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Review

Angiology
2020, Vol. 71(3) 208-216
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DOI: 10.1177/0003319719866958
journals.sagepub.com/home/ang
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Applicability of Transcutaneous Oxygen Tension Measurement in the Assessment of Chronic Limb-Threatening Ischemia

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Abstract

Transcutaneous oxygen tension measurement ($TcPO_2$) is widely applied for the evaluation of chronic limb-threatening ischemia (CLTI). Nevertheless, studies that focused on the clinical value of $TcPO_2$ have shown varying results. We identified factors that potentially play a role in $TcPO_2$ measurement variation such as probe placement, probe temperature, and the use of a reference probe. In this review of the current literature, we assessed the application of these factors. A systematic search was conducted. Parameters that were assessed were probe placement, probe temperature, and mentioning and/or use of a reference probe. In total, 36 articles were eligible for analysis. In 24 (67%) studies, probes were placed on specific anatomical locations. Seven (19%) studies placed probes, regardless of the location of the ulcer, adjacent to an ischemic lesion or ulcer (perilesion). Selected temperature setting of the probe differed; in 18 (50%), a default probe temperature of 44°C was selected, and in 13 (36%), a different temperature was selected. In 31 (84%) studies, the use of a reference probe was not reported. Transcutaneous oxygen tension measurement is applied diversely in patients with CLTI. Homogeneity in $TcPO_2$ protocols is warranted for reliable clinical application and to compare future $TcPO_2$ research.

Keywords

$TcPO_2$, critical limb ischemia, chronic limb-threatening ischemia, diabetes, diabetic foot ischemia, transcutaneous oximetry, peripheral arterial disease

Introduction

Chronic limb-threatening ischemia (CLTI) is an increasing major health-care problem worldwide with a large impact on quality of life, morbidity and mortality, and health-care expenses.[1-3] The main treatment goals of CLTI management are wound healing, prevention of amputation, and preservation of ambulation.[1] Transcutaneous oxygen tension measurement ($TcPO_2$) has been proposed as a promising noninvasive tool for the diagnosis and evaluation of CLTI, especially in diabetes.[4,5]

The measurement of local oxygen pressure is believed to reflect the status of underlying vascularization of the skin. With the use of the so-called "Clark electrode," PO_2 is measured by a platinum cathode and a silver anode covered with a thin membrane which is permeable for oxygen.[6] The electronical reduction of oxygen allows a current to flow which is proportional to the partial pressure of oxygen.[6] To ensure dermal permeability for oxygen, the electrode is heated creating local hyperthermia liquefying the crystalline structure of the stratum corneum. Furthermore, hyperthermia creates underlying capillary vasodilatation allowing more oxygen diffusion.[7,8]

Despite the use of $TcPO_2$ in clinical practice, its added value for the diagnosis and evaluation of therapy in patients with CLTI is strongly debated as studies have shown poor to moderate reliability and reproducibility.[9-13] A recent review on $TcPO_2$ reported a sensitivity ranging from 0.61 to 0.82 for the prognosis of diabetic foot ulcer (DFU) healing.[12] Moreover, reported $TcPO_2$ threshold values for the detection of ischemia or potential non-healing DFUs differ significantly.[10,14-24]

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Recently, the Society of Vascular Surgery proposed the "Wound, Ischemia, and foot Infection, (WIfI)" classification system to assess the risk of limb amputation and chance of successful revascularization in patients with CLTI.[25] Moreover, the European Society for Vascular Surgery has adopted and implemented the WIfI in their most recent guideline on the management of peripheral artery disease (PAD).[26] Based on the aggregate of grades determined by wound presence, level of ischemia, and severity of infection, a treatment strategy can be proposed as well as an estimation of the prognosis can be made. The WIfI recommends that if arterial calcification precludes reliable ankle–brachial index or toe pressure measurement, ischemic grade should be classified with $TcPO_2$.

Since WIfI scores should ideally translate into treatment decisions, it is essential that $TcPO_2$ results are reliable and reproducible. This underlines that $TcPO_2$ measurement should be conducted homogenously and factors that may interfere with the test should be kept to a minimum. We assume that the discrepancies between reported threshold values in studies on $TcPO_2$ are, at least partially, due to differences in protocols for measurement. Our objective is to review methods of $TcPO_2$ measurement and explore potential factors that influence these values in patients with CLTI.

