetrofosmin. The pedal transit time quantifies the time needed for radiotracer flow from the tibial artery to the pedal tissue over time as an indicator of the microvascular blood flow velocity. The peak pedal count temporally measures the maximum tracer activity reached in the pedal region and reflects overall microvascular delivery and perfusion.

Conventional haemodynamic test at skin level

As a conventional microcirculation index,[11] $tcPO_2$ was detected with a TCM400 measuring device (Radiometer, Copenhagen, Denmark). The probes were placed on the dorsal midfoot of both limbs. A probe temperature of 44°C was selected.[12] The value obtained for the dorsal midfoot was used to analyse the correlation between the two parameters derived from RN angiography.

Supportive therapy and podiatric care

Standard podiatric wound care, including daily dressing changes, timely debridement, and negative pressure therapy, was provided when appropriate. Angiogenic therapy (Collategen, AnGes, Japan) was used as another option for patients whose poor run off pedal arteries were determined by conventional transarterial angiography using an iodinated contrast agent. The surgical indications for skin grafting, amputation, or additional revascularisation were discussed, and decisions were made by a multidisciplinary team of vascular surgeons, plastic surgeons, dermatologists, and dedicated nurses.

Clinical assessment of wound healing status

Following the RN imaging study, wound care was continued in the hospital and outpatient clinic. The healing status of the index wound (an ulcer or stump of a minor amputation) was documented via digital photography with a standard digital camera, allowing accurate assignment of wound grades and time stamped confirmation of complete epithelialisation. The patients were allocated to the healing group or non-healing group according to the status of the index limb and the need for re-intervention within one year after treatment. Non-healing was defined as the occurrence of one or more of the following events in the target limb: absence of healing or recurrence of wound healing, additional minor and major amputation, or any re-intervention. Data from the initially asymptomatic contralateral limbs were also subjected to correlation analysis with conventional tests.

Statistical analysis

All the data were analysed with Prism 8 software (GraphPad Software, Inc., La Jolla, CA, USA). Categorical variables are presented as percentages, and continuous variables as

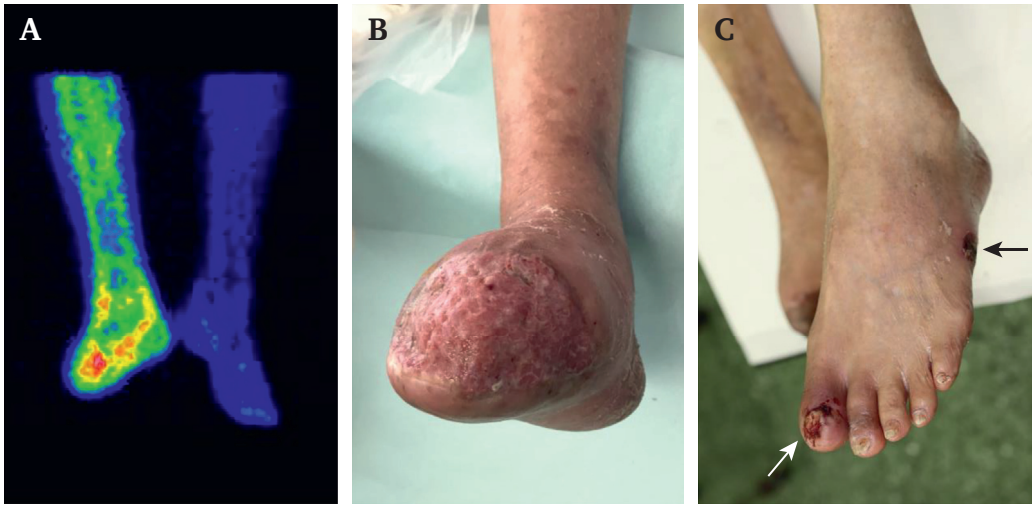

Figure 1. Post-operative ^{99m}Tc-tetrofosmin radionuclide (RN) angiography under resting conditions predicts limb fate. (A) Summed RN angiography image demonstrating the visual differences in microcirculation between the revascularised right and asymptomatic left limbs. (B) The right foot healed two months after revascularisation by skin grafting. (C) The left foot exhibited chronic limb threatening ischaemia after one year. Note the ulcer on the first digit (white arrow) and the gangrene in the midfoot region (black arrow).

mean (± standard deviation). The unpaired Student's *t* test was used for comparisons of normally distributed data with equal variances between two groups, and the unpaired Student's *t* test (with Welch's correction) was used for comparisons of data with unequal variances. For data that were not normally distributed, the non-parametric Mann–Whitney *U* test was used for between group comparisons. Comparisons of categorical data were performed via Fisher's exact test or the chi square test. Correlation analyses between the RN angiography parameters and the $tcPO_2$ were performed via Pearson and Spearman tests. A *p* value $<.05$ was considered statistically significant.

