TRAMUL: TRAnscutaneous oxygen Measurement and diabetic foot ULceration

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Article points

1. It can be difficult to determine the cause of diabetic foot ulcers.
2. Transcutaneous oxygen monitoring is a non-invasive method of measuring tissue perfusion, and therefore identifying ischaemia.
3. Transcutaneous oxygen monitoring identified ischaemia in people with diabetes who did and did not have a foot ulcer and was found to be acceptable as a method of clinical assessment.

Key words

- Assessment
- Diabetic foot ulceration
- Ischaemia
- Transcutaneous oxygen monitoring
- Patient evaluation

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Identifying the cause of ulceration in patients with diabetes will inform the treatment approach and hopefully lead to a greater proportion of patients' foot ulcers resolving in shorter periods of time. Transcutaneous oxygen ($tcpO_2$) monitoring measures the partial pressure of oxygen in tissues and could identify ischaemia in patients with diabetic foot ulcers. The TRAMUL pilot study aimed to establish whether $tcpO_2$ monitoring improved patient assessment and was acceptable to patients in a clinical context. Results suggest that $tcpO_2$ monitoring does identify patients with sub-clinical ischaemia and feedback indicates that patients found this test to be acceptable and comfortable. Further studies are warranted to demonstrate the efficacy of $tcpO_2$ in identifying ischaemia in patients with diabetic foot ulcers, so that they can receive appropriate revascularisation and prevent ineffective and costly conservative treatment being given.

Diabetes mellitus is a common disease, affecting approximately 3.7 million people in the UK (6.6% of the UK population in 2015), and its incidence is increasing at the rate of 100 000 per year. Approximately 10% of patients have type 1 and 90% have type 2 diabetes (Diabetes UK, 2018). Foot ulceration occurs frequently in patients with diabetes, particularly type 2 diabetes, with the prevalence ranging from 4% to 10% (Wu et al, 2015). The lifetime risk of developing a diabetic foot ulcer (DFU) is between 5% and 7%, although some research suggests the risk is as high as 15% (Reiber, 2001; International Working Group on the Diabetic Foot, 2003; NHS Digital and Diabetes UK, 2017).

DFUs often develop after minor trauma, such as stubbing a toe, or soft tissue injury when trimming nails. They are frequently indolent, requiring intensive treatment by podiatrists, often over a long period of time. DFUs cause considerable discomfort and inconvenience to the patient and their treatment costs the NHS an estimated £935 million per year (Kerr, 2017). It is therefore important to establish whether there is an underlying, treatable disease process, such as ischaemia, that will prevent conservative treatment from working.

Patients with diabetes are particularly prone to foot ulceration due to a variable combination of neuropathy and vascular insufficiency. Neuropathy causes numbness of the toes or feet, leaving the patient unaware of skin injury. Vascular insufficiency results in poor blood flow, causing delayed healing or a failure to heal at all. In severe cases of diabetic vascular disease, which are often associated with smoking, high blood pressure and high cholesterol, skin breakdown may occur without trauma. Personal experience has shown that in some patients with diabetes, the treatment of vascular disease has resulted in resolution of numbness in their feet, suggesting that peripheral nerve ischaemia is responsible for non-functioning of the peripheral nerves, rather than a true peripheral neuropathy. From a clinical perspective, this makes assessment of the underlying cause of ulceration difficult, as numbness may itself be caused by vascular disease. Measurement of tissue oxygenation should help to resolve this difficulty. Transcutaneous oxygen

Page points

1. The TRAMUL pilot study aimed to determine whether transcutaneous oxygen measurement could identify undiagnosed ischaemia in patients with diabetic foot ulcers.
2. Patients referred to NHS Lanarkshire podiatry outpatient clinics for conservative treatment were eligible to participate in this trial if they had ulceration, discolouration or necrosis of the foot, heel or toes, their ulcers were not due to vascular insufficiency, and they had no history of peripheral limb ischaemia.