Methods

For this review, we conducted a systematic search on PubMed, EMBASE, and the Cochrane Library for peer-reviewed publications on $TcPO_2$ in patients with CLTI using synonyms for "transcutaneous –oximetry, -oxygen or $TcPO_2$" and "critical limb or peripheral arterial disease and ischemia" and reviewed references of reviews. All observational studies and clinical trials on CLTI and $TcPO_2$ were included. Exclusion criteria were lack of $TcPO_2$ measurement, absence of CLTI, for example, DFUs without ischemia, nonhuman studies, language other than English, or if no full text was available. All eligible articles were analyzed for the protocol used to measure $TcPO_2$ and—if available—the relation of $TcPO_2$ values and outcomes. The following potential parameters were assessed: probe placement, probe temperature, and mentioning and/or use of a reference probe. All studies were reviewed by two researchers (B.L. and J.W.) independently.

Results

A flowchart of the systematic search is shown in Figure 1. A total of 437 publications were screened. After exclusion, 36 articles remained eligible for analysis. An overview of the study characteristics and results is demonstrated in Table 1. A total of 13 studies involved an experimental intervention, 8 studies on success of percutaneous transluminal angioplasty (PTA), 7 observational studies, 6 studies on experimental diagnostics, and 2 studies on wound healing after amputation.

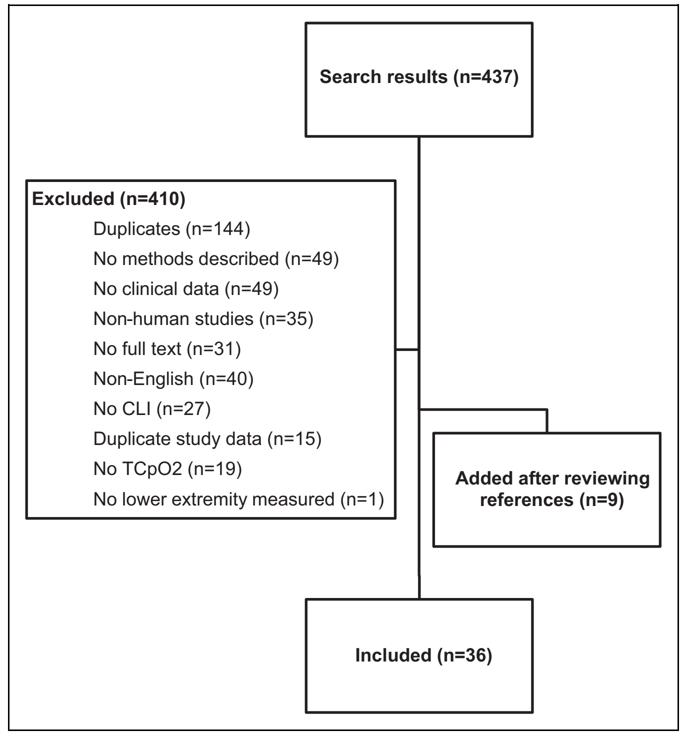

Figure 1. Overview of study selection.

Probe Placement

In 24 (67%) studies, 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%; Table 1). A total of 7 (19%) studies placed probes adjacent to an ischemic lesion or ulcer (perilesion) irrespective of the location of the lesion. In 5 (14%) studies, the specific location was not reported (Table 1).

Probe Temperature

Among the selected temperature settings of the probe, the following was noted: in 18 (50%) studies, a default probe temperature of 44°C was selected, in 8 (22%) studies 45°C, in 2 (5%) studies 43.5°C, in 2 (5%) studies 44.5°C, and in 1 (3%) study 42°C. In 5 (14%) studies, probe temperature was not reported.

Reference Probe

In 31 (84%) studies, the use of a reference probe was not reported. In 4 (11%) studies, the reference probe was applied at the chest (eg, subclavicular) region, in 1 (3%) study on the arm, and in 1 (3%) on the contralateral limb. Only one study used reference probe values for the interpretation of systemic oxygenation.