RESULTS

Patient characteristics and revascularisation

The demographics and baseline characteristics of the 13 patients are shown in Table 1. The mean age at the index treatment was 73 years; nine patients (69%) were male. Six patients (46%) had hypertension, nine patients (69%) had diabetes mellitus, four patients (31%) had dyslipidaemia, seven patients (54%) had a history of coronary artery disease, four patients (31%) had a history of cerebrovascular disease, and seven patients (54%) were on regular haemodialysis. Three patients (23%) had collagen disease, two patients had a history of malignancy, and 10 patients (77%) were ever smokers. There were no significant differences in patient background characteristics between the healing ($n = 6$) and non-healing ($n = 7$) groups (Table 1).

The degree of disease severity in the 13 affected limbs is shown in Table 2. According to the Rutherford classification, eight limbs (61.5%) were class 5, and five limbs (38.5%) were class 6. Eleven of the 13 (85%) limbs were classified as WIfI stage 4. There was no significant difference in limb severity between the healing and non-healing groups ($p = .59$ for Rutherford class, $p > .99$ for WIfI stage, $p = .10$ for

Table 1. Baseline characteristics of 13 patients with chronic limb threatening ischaemia.

Patient characteristics	Total ($n = 13$)	Healing group ($n = 6$)	Non-healing group, n (%) ($n = 7$)	*p* value
Age − y	73.0 ± 9.2	77.5 ± 8.1	69.1 ± 8.8	.10
Sex (male)	9 (70)	4 (67)	5 (71)	1.0
Hypertension	6 (46)	2 (33.3)	4 (57)	.59
Diabetes	9 (69)	4 (67)	5 (71)	1.0
Dyslipidaemia	4 (31)	2 (33)	2 (29)	1.0
Coronary artery disease	7 (54)	5 (83)	2 (29)	.10
Cerebrovascular disease	4 (31)	3 (50)	1 (14)	.27
ESRD on haemodialysis	7 (54)	4 (67)	3 (43)	.59
Collagen disease	3 (23)	2 (33)	1 (14)	.56
History of malignancy	2 (15)	1 (17)	1 (14)	1.0
Ever smoker	10 (77)	5 (71)	5 (71)	1.0

Data are presented as *n* (%) or mean ± SD. ESRD = end stage renal disease.

Table 2. Severity of the 13 index limbs with chronic limb threatening ischaemia.

Limb severity	Total ($n = 13$)	Healing group ($n = 6$)	Non-healing group ($n = 7$)	*p* value
Rutherford class				.59*
5	8 (62)	3 (23)	3 (43)	
6	5 (39)	3 (23)	4 (57)	
WIfI stage				1.0*
3	2 (15)	1 (17)	1 (14)	
4	11 (85)	5 (83)	6 (86)	
Wound grade				.10*
1	0 (0)	0 (0)	0 (0)	
2	8 (62)	2 (33)	6 (86)	
3	5 (39)	4 (67)	1 (14)	
Ischaemia grade				1.0*
1	1 (8)	0 (0)	1 (14)	
2	0 (0)	0 (0)	0 (0)	
3	12 (92)	6 (100)	6 (86)	
Foot infection grade				.18†
0	8 (62)	2 (33)	6 (86)	
1	2 (15)	1 (17)	1 (14)	
2	2 (15)	2 (33)	0 (0)	
3	1 (8)	1 (17)	0 (0)	

Data are presented as *n* (%). WIfI = Wound, Ischaemia, Foot Infection.

* Fisher's exact test.

† Chi square test.

wound grade, $p > .99$ for ischaemia grade, $p = .18$ for foot infection grade).

The treatment procedures are shown in Table 3. Bypass surgery was performed for revascularisation in nine limbs (69%), endovascular treatment in one limb (8%), and a hybrid procedure in one limb (8%). None of the patients in the revascularised group underwent concurrent minor amputation. Primary minor amputation of a digit was performed for one limb (8%), and therapeutic angiogenesis was performed for one limb (8%) without a preceding revascularisation procedure. Treatment in the healing group included revascularisation in five patients (83%) and primary minor amputation without revascularisation in one patient (17%). Treatment in the non-healing group included revascularisation in six patients (86%) and therapeutic angiogenesis in one patient (14%). There was no significant difference in the treatment type between the healing and non-healing groups ($p = .90$). The baseline main occlusion and revascularisation target artery levels of the healing and non-healing groups were not significantly different ($p = .59$ and $p = .46$, Table 4).

