

Relationship between ulcer healing after hyperbaric oxygen therapy and transcutaneous oximetry, toe blood pressure and ankle–brachial index in patients with diabetes and chronic foot ulcers

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Received: 25 April 2010 / Accepted: 1 September 2010 / Published online: 19 October 2010
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Abstract

Aims/hypothesis The randomised, double-blind, placebo-controlled Hyperbaric Oxygen Therapy (HBOT) in Diabetic Patients with Chronic Foot Ulcers (HODFU) study showed beneficial effect of HBOT. As this treatment is expensive and time-consuming, being able to select patients for therapy would be very useful. The aim of this study was to evaluate whether circulatory variables could help in predicting outcome of HBOT.

Methods All HODFU study participants who completed therapy, predefined as receiving at least 36 out of 40 scheduled HBOT/placebo sessions, were included in this study ($n=75$). Baseline transcutaneous oximetry (TcPO₂), toe blood pressure (TBP) and ankle–brachial index (ABI) were measured. Ulcer healing rate was registered at the 9-month follow-up visit. An ulcer was considered healed when it was completely epithelialised and remained so at the 12-month follow-up.

Electronic supplementary material The online version of this article (doi:10.1007/s00125-010-1946-y) contains supplementary material, which is available to authorised users.

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Results In the HBOT group TcPO₂ were significantly lower for patients whose ulcer did not heal as compared with those whose ulcers healed. A significantly increased healing frequency was seen with increasing TcPO₂ levels in the HBOT group (TcPO₂/healing rate: <25 mmHg/0%; 26–50 mmHg/50%; 51–75 mmHg/73%; and >75 mmHg/100%). No statistically significant relation between the level of TBP or ABI and healing frequency was seen.

Conclusions/interpretation Our results indicate that TcPO₂ in contrast to ABI and TBP correlates to ulcer healing following HBOT. We suggest HBOT as a feasible adjunctive treatment modality in diabetic patients with chronic non-healing foot ulcers when basal TcPO₂ at the dorsum of the foot is above 25 mmHg.

Trial registration NCT00953186

Funding Mrs Thelma Zoegas Foundation and Faculty of Medicine, Lund University.

Keywords ABI · Chronic hyperbaric oxygen therapy · Diabetes · Foot ulcer · TcPO₂ · Toe blood pressure

Abbreviations

ABI	Ankle–brachial index
HBOT	Systemic hyperbaric oxygen therapy
HODFU	Hyperbaric oxygen treatment in diabetic patients with chronic foot ulcers
TBP	Toe blood pressure
TcPO ₂	Transcutaneous oximetry

Introduction

Systemic hyperbaric oxygen therapy (HBOT) has been suggested as a treatment for diabetic foot ulcers [1–3]. This

treatment modality is expensive and time consuming, so being able to predict which patients will benefit from therapy would be very useful [4].

In the randomised, double-blind, placebo-controlled Hyperbaric Oxygen Treatment in Diabetic Patients with Chronic Foot Ulcers (HODFU) study, the effect of HBOT in diabetic patients with chronic foot ulcers Wagner grade 2, 3 and 4 was compared with the effect of hyperbaric air therapy (placebo) [5]. This study showed a beneficial effect of HBOT [6]. Therefore, we evaluated whether baseline arterial toe blood pressure (TBP), ankle-brachial index (ABI) or transcutaneous oximetry (TcPO₂) could help in predicting the effect of HBOT.

Methods

Design and rationale of the HODFU study and results of ulcer healing outcome have been reported in detail previously [5, 6]. All HODFU study participants who completed therapy, predefined as receiving at least 36 out of 40 scheduled HBOT/placebo sessions, were included in this study ($n=75$ out of 94). Baseline characteristics are given in Electronic supplementary material (ESM) Table 1.

The protocol was approved by the Ethics Committee at Lund University, Sweden. All participants provided written informed consent.

TcPO₂ measurements TcPO₂ measurements were obtained with a Radiometer TCM2 (Radiometer, Copenhagen, Denmark) device. Calibration was performed before each measurement. All measurements were performed at 1 ATA and in supine position after 20 min of rest. Room temperature was kept between 21°C and 24°C. Patients were asked to avoid smoking or drinking coffee for at least 2 h before investigations.

According to our protocol, TcPO₂ was measured on the dorsum of the foot, 2 cm proximal to the base of the third toe, or as close to this location as possible. Areas directly overlying bone or superficial veins were avoided. The measuring site was carefully cleaned and the electrochemical transducer was then applied to the skin using adhesive rings and contact liquid supplied by the manufacturer. To increase skin oxygen permeability the transducer was heated to 42°C. After baseline equilibration, TcPO₂ values were recorded once every minute while the patient was breathing room air for 6 min, followed by 100% oxygen for another 6 min. The highest TcPO₂ values while breathing air or oxygen were chosen as the basal and stimulated TcPO₂, respectively.

Methods for measuring TBP and ABI have been described previously [6].

Statistics Comparisons were tested with Mann–Whitney *U* test. Correlations were tested with Pearson's test of correlations. Differences in frequencies were analysed with Fisher's exact test. A binary logistic regression was used to evaluate factors influence on outcome, with healing as the dependent variable.