Relation of $TcPO_2$ and Outcome

As apparent from the studies shown in Table 1, ulcer healing and limb prognosis were in general poor if $TcPO_2$ is <20 mm

Table 1. Overview of Included Studies.

Study	Participants	Reference Probe	Probe Placement	Probe Temperature (°C)	Study Aim	Study Type	Conclusion
Wagner et al[27]	34	Yes, subclavicular	Dorsum	45	Effect of PTA on $TcPO_2$ level	Prospective controlled trial	No deterioration with $TcPO_2$ >45 mm Hg (±20)
Benhamou et al[28]	48	NR	1st MT (metatarsal)	44	Predictive value of $TcPO_2$ on vascular outcome in hemodialysis population	Prospective observational	A $TcPO_2$ less than 40 mm Hg at the onset of hemodialysis could identify patients at high risk of death and patients requiring vascular treatment
Kalani et al[14]	50	Yes, subclavicular	1st MT	44	Predictive value of $TcPO_2$ for ulcer healing in patients with diabetes and chronic foot ulcers	Prospective observational	Probability of ulcer healing is low when $TcPO_2$ is <25 mm Hg
Petrakis and Sciacca[24]	60	NR	Foot dorsum	44	$TcPO_2$ as prognostic parameter in selecting diabetic patients for permanent spinal cord device implantation	Prospective observational	Limb salvage in trophic lesions <3 cm^2 24.2 (± 6.2) mm Hg, trophic lesions >3 cm^2 20.7 (±5.3) mm Hg
Khodabandehlou and Le Devehat[15]	33	NR	1st MT	44	Predict value of red blood cell aggregation on wound healing	Prospective observational	94% of patients with $TcPO_2$ <10 mm Hg deteriorated, while only 53% of those with 10 < $TcPO_2$ < 30 mm Hg, improved
Caselli et al[17]	43	NR	2nd MT	44	Effect of PTA on $TcPO_2$ level in diabetic patients with ischemic foot ulcers	Retrospective analysis	$TcPO_2$ <20 mm Hg no limb salvage, $TcPO_2$ >35 mm Hg limb salvage
Jacqueminet et al[29]	32	NR	1st MT	44	Effect of PTA in severe diabetic foot ischemia	Retrospective analysis	Partial or total healing with $TcPO_2$ > 27 ± 9 mm Hg, clinical deterioration with $TcPO_2$ < 20 ± 9 mm Hg
De Graaff et al[30]	96	NR	1st MT	44	Diagnostic value of $TcPO_2$ in CLTI population	Randomized controlled trial	Use of $TcPO_2$ and toe pressure measurements in management of suspected CLI does not have advantage over the clinical judgment of an experienced vascular surgeon
Faglia et al[31]	564	NR	Perilesional (dorsum)	NR	Effectiveness of PTA in preventing major amputation in patients with CLTI	Prospective observational	In patients in whom PTA is effective in only the iliac–femoral–popliteal, or only in the peroneal axis, the change in $TcPO_2$ can help to determine the probability of avoiding major amputation
Gersbach et al[32]	87	NR	1st MT	45	Discriminative microcirculatory screening of patients with CLTI for dorsal column stimulation	Prospective observational	$TcPO_2$ determinations were insufficiently reliable: 10 of 12 limbs (83%) with $TcPO_2$ >15 mm Hg were salvaged, yet also in 5 of 12 limbs with $TcPO_2$ < 15 mmHg were salvaged
Nouvong et al[16]	54	NR	Ankle	44	Hyperspectral imaging technology to predict healing potential of diabetic foot ulcers	Prospective observational	Nonhealing ulcer (46 ± 16 mm Hg) and healed ulcer (48 ±15 mm Hg)
Ferraresi et al[33]	101	NR	Perilesional (dorsum)	NR	Long-term results of successful PTA for limb salvage in patients with CLTI	Retrospective analysis	NA

(continued)

Table 1. (continued)