Representative radionuclide angiography and uptake kinetics of ^{99m}Tc-tetrofosmin correspond with a one year outcome in the affected and initially asymptomatic contralateral limb

Real time RN angiography of the lower thighs of a 90 year old man after bypass surgery to the peroneal artery and concurrent transmetatarsal amputation of the right limb is shown in Supplementary Video S1. The contralateral left limb was asymptomatic at this point and therefore did not need any treatment. Note that the summed RN angiography image revealed abundant microcirculation in the right foot, in contrast to the scarce microcirculation in the left foot. The right foot healed two months after revascularisation with skin grafting; the left foot, though initially asymptomatic, progressed to CLTI one year after the assessment (Fig. 1).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.ejvsvf.2024.11.002.

Microcirculation parameters are associated with limb outcomes

The representative case result above, in which the activity of the RN tracers clearly corresponded with the limb outcome at one year, prompted us to develop parameters that can depict the dynamics of the RN tracers in the lower thighs. The pedal transit time in 13 patients was calculated from the TAC of RN angiography in two ROIs per limb via ^{99m}Tc-tetrofosmin (Fig. 2A and B). For two patients with CLTI who underwent RN angiography before and after revascularisation, the mean rates of pedal transit time and peak pedal count change from pre-to post-revascularisation were 24% (pedal transit time) and 131% (peak pedal count), respectively. The mean pedal transit time of the affected limbs in the non-healing group was significantly higher than

Table 3. Revascularisation and procedures for 13 index limbs with chronic limb threatening ischaemia.

Procedures	Total, ($n = 13$)	Healing group ($n = 6$)	Non-healing group ($n = 7$)	p value
Revascularisation	11 (85)	5 (83)	6 (86)	.16*
Bypass	9 (70)	5 (83)	4 (57)	
Endovascular	1 (8)	0 (0)	1 (14)	
Hybrid procedure	1 (8)	0 (0)	1 (14)	
Non-revascularisation procedures only	2 (15)	1 (17)	1 (14)	.16*
Therapeutic angiogenesis	1 (8)	0 (0)	1 (14)	
Primary amputation, minor	1 (8)	1 (17)	0 (0)	

Data are presented as *n* (%).
* Chi square test.

Table 4. Anatomy and revascularisation details of 11 index limbs with chronic limb threatening ischaemia.

Procedures	Total ($n = 11$)	Healing group ($n = 5$)	Non-healing group ($n = 6$)	p value
Main occlusion site				.59*
Iliac	2 (18)	1 (20)	1 (17)	
Femoral	4 (36)	2 (40)	2 (33)	
Popliteal	1 (9)	1 (20)	0 (0)	
Crural	4 (36)	1 (20)	3 (50)	
Bypass, TEA, or EVT target				.46*
Femoral	4 (36)	1 (20)	3 (50)	
Popliteal	3 (27)	2 (40)	1 (17)	
Crural	1 (9)	1 (20)	0 (0)	
Pedal	3 (27)	1 (20)	2 (33)	

Data are presented as *n* (%). TEA = thrombo-endarterectomy; EVT = endovascular therapy.
* Chi square test.

