Measurement of peripheral arterial tonometry in patients with diabetic foot ulcers during courses of hyperbaric oxygen treatment

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Key words
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Abstract
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Introduction: Treatment of diabetic foot ulcers is complex and often protracted. Hyperbaric oxygen treatment (HBOT) improves wound healing in diabetic ulcers and serves as an important adjunct to regular diabetic wound care. Endothelial dysfunction plays a central role in diabetes-related vascular complications and may be evaluated by a non-invasive technique called peripheral arterial tonometry which measures a reactive hyperaemia index (RHI). We hypothesized that endothelial function measured by peripheral arterial tonometry is impaired in diabetic foot ulcer patients and that HBOT might improve endothelial function.
Methods: Endothelial function was prospectively assessed by peripheral arterial tonometry in 22 subjects with diabetic foot ulcers and 17 subjects without diabetes during courses of HBOT. Endothelial function was evaluated before first (baseline) and 30th treatments, and at 90-day follow-up. Serum insulin growth factor-I (IGF-I) concentrations were determined by immunoassay. Results were compared to 23 healthy subjects.
Results: No baseline differences were found in endothelial function between subjects with diabetes, HBOT patients without-diabetes and healthy control subjects (RHI; 1.26, 1.61 and 1.81, respectively). No significant changes in RHI were found in patients with ($P = 0.17$) or without ($P = 0.30$) diabetes during courses of HBOT. At 90-day follow-up IGF-I was significantly reduced in the subjects with diabetes ($P = 0.001$) and unchanged in the group without diabetes ($P = 0.99$).
Conclusions: We found no significant differences in RHI between subjects with diabetic foot ulcers and patients without diabetes, nor improvement in endothelial function assessed by peripheral arterial tonometry during courses of HBOT.

Introduction

The incidence and prevalence of type 2 diabetes have quadrupled between 1980 to 2004 mainly due to rise in sedentary lifestyles, obesity and an ageing population.[1] Diabetes is predicted to affect more than 300 million people by 2025[2] and 642 million by 2040[1] which has brought increased attention to serious complications such as diabetic foot ulcers. Treatment of diabetic foot ulcers is often protracted and ulcers are reported as non-healing in 19–34%.[3] Diabetic foot ulcers account for more than 60% of all non-traumatic lower limb amputations in the United States[4] and the five year mortality rate for amputated persons with diabetes is 60%.[4]

The pathophysiology of diabetic foot ulcers is well described including autonomic neuropathy, arterial flow insufficiency and microangiopathy,[5] and in general the lower extremities are more prone to the development of peripheral arterial disease (PAD)[6] causing diabetic foot ulcers. The complex sequence in successful wound healing includes "*removal of necrotic debris, resolution of inflammation, repair of the connective tissue matrix, angiogenesis and resurfacing*".[5] The dependency of these processes on oxygen has been well established.[7,8] However, chronic diabetic foot ulcers have failed to follow this orderly sequence and treatment often requires regular outpatient wound care, antibiotics and sometimes long-term hospitalization.

Hyperbaric oxygen treatment (HBOT) has been demonstrated to improve wound healing in chronic diabetic foot ulcers in several double-blinded randomized controlled trials[3,9] and

meta-analyses have shown that HBOT reduces the risk of major amputations.[10,11]

HBOT has been shown to enhance leukocyte function, stimulate angiogenesis, improve fibroblast function and promote granulation; all central processes in wound healing.[12–15] HBOT-mediated angiogenesis seems partly to be explained by increased vascular endothelial growth factor (VEGF)[16] which is among the most specific growth factors for neovascularization.[17] Insulin-like growth factor I (IGF-I) has also been shown to increase with HBOT and promotes wound healing in patients with diabetic foot ulcer.[18]

Diabetes-induced endothelial dysfunction plays a central role in diabetes related vascular complications.[19] Endothelial dysfunction may be evaluated by peripheral arterial tonometry (PAT), which in several clinical studies have demonstrated impaired endothelial function in persons with diabetes.[20–24]

It is plausible that the beneficial effect of HBOT on angiogenesis and neovascularization might be reflected in improved endothelial function. However, to date, this has never been investigated in persons with diabetic foot ulcers. The aim of this study was to evaluate endothelial function by peripheral arterial tonometry in persons with diabetic foot ulcers and to determine whether HBOT would have an impact on peripheral vascular function. We hypothesized that endothelial function is impaired in persons with diabetic foot ulcers compared to both healthy controls and to persons without diabetes also undergoing HBOT for various other indications such as bony- or soft tissue radiation injuries and non-diabetic ischemic wounds. We also hypothesized that courses of HBOT would improve endothelial function measured by peripheral arterial tonometry. Furthermore, we tested for correlations between endothelial function and IGF-I.

Methods

The study was designed as a prospective longitudinal single-centre study.

ETHICS

The study was approved by the Regional Ethical Committee of Copenhagen Region (H-3-2013-208) and the Data-Protection agencies in Denmark (30-1181). The study was registered at: https://clinicaltrials.gov/ (ID: NCT02221466). The study abided by the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from each patient.