Study	Participants	Reference Probe	Probe Placement	Probe Temperature (°C)	Study Aim	Study Type	Conclusion
De Marchi et al[34]	48	NR	NR	44	Effect of propionyl-L-carnitine on microcirculation, endothelial function, and pain relief in patients affected by CLTI	Randomized controlled trial	NA
Ladurner et al[22]	141	NR	Foot dorsum	NR	Predict the risk of nonhealing and amputation in diabetic foot ulcer patients	Prospective observational	The overall amputation rate increased with decreasing $TcPO_2$ readings (group <20 mm Hg: 26%, group 20-40 mm Hg: 10%, group >40 mm Hg: 5%, $P = .014$
Uccioli et al[10]	510	NR	2nd MT	44	Long-term outcomes of diabetic patients with CLTI	Retrospective analysis	Healing 46.8 $\pm$ 1.4 mmHg, nonhealing 41.8 $\pm$ 3.2 mm Hg
Prochazka et al[19]	96	NR	Perilesional	NR	Effect of autologous bone marrow stem cells for the prevention of major amputation in patients with CLTI	Randomized controlled trial	NA
Ruangsetakit et al[20]	50	Yes, subclavicular	Dorsum	45	Determination threshold of transcutaneous oxygen tension ($TcPO_2$) values in predicting ulcer healing in patients with CLTI	Prospective observational	None of patients with a $TcPO_2$ of <20 mm Hg (group 1) showed signs of ulcer healing, whereas all of the patients with a $TcPO_2$ of >40 mm Hg (group 3) showed a progression toward healing during the study period
Löndahl et al[21]	75	NR	3rd MT	42	To evaluate circulatory variables in predicting outcome of hyperbaric oxygen therapy	Randomized, double-blind, placebo controlled trial	No ulcer healed when basal $TcPO_2$ was <25 mm and all ulcers healed when $TcPO_2$was >75 mm Hg. In patients with $TcPO_2$ 26-50 mm Hg and 51-75 mm Hg, healing rates were 50% and 73%, respectively
Kim et al[35]	23	NR	Perilesional (plantar)	44	The effect of PTA on tissue oxygenation in ischemic diabetic feet	Prospective observational	In the 28 limbs with ulcers, 25 limbs revealed marked improvements in $TcPO_2$ values (>30 mm Hg)
Redlich et al[23]	28	NR	1st MT	NR	Predict value of $TcPO_2$ in outcome after infrageniculate PTA in diabetic patients with CLTI	Prospective observational	In the nonamputation group, at 3 months after PTA, $TcPO_2$ values 41.0 $\pm$ 4.5 mm Hg, from 22.8 $\pm$ 4.3 mm Hg at baseline. Amputation group was 18.9 $\pm$6.1 mm Hg at day 9 post PTA
Andrews et al[36]	307	NR	Dorsum	45	Determination of $TcPO_2$ cutoff points to predict wound healing or healing of partial foot amputation	Retrospective analysis	10 (29%) of 34 patients with supine $TcPO_2$ values lower than 20 mm Hg and uncontrolled diabetes mellitus healed within 3 months. The optimal cut point (healing or failure of healing) in the data of this study was 38 mm Hg
Humeau-Heurtier et al[37]	84	Yes, chest	Ankle and toe	44.5	Feasibility of laser speckle contrast imaging in patients with CLTI	Prospective observational	NA

(continued)

Table 1. (continued)