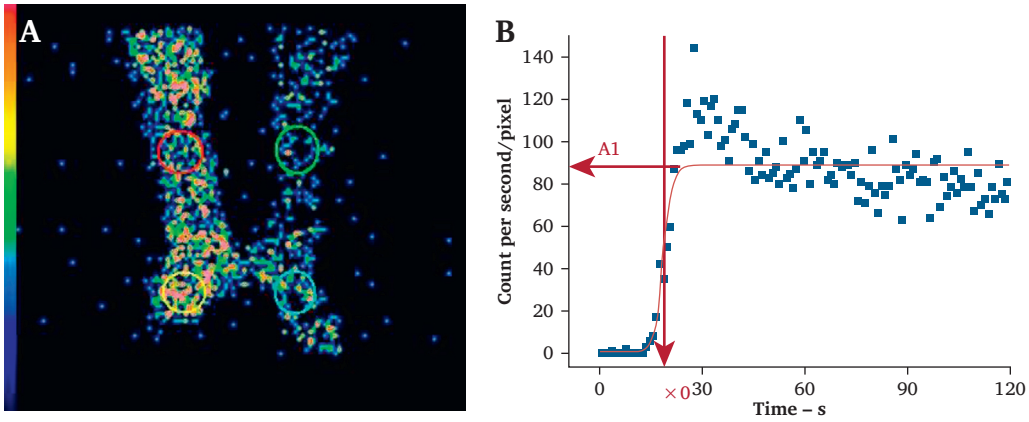

Figure 2. Development of an evaluation method for ^{99m}Tc-tetrofosmin uptake kinetics. (A) Region of interest (ROI) setting at the bilateral mid-lower thigh (red and green circles) and the midfoot (yellow and blue circles). (B) Bolus arrival time. The time—activity curve (TAC) of the detected radionuclide at each ROI was subjected to Boltzmann sigmoid fitting. The inflection point (×0) time was recorded as the bolus arrival time. The pedal transit time was calculated by subtracting ×0 at the mid-lower thigh from ×0 at the midfoot. A1 represents the plateau phase of tracer detection. A1 data were obtained from the midfoot for analyses.

that in the healing group (19.1 ± 18.6 seconds *vs*. 2.9 ± 2.1 seconds, $p = .001$; Fig. 3A). The mean peak pedal count, obtained from the ROI at the midfoot, in the healing group was significantly higher than that in the non-healing group (72.0 ± 36.1/sec/pixel/GBq *vs.* 24.4 ± 19.0/sec/pixel/GBq, $p = .008$; Fig. 3B).

Correlations between radionuclide angiography parameters and conventional test results

Since the novel parameters derived from RN angiography are clearly associated with limb outcomes, next a correlation analysis was performed between the two novel parameters and $tcPO_2$, the conventional functional test for CLTI. Since one patient had a history of prior limb amputation on the contralateral side at the time of inclusion, a total of 25 limbs in 13 patients were subjected to analysis. In the 25 affected and contralateral unaffected limbs, the pedal transit time and $tcPO_2$ of the foot were weakly correlated ($r = 0.26$, Fig. 4A). The pedal peak count and $tcPO_2$ of the foot were not correlated ($r = -0.11$, Fig. 4B). However, the pedal transit time and peak pedal count showed a moderate inverse correlation ($r = -0.49$, Fig. 4C and D).

DISCUSSION

In this study, the aim was to develop a novel non-invasive approach for assessing microvascular perfusion in patients with CLTI. It was demonstrated that novel parameters derived from RN angiography were related to the one year outcome of treated limbs, suggesting the prognostic value of these parameters. Such non-invasive radiotracer imaging analysis may provide novel opportunities to assess pathophysiological indices of foot microcirculation in patients with CLTI.

To address the need for a quantitative microcirculation assessment method, dynamic ^{99m}Tc-tetrofosmin planar RN imaging was performed with a standard SPECT camera without CT based imaging, to evaluate temporal changes in pedal tissue perfusion directly. Alvelo *et al.*[13] and Chou *et al.*[14] reported the application of ^{99m}Tc-tetrofosmin

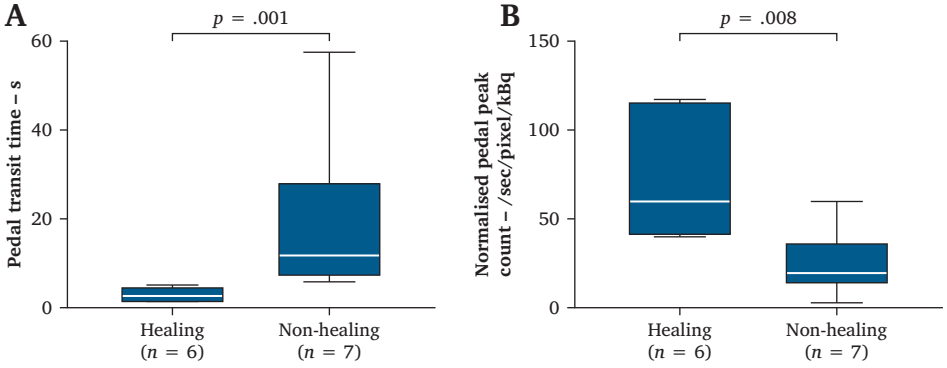

Figure 3. Post-procedural delayed transit time and a diminished peak count are associated with poor limb outcomes at one year. (A) The mean pedal transit time of the affected limbs in the non-healing group ($n = 7$) was greater than that in the healing group ($n = 6$) (19.1 ± 18.6 seconds *vs*. 2.9 ± 2.1 seconds, $p = .001$). (B) The mean peak pedal count in the healing group ($n = 6$) was greater than that in the non-healing group ($n = 7$) (72.0 ± 24.4/sec/pixel/GBq *vs.* 24.4 ± 19.0/sec/pixel/GBq, $p = .008$).