($tcpO_2$) monitoring measures the partial pressure of arterial oxygen within the tissues and could therefore potentially identify ischaemia in patients with DFUs.

Aim and objective

This study aimed to determine whether $tcpO_2$ measurement can identify ischaemia and, therefore, undiagnosed critical limb ischaemia (CLI), in patients presenting with DFUs who are assessed clinically as having no significant vascular disease. This pilot study aimed to establish whether $tcpO_2$ measurement:

- Is acceptable to patients in a routine clinical context
- Improves patient assessment by identifying an underlying cause, preventing lengthy and futile conservative management
- Enables earlier referral for investigation and treatment of underlying ischaemia, resulting in better clinical outcomes
- Justifies subsequent study in a larger population.

Method

Participants

Patients referred to NHS Lanarkshire podiatry outpatient clinics for conservative treatment were eligible to participate in the trial if they had ulceration, discolouration or necrosis of the foot, heel or toes, their ulcers were not due to vascular insufficiency, and they had no history of peripheral limb ischaemia. Some patients had already been assessed in a combined diabetic and vascular outpatient clinic. Only patients who were able to give informed consent were included. Patients were excluded from the trial if they had a preexisting clinical diagnosis of CLI or if they had, or were likely to have, an allergy to the cups for the sensors.

At the end of the initial recruitment period, it was decided to recruit additional patients with DFUs, as well as patients with diabetes but no foot ulceration as a control group. Patients in the control group were recruited from the diabetic outpatient clinic.

Transcutaneous oxygen monitoring

A TCM400 $tcpO_2$ monitor with six-channel input was loaned by Radiometer for a period of 6 weeks to perform this study. Radiometer also trained our study technicians, two podiatrists and a staff nurse, to carry out the measurements.

Small adhesive cups were attached to the skin, a few drops of a coupling fluid were placed into the cups and the $tcpO_2$ sensor attached to the cups with a screw connection. The overall appearance and size of the cups were similar to an ECG electrode. The sensors became warm, reaching 44°C, and it took approximately 15 minutes for tissue oxygenation and the sensor to equilibrate to determine an accurate value. As the sensors are effectively in contact with patients' skin, they were sterilised by immersion in electrolysed water for a period of 30 seconds between each patient (Dancer et al, 2015).

Process

Patients were given a participant information sheet on attending the outpatient clinic in advance of signing a consent form at their next visit. All patient data were anonymised by allocating a study number to each patient once they had consented. A study data form was then completed for each patient by the study technician recording:

- Which foot was to be measured
- Ulcer status (healing, static or progressing)
- Ulcer duration
- The referring clinician's clinical assessment about ischaemia and/or peripheral neuropathy as the underlying cause of the ulcer.

Information about medication, diabetes history and other medical conditions was obtained from the patient's notes.

$TcpO_2$ readings were taken by the study technician in a warm, comfortable environment with the patient lying supine. All measurements were taken with reference to the user's manual. The $tcpO_2$ probes were attached to the skin as directed in the manual. Six simultaneous readings were acquired by probes placed as follows:

- Lower chest/upper abdomen, as a baseline for that patient
- Thigh, 10 cm above the knee
- Dorsum of the calf, approximately one-third of the way up the calf from the ankle to the knee, being the most distal part of the flap required to close a below-knee amputation
- Dorsum of the foot medially

- Dorsum of the foot laterally
- As near as possible to the area of ulceration, on healthy skin.

For the $tcpO_2$ readings to be reproducible and comparable, they were performed using a standard routine. This routine involved calibration of the equipment, the patient avoiding caffeine and smoking prior to readings and lying supine in a room with an ambient temperature of 21–23°C. Equilibration between the tissue oxygen and the sensor required approximately 15 minutes, before stable readings are acquired.

Afterwards, patients were asked to complete a brief study evaluation questionnaire. They were asked 'How much would you say that you were inconvenienced by your participation in this research study?' and 'How much discomfort or itching did you experience due to the application of the monitor sensors?' There were five possible responses to each question:

- No inconvenience/discomfort
- Minor inconvenience/discomfort
- Some inconvenience/discomfort
- Major inconvenience/discomfort
- Not sure.