Study	Participants	Reference Probe	Probe Placement	Probe Temperature (°C)	Study Aim	Study Type	Conclusion
Katsui et al[38]	16	NR	Ankle and 1st MT	44	Laser speckle contrast imaging of the fluctuation in blood perfusion after local heating after PTA	Prospective observational	NA
Pardo et al[39]	40	NR	Dorsum	44	Comparison of ankle–brachial index with $TcPO_2$ in patients with CLTI prior and after PTA	Prospective observational	NA
Kavros et al[40]	48	NR	Perilesional	45	Effect of intermittent pneumatic compression in patients with CLTI	Retrospective analysis	NA
Klingel et al[41]	12	NR	Dorsum	44	Effect of Rheopheresis in patients with CLTI	Prospective pilot trial	NA
Kram et al[42]	40	Yes, arm	Calf	44	Prediction of wound healing in below-knee amputation	Prospective observational	In patients with calf $TcPO_2$ values greater than 20 mm Hg, 96% (27/28) had successful healing after below-knee amputation
Kumagai et al[43]	10	NR	NR	43.5	Effect of sustained release of basic fibroblast growth factor using gelatin hydrogel in patients with CLTI	Prospective interventional	NA
Lenk et al[44]	7	NR	NR	43.5	Safety of intra-arterial application of autologous circulating blood-derived progenitor cells in patients with CLTI	Prospective intervention	NA
Madaric et al[45]	62	NR	Forefoot	44	Effect of autologous bone marrow cell therapy in patients with CLTI	Prospective interventional	Surviving patients with limb salvage at the 12-month follow-up (39/62 patients) were characterized by higher $TcPO_2$ levels (16 $\pm$ 10 vs 10 $\pm$ 9 mm Hg, $P = .01$
Malyar et al[46]	16	NR	Perilesional	44.5	Effect of autologous bone marrow cell therapy in patients with CLTI	Prospective interventional	NA
Melillo et al[47]	26	Yes, contralateral limb	NR	45	Effect of iloprost treatment in patients with CLTI	Prospective interventional	Iloprost treatment success was almost certain when $TcPO_2$ was >23 mm Hg
Nilsson et al[48]	10	NR	NR	45	Effects of atrinositol in patients with CLTI	Prospective interventional	NA
Paraskevas et al[49]	74	NR	Perilesional	45	Effect of leg elevation on $TcPO_2$ measurement in patients with CLTI	Prospective observational	NA
Scheffler et al[50]	64	NR	Forefoot	44	Effects of oxygen inhalation and leg elevation in patients with CLTI	Prospective observational	In conclusion, $TcPO_2$ limits of 10 and 45 mm Hg for room air breathing readings in supine and sitting position, respectively, should be applied as discriminatory values. Measurements localized outside this 2-dimensional range most probably are not associated with critical limb ischemia
Ubbink et al[51]	49	NR	Dorsum	44	Establishment of optimal $TcPO_2$ cutoff values in patients with CLTI	Prospective observational	The optimal $TcPO_2$ cutoff value for presence of CLTI is 35 mm Hg

Abbreviations: CLTI, chronic limb-threatening ischemia; MT, metatarsal, NA, not available; NR, not reported; PTA, percutaneous transluminal angioplasty; $TcPO_2$, transcutaneous oxygen tension measurement.

Hg and were in general good if >40 mm Hg; however, even these values varied between studies.

Discussion

We found substantial differences in probe placement, probe temperature, and reference probe application in studies on $TcPO_2$ use in CLTI. Moreover, cutoff values for wound healing and limb prognosis varied between studies.

It is known that the abovementioned variations in $TcPO_2$ protocols affect the obtained values. For example, in general, the lower extremity has different oxygen tension levels influenced by local factors, such as skin thickness.[52] Hence, the selected probe site affects $TcPO_2$ value. Although ischemic lesions may occur on different anatomical locations on the lower extremity,[53] standardization of $TcPO_2$ probe location is crucial to reduce the intra- and interpatient variability.

Furthermore, $TcPO_2$ measurement using the Clark electrode is influenced by the selected probe temperature.[54-57] Cutaneous warming of, for example, the diabetic foot has shown a profound effect on $TcPO_2$ values showing a 40.8 $\pm$ 23.8 mm Hg difference between a probe temperature of 37°C and 44°C.[54] The $TcPO_2$ manuals suggest a probe temperature between 43°C and 45°C,[58] 44°C and 45°C,[59] or 45°C[60]; hence, the majority of studies used 44°C as default temperature. However, a consensus statement of an expert panel proposed a default temperature of 45°C.[61] Since studies on the effect of $TcPO_2$ probe temperature on $TcPO_2$ values in CLTI and its relation with prognosis are lacking, the optimal probe temperature in CLTI remains unknown.