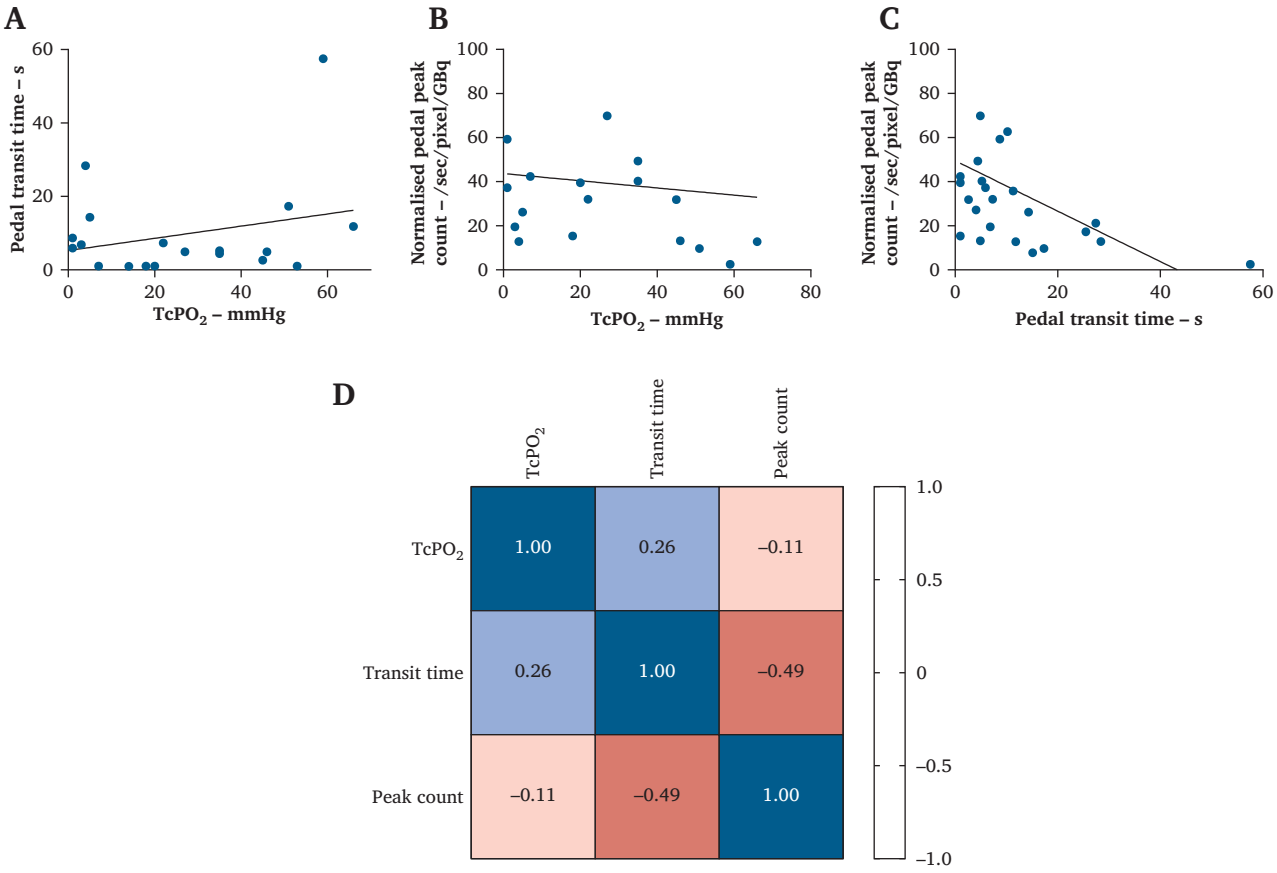

Figure 4. The novel radionuclide angiography parameters are weakly correlated with the conventional microcirculation surrogate. (A) Correlations between pedal transit time and $tcPO_2$ ($r = 0.26$) in 25 limbs of 13 patients. (B) Correlation between the peak count per second and $tcPO_2$ ($r = -0.11$) in 25 limbs of 13 patients. (C) Correlations between pedal transit time and peak pedal count ($r = -0.49$) in 25 limbs of 13 patients. (D) Pearson r correlation matrix between the pedal transit time, peak pedal count, and $tcPO_2$ in 25 limbs of 13 patients.