Participants were asked to tick the box that most closely related to their experience. They were also invited to add additional comments, if they wished.

Patients were reassessed clinically at 12 months and placed in to one of four categories: healed, improving, static or deteriorating.

Results

Forty-six patients with a DFU and 26 patients with diabetes but without a foot ulcer were entered into the trial. In the ulcerated group there were 39 male patients (85%) with an average age of 64 (range 39–87 years) and seven female patients (15%) with an average age of 49 (range 36–66 years). In the non-ulcerated control group there were 14 male patients (54%) with an average age of 65 (range 33–84 years) and 12 female patients (46%) with an average age of 63 (range 49–74 years). *Table 1* summarises the clinical characteristics of the participants. Some information was not recorded, accounting for the discrepancies in the percentages. Interestingly, the prevalence of hypertension and hyperlipidaemia was higher in the patients without ulcers.

Table 1. Characteristics of participants, as percentages.

Characteristic	Patients with ulcers (*n*=46)	Patients without ulcers (*n*=26)
Diabetes:*		
• Type 1	17	19
• Type 2	76	77
Diabetes control:*		
• Diet only	4	4
• Oral medication	37	42
• Insulin	50	50
• Insulin plus oral medication	7	0
Smoking history:*		
• Smoker	13	23
• Non-smoker	48	50
• Ex-smoker	33	19
Hypertensive	37	62
Hyperlipidaemia	24	73

*Information was not recorded in some cases.

The $tcpO_2$ results for patients with ulceration are given in *Table 2*. Of the 37 patients who were re-assessed after 12 months, 16 patients' ulcers (34.7%) had healed and eight (17.5%) were showing signs of improvement, three (6.6%) were static and the remaining 10 (21.7%) were showing signs of deterioration. The other nine patients (19.5%) with DFUs died during the study period.

Table 3 gives the $tcpO_2$ results for patients in the control group, who did not have a diabetic foot ulcer. There is no striking difference between the readings for the non-ulcerated group and the ulcerated group. This is, perhaps, not unexpected as the majority of the patients with ulcers did not have underlying ischaemia.

Four patients (15.4%) in the non-ulcerated group died during the follow-up period; a similar proportion to those patients with ulceration. One of these patients (patient 1005) had ischaemic $tcpO_2$ readings and another (patient 1021) had a high $tcpO_2$ reading. Two patients (7.7%) were referred to podiatry for foot ulceration. One of these patients (patient 1001) had ischaemic $tcpO_2$ readings.

A similar proportion of individuals in both groups had a $tcpO_2$ of ≤30 mmHg: eleven out of 46 (23.9%) in the group with diabetic foot ulcers and five out of 26 in the control group (19.3%). There was also no real difference in the proportions of patients in each group with high distal readings (26.0% in the group with foot ulceration versus 34.6% in the control group).

Table 2. Transcutaneous oxygen readings in mmHg for patients with a diabetic foot ulcer at 12 months, *n*=37.