Finally, it is suggested that $TcPO_2$ values are influenced by the systemic oxygen level. Therefore, the placement of a reference probe on the thorax is recommended to correct for systemic hypoxia. We found that 6 studies mentioned the use of a reference probe. However, in 2 of these studies, values or interpretation of the reference probe remained unclear. An indicator which takes into account the systemic oxygen influence is the regional perfusion index (RPI),[62,63] which is calculated by dividing the $TcPO_2$ values of the limb by $TcPO_2$ thorax values. The RPI has been successfully applied to evaluate vascularization of the extremities,[64-66] which is also recommended by $TcPO_2$ measurement device manufacturers. However, thorax $TcPO_2$ values are subject to the same variability as for the limb; hence, the ratio of the two could mathematically result in a greater variability than that of each factor separately. Therefore, more comparative research is required to validate and determine accurate thresholds for RPI and their added value in comparison to absolute cutoff $TcPO_2$ values in CLTI for usage in clinical practice. Another proposed strategy is to add pulse oximetry (SO_2) to rule out arterial hypoxemia.[58-60] However, studies on SO_2 and its correlation with $TcPO_2$ values of the lower limb are lacking.

A major limitation in this review is the impossibility to address the specific impact of probe location, probe temperature, and use of reference probe on the measured $TcPO_2$ values due to the fundamental differences in study aim and therefore patient population in the individual studies. Moreover, the study design of the included studies was very heterogeneous: 13 studies involved an experimental intervention, 8 studies on success of PTA, 7 observational studies, 6 studies on experimental diagnostics, and 2 studies on wound healing after amputation. Still, we demonstrate that the method of $TcPO_2$ use differs undoubtedly and point out the sensitivity of $TcPO_2$ measurement in general. Hence, it might be suggested that heterogeneity in method of use alters $TcPO_2$ values.

With the recently introduced WIfI classification system in the current ESC guidelines,[26] $TcPO_2$ plays a role in grading ischemia and the determination of the treatment strategy in patients with CLTI. For example, if a patient has a shallow ulcer on the foot without gangrene and no signs of infection and $TcPO_2$ measurement is 40 mm Hg, the patient is categorized as having a very low risk of limb amputation and low requirement for revascularization. However, if the same patient has a $TcPO_2$ of 29 mm Hg, there is a moderate risk of limb amputation and a high requirement for revascularization.[26] This indicates a prominent role for $TcPO_2$ to determine treatment strategy. Moreover, the usefulness of the ankle systolic pressure, imbedded in the WIfI classification, to predict the risk of major amputation in CLTI is currently under debate.[67] Especially in patients with CLTI with concomitant diabetes mellitus or chronic renal failure, $TcPO_2$ seems more reliable in comparison to current macrovascular diagnostics.[68] Furthermore, other factors in method of $TcPO_2$ use should be addressed to provide an adequate risk stratification scheme for $TcPO_2$, such as positioning of the patient (supine vs sitting) and additional oxygen inhalation, both methods have proven to increase the predictive value of wound healing prognosis.[69,70] All these factors underline the importance of a standardized method of $TcPO_2$ measurement and careful interpretation of these values. The effect of altering specific variables during $TcPO_2$ assessment remains unclear. Therefore, we are currently conducting an observational study to investigate the influence of probe location and the added value of the RPI on wound healing prognosis. Also, in our vascular laboratory, we are conducting experimental $TcPO_2$ studies to investigate a new photo-optical form of $TcPO_2$. It has been suggested that photo-optical $TcPO_2$ is not affected by probe temperature compared with the standard electrochemical $TcPO_2$.

Conclusions

Transcutaneous oxygen tension measurement for the evaluation of limb perfusion in patients with CLTI is applied in standard clinical practice and is included in WIfI and international guidelines on PAD management, therefore affecting treatment decisions. However, there is a strong heterogeneity in methods used to assess $TcPO_2$. A substantial diversity in probe temperature, probe location, and the use of a reference probe was found among studies regarding $TcPO_2$ in CLTI. The varying values and different conclusions of the reviewed studies underline the importance of a homogeneous protocol in order to interpret and possibly compare measurement values and use these values to guide treatment decisions. Prior to the implementation of $TcPO_2$ as part of treatment guidelines, it is mandatory that (international) $TcPO_2$ measurement protocols become available and are validated to guarantee reliable and reproducible $TcPO_2$ results.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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