SPECT/CT imaging to assess regional foot perfusion. While their methodology assesses the relatively static phase of foot perfusion, the current method provides quantitative data on the dynamic perfusion patterns and extent of microvascular perfusion across the whole foot.

In this cohort, these two novel quantitative parameters derived non-invasively from RN TAC analysis were associated with the one year limb outcome in the CLTI patient cohort. The mean pedal transit time in the non-healing group was strikingly prolonged, and the mean peak pedal count in the non-healing group significantly decreased to almost one third of that in the healing group. Planar RN imaging approaches are thought not to have been used previously to derive foot microcirculatory parameters that are predictive of long term prognosis in patients with CLTI.

Correlation analyses revealed that the novel parameters were moderately correlated with each other. In contrast, the parameters showed little to no correlation with conventional skin perfusion test results. The observations parallel those in a previous report by Alvelo *et al.*, who reported that SPECT/CT imaging derived parameters of the regional foot microcirculation were not significantly correlated with the conventional index of macrocirculation, namely the ankle brachial index.[13] The reliance on macrovascular delivery *vs.* direct microvascular diffusion probably underlies the weak correlation observed between the RN derived perfusion parameters and the skin perfusion test results. More importantly, these findings suggest that RN derived metrics provide complementary clinical information beyond that available from standard assessments alone, as these metrics appear to be capable of directly predicting one year outcomes.

These parameters might influence the CLTI treatment decision making process, each in a distinct manner. The mean pedal transit time may help specialists understand the pathophysiological significance of the so called slow flow phenomenon, which is often observed during endovascular therapy or diagnostic procedures by conventional transarterial angiography. On the other hand, the mean peak pedal count should reflect the functional perfusion volume in the early time frame caused by the balance between the inflow and vascular bed. Despite this innate difference between the parameters, the results indicate a positive correlation between foot perfusion efficiency and magnitude, both of which are independent of the conventional surrogate marker of microcirculation at the skin level. The observations may reflect the difference between this methodology and conventional methods, i.e., the difference between directly assessing the total foot microcirculation and measuring a percutaneous surrogate of the

microcirculation. In the clinical setting, it is expected that revascularised non-healing patients and non-revascularised non-healing patients with below knee and below ankle arterial disease will benefit the most from this methodology. Broad application of this methodology has the potential to further the understanding of not only the probability of wound healing, but also various pathophysiological conditions related to chronic ischaemia in the foot, such as scarce vascular beds in vasculitis associated limb ischaemia or bypass graft failure after revascularisation.

There are certain limitations to this study. First, this was a proof of concept study with intrinsic limitations. While the study design is appropriate for an initial feasibility evaluation, the modest sample size prevents the drawing of definitive conclusions about the predictive utility and incremental value of the quantitative parameters beyond established clinical factors. Second, although the consistency and reliability of RN imaging are generally well established,[15–17] particularly for quantitative analysis, the exact reproducibility of RN angiography in the lower limb could not be confirmed. Third, confounders such as infection and inflammation may have influenced microvascular perfusion. Dual isotope imaging with radiolabelled inflammatory cells that migrate to foci of infection enables the discernment of infection from normal post-operative inflammation.[18]

In conclusion, this proof of concept study demonstrates the feasibility of a non-invasive RN imaging approach for directly quantifying microcirculatory perfusion patterns in patients with CLTI. The results demonstrate that an analysis of the TAC obtained by RN angiography is promising for quantifying foot microcirculation in CLTI patients. Such non-invasive radiotracer imaging analysis may provide novel opportunities to assess pathophysiological indices of foot microcirculation, complementary to those of established clinical criteria for this high risk population with complex treatment considerations. While preliminary, these findings suggest that further research on RN imaging is warranted to determine how quantitative microcirculatory measures could facilitate individualised decision making regarding revascularisation compared with other options, such as amputation. Additional validation in larger cohorts is needed to clarify the clinical utility and applicability of this approach. It is expected that the insights from the study on directly assessing microcirculation will ultimately guide the refinement of optimal revascularisation strategies and lead to improved clinical decision making for these patients.

CONFLICT OF INTEREST

None.

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