SUBJECTS

Twenty-two subjects with type 1 and type 2 diabetes admitted to The Hyperbaric Oxygen Treatment Unit at Copenhagen University Hospital for chronic diabetic foot ulcers were prospectively included in this study. Subjects without diabetes (n = 17) who received hyperbaric oxygen treatment in our ward were recruited as controls. Historical data from 23 healthy individuals earlier published in a stroke study were included as normal values for endothelial function.[25] Study treatment was given as an adjunct to regular diabetic wound care treatment and as part of the clinical routine for persons with diabetic foot ulcers.

Blood samples were collected and assessments of peripheral endothelial function were performed before the first (baseline) and 30th HBOT sessions. Additionally, all patients were invited for a 90-day follow-up examination.

HYPERBARIC OXYGEN THERAPY

All subjects received HBOT in a multiplace hyperbaric chamber (Drass Galeazzi S.p.A., Type HPO4000/HPE50.2.A, 1998). Oxygen (100%) was administered by hood (Amron International, Aspen, Canada). All sessions were performed in ambulatory settings. The subjects received HBOT five days per week for six weeks (30 sessions). All subjects were treated with Table RH14 (treatment pressure: 245 kPa (~14 metres' seawater equivalent), compression / decompression rate: 3 m·min^{-1}, treatment duration: 90 min, no air breaks).

ASSESSMENT OF PERIPHERAL ENDOTHELIAL FUNCTION

Peripheral endothelial function was assessed by peripheral arterial tonometry (EndoPAT 2000, Itamar Medical Ltd, Caesarea, Israel). The apparatus consists of a two finger-mounted plethysmograph probe capable of sensing volume changes in the vessels in relation to arterial pulsation. The examination includes three phases: a 5-minute equilibration period; a 5-minute period where a blood pressure cuff on one arm is inflated to supra-systolic pressure to occlude blood flow; and once released, a 5-minute period of reactive hyperaemia.

The system collects data digitally and performs operator-independent analysis of the endothelial function including a post-occlusion/pre-occlusion ratio called the reactive hyperaemia index (RHI). An alternative method when calculating the vascular response, but with improved association with cardiovascular risk factors (called the Framingham reactive hyperaemia index (fRHI)) was included in the analysis. Moreover, the system provides two other outcomes called augmentation index (AI) and AI standardized to a heart rate of 75 bpm (AI@75bpm) that measures arterial stiffness derived from the morphology of the arterial pulse waveform. For ease of comparison between individuals the result is related to the heart rate with adjusting to standard heart rate of 75 bpm. We have earlier reviewed the method including reproducibility, advantages and limitations of the apparatus.[26]

LABORATORY BLOOD ASSAYS

Blood samples were collected immediately before assessment with the peripheral arterial tonometer and stored at -80°C until analysis. IGF-I was measured by a chemiluminescence immunoassay on the IDS-iSYS automated platform (Immuno Diagnostic Systems, East Boldon, UK) at the Hormone Laboratory of the Department of Growth and Reproduction, Rigshospitalet, Copenhagen University, Denmark. Interassay coefficient of variation was < 8% and the limit of detection was 10 $\mu g \cdot L^{-1}$.

ENDPOINTS AND STATISTICAL ANALYSIS

The primary endpoint was the RHI. Secondary endpoints were the fRHI, AI, AI@75bpm, and IGF-I assays.

Statistical analyses were performed using R 3.0.2 software for Mac (The R Foundation for Statistical Computing Platform) with additional RStudio 0.98.507 (RStudio, Inc.) software attached. Tests for normality were conducted using the Shapiro-Wilks test. Groups were compared using the Welch two sample *t*-test or Wilcoxon rank-sum test at baseline. A paired *t*-test or the Wilcoxon signed-rank test was used to analyze the effect of HBOT courses. Correlations between variables were analyzed with Kendall's rank correlation tau. Categorical variables were analysed using Fisher's exact test.

Values are given as mean (SD), unless otherwise indicated. *P*-values are reported as exact values, unless less than 0.001. Statistical significance was assumed at $P < 0.05$.

Results

Data from 22 subjects with diabetic foot ulcers, 17 subjects without diabetes and 23 healthy individuals entered the analysis. Subject characteristics and notable differences among study groups are presented in Table 1. The group with diabetes consisted of more men, were older and had in general higher systolic blood pressure, higher body mass index (BMI) and lower cholesterol levels compared to the group without diabetes. Twelve (54%) subjects with diabetes and five (29%) subjects without diabetes were examined at day 90.

Peripheral arterial tonometry was feasible in almost all subjects. There was a significant drop-out during the entire courses of treatments due variously to: amputation and thereby end of therapy (n = 3, all with diabetes); drop-out due to other sickness (n = 3, two without diabetes, one with diabetes); inability to cooperate (n = 1, without diabetes); and lack of response to 90-day follow-up invitation (n = 22, 12 without diabetes, 10 with diabetes). Results obtained from the peripheral arterial tonometry and IGF-I analyses are presented in Table 2. Data from the historical healthy controls[25] are presented in the first column of Table 2.