Patient number	eGFR	Thigh	Calf	Medial foot	Lateral foot	Ulcer	Progression of ulcer
1	55	55	1	3	-	16	Deteriorating
11	58	63	57	66	-	49	Deteriorating
14	36	70	58	67	63	55	Deteriorating
21	49	67	41	77	63	34	Deteriorating
27	>59	45	56	47	30	4	Deteriorating
28	>59	61	50	65	81	80	Deteriorating
31	>59	69	62	43	48	48	Deteriorating
35	12	95	73	40	70	71	Deteriorating
19	>59	48	23	27	56	64	Deteriorating
45	>59	38	17	67	59	71	Deteriorating
15	22	58	56	44	34	22	Static
23	>59	57	68	38	37	25	Static
34	>59	66	31		53	67	Static
3	>59	51	69	57	74	48	Improving
10	>59	24	45	41		31	Improving
20	50	70	67	60	90	92	Improving
22	>59	82	51	62	62	84	Improving
24	>59	64	68	68	48	77	Improving
25	>59	75	76	54	144	93	Improving
26	>59	63	72	41	80	56	Improving
39	>59	64	3	29	78	46	Improving
2	>59	51	53	2	-	62	Healed
5	>59	56	48	41	85	50	Healed
7	>59	55	45	39	60	86	Healed
13	>59	49	43	38	63	35	Healed
16	>59	35	55	81	-	64	Healed
18	>59	65	34	62	-	-	Healed
29	>59	68	89	152	85	-	Healed
30	58	70	98	73	64	85	Healed
32	>59	71	58	106	31	83	Healed
33	>59	83	81	46	84	95	Healed
38	52	75	34	47	85	-	Healed
40	>59	56	29	54	71	54	Healed
41	>59	38	31	70	88	38	Healed
43	32	51	46	45	43	67	Healed
44	>59	56	5	81	61	61	Healed
46	>59	60	23	37	26	34	Healed

Critical limb ischaemia, suggested by ≤30 mmHg

High distal readings ≤80 mmHg

There were a number of high peripheral readings, which have been highlighted in pink, in both groups.

Patient evaluation survey

All patients completed the evaluation questionnaire. Only one patient commented upon experiencing mild discomfort. All other responses indicated that $tcpO_2$ measurement caused no inconvenience or discomfort. There were no negative comments; where offered, respondents remarked that the experience was comfortable, relaxed, and even pleasurable. The routine use of this investigation was found to be acceptable by participants.

Discussion

In this pilot study, there was remarkable similarity in the clinical make up of the two cohorts of patients. Surprisingly, perhaps, there was a higher prevalence of hypertension and hyperlipidaemia in the patients without DFUs. The group of patients with ulcers were thought clinically to have neuropathic rather than ischaemic DFUs and the aim of the study was to try to identify those patients with sub-clinical ischaemia.

$TcpO_2$ measurement is a non-invasive method of measuring oxygen concentration (pO_2 in mmHg) in the subcutaneous tissues, providing an objective measurement of oxygenation and an indication of perfusion. It is a useful method of identifying and assessing CLI and is more accurate than ankle/brachial pressure index (ABPI), particularly in patients with diabetes whose vessels are often calcified and non-compressible. $TcpO_2$ measurement has also been used to predict whether ulcers are likely to heal without revascularisation (Ruangsetakit et al, 2010) and to predict healing after revascularisation procedures (Caselli et al, 2005).

A $tcpO_2$ of ≤30 mmHg is indicative of CLI (Norgenn et al, 2007). There was no difference in the proportion of participants with CLI in either group, according to their $tcpO_2$ readings. Several low readings were from the sensor on the calf, the significance of which is unclear. If only the low readings from the foot sensors are used, then eight patients in the ulcerated group (17%) and two from the control group (8%) had readings suggestive of CLI. Of these eight patients, two patients' ulcers healed (patients 2 and 46) and one was improving (patient 39) after 12 months of conservative treatment. Two patients' DFUs remained static over this period (patients 15 and 23) and three deteriorated (patients 1, 19 and 27). The five patients whose ulcers failed to heal (13% of the DFU group) are likely to have had ischaemia as an underlying cause and would have benefitted from vascular investigation and consideration of revascularisation, despite having already been assessed clinically as having no vascular disease. The two patients whose DFUs healed with conservative treatment may have healed more quickly if underlying vascular disease, suggested by the low $tcpO_2$ readings, had been identified and treated.

Table 3. $TcpO_2$ results in mmHg for patients without ulceration (the control group), *n*=26.