A two-sided *p* value below 0.05 was considered statistically significant. Statistical analysis was performed using Statistica software, version 9.0 (Statsoft Inc, Tulsa, OK, USA).

Results

In total, 75 patients were included in the study: 38 randomised to HBOT, 37 to placebo treatment. Patients' baseline characteristics did not differ between HBOT and placebo [6]. Median ulcer duration at inclusion was 11.8 and 10.3 months (HBOT vs placebo, NS). TBP, ABI and basal/stimulated TcPO₂ at 1 ATA did not significantly differ between the HBOT and placebo groups.

There was a statistically significant correlation between TBP and ABI ($r^2=0.42$, $p=0.0003$, $n=68$), and between basal and stimulated TcPO₂ ($r^2=0.53$, $p<0.000001$, $n=75$). By contrast, no significant correlation was seen between TBP or ABI and TcPO₂.

In the HBOT group, basal and stimulated TcPO₂ were significantly lower for patients whose ulcer did not heal (non-healers) compared with those whose ulcers healed (healers) (Fig. 1). A statistically significant increased healing frequency was seen at higher TcPO₂ levels (Fig. 2). These findings are also valid for the HBOT group in the intention-to-treat population of the HODFU study. No statistically significant relation between the level of TBP or ABI and healing frequency was seen. In the placebo group, basal and stimulated TcPO₂ values were similar for healers compared with non-healers. In a binary regression analysis healers were compared with non-healers, including basal and stimulated TcPO₂, TBP, ABI, age, diabetes duration and ulcer depth according to the Wagner classification scale. In the HBOT group basal TcPO₂ was significantly related to ulcer healing (data not shown).

Discussion

Vascular complications in diabetes might be considered secondary to impaired macro- and/or microvascular disease. Both ABI and TBP are used in the evaluation of macrovascular circulation. TcPO₂, being a composite measure of several factors such as arterial pressure, arterial oxygen content, local tissue perfusion pressures, neurovascular

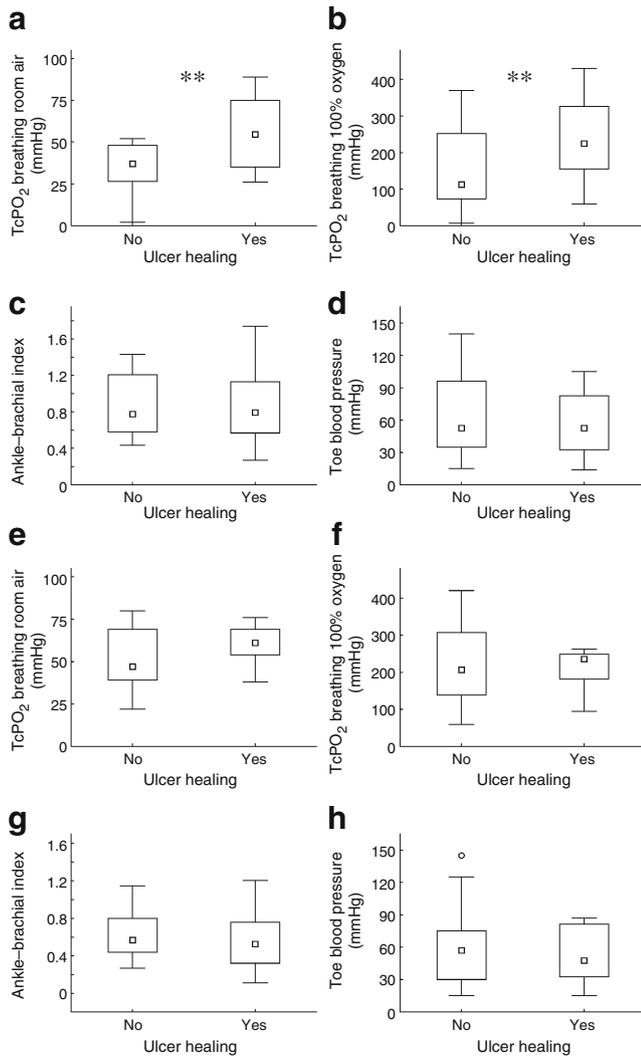


Fig. 1 Median basal TcPO₂, stimulated TcPO₂, TBP and ABI in patients with healed foot ulcers compared with patients with unhealed foot ulcers at 9-month follow-up after HBOT (a–d) or placebo (e–h), respectively. Data given as median, 25–75% and non-outlier min–max. ***p*<0.01

function and local oxygen consumption, may be a more relevant measure, as it seems to reflect micro- as well as macrocirculation. TcPO₂ has previously been shown to be related to outcome in diabetic foot ulcers [7]. Case series indicate that TcPO₂ might be a predictor for healing after HBOT, but large comparative studies are still lacking. In our diabetic patients no correlation between foot ulcer healing and ABI was seen. Similarly, ABI was not reported as a factor influencing outcome of lower-extremity diabetic ulcers in a retrospective study including 1,006 patients from five hyperbaric facilities in the USA [8]. However, an absolute ABI value reduction of 0.1 was associated with a 1.7 times increased risk of major amputation in a randomised study by Faglia et al. [1]. Most studies evaluating the effect