Patient number	Thigh	Calf	Medial foot	Lateral foot	Great toe	Events during follow-up period
1001	52	39	19	34	18	Attended Podiatry
1002	81	23	52	77	54	
1003	80	31	46	86	51	
1004	45	20	80	57	69	
1005	54	3	13	27	34	Deceased
1006	76	40	63	93	63	
1007	54	56	43	45	51	
1008	54	66	63	80	55	Attended Podiatry
1009	50	58	67	66	52	
1010	56	-	53	86	67	
1011	59	41	68	88	54	
1012	65	51	53	86	66	
1013	34	38	60	82	59	
1014	70	62	64	75	78	
1015	67	67	50	68	57	
1016	68	46	51	38	64	
1017	48	56	78	59	61	
1018	61	67	52	43	82	
1019	57	49	62	68	62	
1020	69	49	75	56	78	Deceased
1021	64	55	68	61	86	Deceased
1022	58	37	64	56	52	
1023	59	56	45	73	63	
1024	70	54	71	73	63	
1025	39	64	43	57	49	Attended Podiatry
1026	62	28	50	45	64	Deceased

Critical limb ischaemia, suggested by ≤30 mmHg

High distal readings ≤80 mmHg

The high peripheral readings are difficult to explain. A high peripheral $tcpO_2$ may be highly significant in patients with DFUs. One patient consented to have $tcpO_2$ readings taken during a peripheral angioplasty procedure. The patient had diabetes, diffuse disease of the calf vessels and a necrotic great toe. $TcpO_2$ sensors were placed on the lateral and medial aspects of the foot and a sensor at the base of the second and third toes, as close to the necrotic great toe as possible. The $tcpO_2$ readings at the start of the procedure were 42 mmHg at the lateral foot, 13 mmHg at the medial foot and 86 mmHg at the base of the toes. The high reading at the base of the toes was unexpected. On inflating the angioplasty balloon in the posterior tibial artery, the $tcpO_2$ reading over the medial foot dropped to 2 mmHg, suggesting no collateral flow. On releasing the balloon, it started to rise above 20 mmHg, but the $tcpO_2$ at the base of the toes started to fall to below 60 mmHg. Possibly the only explanation is that the last collateral flow that can occur is through the skin vessels, so skin over the base of the toes was receiving a much larger blood supply than it required as blood made its way to supply the necrotic great toe. This would have an impact on the clinical assessment of this patient: good perfusion at the base of the necrotic toe makes a clinical diagnosis of ischaemia unlikely.

On the basis of the pilot study results, $tcpO_2$ measurement seems a potentially good method of identifying ischaemia in patients with DFUs. A larger trial would seem more than justified in view of the considerable cost to the NHS of treating these patients. A number of changes, both technical and procedural, should be considered in such a trial:

- The measurements carried out during the angioplasty procedure suggest ischaemia may be very localised, as although the adherent cup was positioned as close as possible to the necrotic toe, the $tcpO_2$ was unusually high. Smaller adherent cups or some other connection is required
- The adhesive holding the cup to the skin was very strong and caused some damage to the skin, which is already delicate, in a small number of patients. The adhesive has to be water-resistant, as a water-based liquid is used as the coupling agent with the sensor. A nontoxic solvent is required to remove the cups
- To maximise the opportunity to identify ischaemia, the measurements should be taken with the leg elevated by 30°, as this reduces the $tcpO_2$ in patients with ischaemia, increasing the sensitivity of the test (Ruangsetakit et al, 2010).

If a larger study can demonstrate the efficacy of $tcpO_2$ in identifying ischaemia in patients with DFUs, this could be used to assess all new referrals to ensure ulcers requiring revascularisation are not overlooked. This would avoid the patient embarking on a long, unnecessary treatment programme — often with weekly hospital visits — with little chance of a successful outcome.

Conclusion

The results of this pilot study suggest that $tcpO_2$ measurement may be a suitable method for identifying ischaemia in DFUs. Participants found it to be comfortable and convenient. A larger trial should be considered with the aim of demonstrating the efficacy of $tcpO_2$ in identifying ischaemia in patients with DFUs and preventing the instigation of intensive and costly treatment with little chance of a successful outcome. ■

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