of HBOT on diabetic foot ulcers do not report TBP. In our study TBP could not be used as a predictor for ulcer healing, which is in agreement with the study by Kalani et al., in which major amputation was performed in nine (of 38) patients, with TBP normal in four, moderately decreased in three and severely decreased in two [3]. In our study, basal TcPO₂ was significantly correlated with ulcer healing. Healing rates following HBOT decreased with decreasing basal TcPO₂. No ulcer healed when basal TcPO₂ was <25 mm and all ulcers healed when TcPO₂ was >75 mmHg. In patients with TcPO₂ 26–50 and 51–75 mmHg, healing rates were 50% and 73%, respectively. Similar results have been reported by others. In a study by Fife et al., 629 patients with basal TcPO₂ below 25 mmHg were less likely to benefit from HBOT than those with higher TcPO₂ values [9]. Wattel et al. reported a mean basal TcPO₂ of 32 mmHg in healers (*n*=15), compared with 12 mmHg in non-healers in a case-series of 20 patients (11 with diabetes and nine arterial insufficiency without diabetes) given adjunctive treatment with HBOT [10]. In a retrospective study of 35 patients who received 16–20 sessions of HBOT after partial foot amputation, healing was achieved in all patients with a TcPO₂ above 29 mmHg [11]. Oubre et al. performed a retrospective analysis of 73 HBOT-treated patients (37 with diabetes) with 85 chronic lower extremity ulcers [12]. Robust healing was achieved in 33 ulcers, minimal healing in 33 and no healing in 21. Basal mean TcPO₂ in each of those groups were 57 mmHg, 44 mmHg and 38 mmHg, respectively. In the present study, stimulated TcPO₂ was significantly higher in healers compared with non-healers. However, in a regression analysis, stimulated TcPO₂ was not superior to basal TcPO₂ in predicting ulcer healing. In the placebo group—mirroring routine clinical care—TcPO₂ was of no prognostic value, possibly owing to a lower healing rate.

Although TcPO₂ appears to be more useful as a prognostic factor for HBOT outcome than TBP and ABI, the method

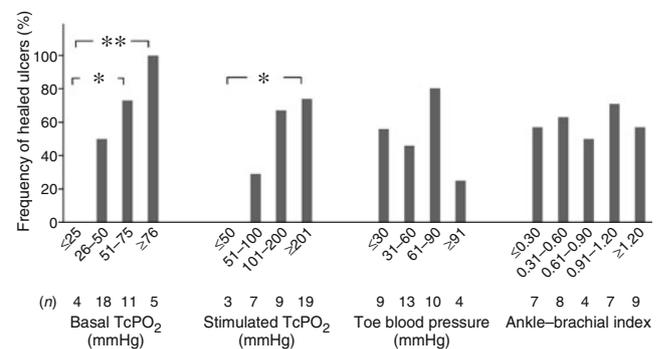


Fig. 2 Ulcer healing frequency at the 9-month follow-up according to basal TcPO₂, stimulated TcPO₂, TBP and ABI in patients who received HBOT (*n*=38). **p*<0.05, ***p*<0.01

has several limitations. Measurements might be hampered by individual factors, such as electrode localisation, skin thickness and skin oxygen consumption, as well as ointments. Variation in patients' respiratory or cardiac condition may influence TcPO₂, and the presence of oedema could be an important confounding factor. In our study 7% of TcPO₂ measurements were postponed for oedema reduction including transient soft tissue infection. Skin heating reduces the barrier to transcutaneous diffusion of oxygen, and even small changes in temperature might have an impact on TcPO₂. A heating element keeps a constant electrode temperature, usually between 42°C and 45°C. At our hyperbaric unit, skin blistering and ulcer development have been seen as adverse reactions to TcPO₂ measurement at 44°C. As a consequence, we use a transmitter temperature of 42°C, which might give 2–6% lower TcPO₂ values compared with those taken at 44°C. Arguments have been raised in favour of TcPO₂ measurement at hyperbaric conditions as a better way to predict benefit from HBOT in diabetic patients with chronic foot ulcers. We did not use this method in our study, because it is not practical in a diabetic foot clinic.

In conclusion, these results indicate that basal and stimulated TcPO₂ in contrast to ABI and TBP, correlate to ulcer healing following HBOT. Further, we suggest hyperbaric oxygen therapy as a feasible adjunctive treatment modality in selected diabetic patients with chronic non-healing foot ulcers when basal TcPO₂ at the dorsum of the foot is above 25 mmHg.

Acknowledgements The authors are grateful to J. Jeffery for scientific advice and help with the English text; to registered nurse C. Johansson and assistant nurses G. Torildsson and M. Andersson at the Hyperbaric Unit for collaboration and invaluable help. This study was supported by unrestricted grants from Zoégas Foundation, Region Skåne Foundation and the Medical Faculty of Lund University.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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