RHI AND fRHI

The Shapiro-Wilk test showed non-normally distributed values in the diabetic and non-diabetic groups (P = 0.02 and 0.01, respectively). No significant baseline differences were found between the latter groups (P = 0.20) or between the diabetic group and healthy controls (P = 0.09) (see data in Table 2). Moreover, no baseline differences were found between the patient group without diabetes and healthy controls (P = 0.29). The same results were found for the fRHI variables where no baseline differences were found between the group with diabetes and without diabetes (P = 0.59) or the healthy controls (P = 0.36). Likewise, no differences were found between the group without diabetes and healthy controls (P = 0.29). In the group of subjects with diabetes the Wilcoxon signed-rank test showed no statistically significant differences from baseline to 30th treatment or to 90-day follow-up (P = 0.17 and P = 0.95, respectively). Neither differences were found in fRHI in the same group (P = 0.14 and 0.76, respectively). Likewise, in the group without diabetes no differences were found between baseline and 30th treatment or 90-day follow up (P = 0.30 and 0.31, respectively). The same non-significant differences were found concerning fRHI in this group (P = 0.95 and P = 0.19). No correlations were found between RHI and the other measured variables in either groups.

AI AND AI@75BPM

Shapiro-Wilk test showed normally distributed values in both the group with diabetes and the group without diabetes (P = 0.75 and P = 0.54, respectively). No baseline differences in AI were found between the group with diabetes and the group without (P = 0.62) or the healthy controls (P = 0.1) (see data in Table 2). A significant baseline difference was found when comparing the group without diabetes to the healthy controls (P = 0.03). Evaluating AI@75bpm, significant differences were found between persons with diabetes and healthy controls (P = 0.01) and between the persons without diabetes and healthy controls ($P < 0.001$). No baseline differences in AI@75bpm were found between the group with diabetes and without (P = 0.44).

In the subjects with diabetes a paired *t*-test showed no statistical differences in AI from baseline to either 30th treatment or 90-day follow up (P = 0.28 and P = 0.14, respectively). In the group without diabetes significant differences were found between baseline and the 30th treatment and 90-day follow up (P = 0.02 and P = 0.02, respectively). Regarding AI@75bpm no differences were found in the group with diabetes from baseline to either 30th treatment or 90-day follow-up (P = 0.31 and P = 0.28). No significant differences were found in the group without diabetes from baseline to either 30th treatment or follow-up (P = 0.13 and P = 0.06)

Table 1
Baseline characteristics of the study groups. Tabulated values are mean (SD), unless otherwise is indicated in the table

Parameter	Diabetic (*n* = 22)	Non-diabetic (*n* = 17)	*P*-value	Parameter	Diabetic (*n* = 22)	Non-diabetic (*n* = 17)	*P*-value
Male gender, *n* (%)	19 (86%)	3 (18%)	< 0.001	Current smoking, *n* (%)	2 (9%)	3 (18%)	0.64
Age, years	68 (8)	56 (14)	0.002	Diabetes duration, years	21 (14)		
Height, cm	177 (9)	167 (7)	< 0.001	HbA1c, mmol·mol^{-1}	54 (11)	34 (4)	< 0.001
Weight, kg	82 (16)	59 (12)	< 0.001	Glucose, mmol·L^{-1}	8.7 (1.6)	5.9 (0.6)	< 0.001
Body mass index, kg·m^2	26 (4)	21 (4)	< 0.001	Total cholesterol mmol·L^{-1}	3.6 (0.9)	5.3 (0.9)	< 0.001
Systolic BP, mmHg	144 (23)	129 (27)	0.038	HDL cholesterol mmol·L^{-1}	1.1 (0.4)	1.6 (0.6)	0.004
Diastolic BP, mmHg	81 (11)	84 (14)	0.60	HDL/total cholesterol ratio	3.6 (1.5)	3.7 (1.2)	0.71
Heart rate, beats·min^{-1}	77 (13)	78 (11)	0.84				

Table 2
Outcome measures obtained by peripheral arterial tonometry during courses of hyperbaric oxygen therapy. Values from historical healthy control persons published in a previous stroke study are presented in first column.[24] Tabulated values for RHI and fRHI are median (IQR). Values for AI, AI@75bpm and IGF-I are mean (SD)

Outcome measure	Group	Baseline Diabetic *n* = 22 Non-diabetic *n* = 17	After 30 HBOT Diabetic *n* = 16 Non-diabetic *n* = 15	90-day follow-up Diabetic *n* = 12 Non-diabetic *n* = 5
RHI	Diabetic Non-diabetic Healthy control	1.26 (1.0) 1.61 (0.82) 1.81 (0.52)	1.63 (0.96) 1.60 (0.42)	1.29 (0.67) 2.9 (0.51)
fRHI	Diabetic Non-diabetic Healthy control	0.14 (0.73) 0.26 (0.60) 0.34 (0.36)	0.48 (0.62) 0.29 (0.41)	0.07 (0.44) 0.94 (0.19)
AI	Diabetic Non-diabetic Healthy control	7.55 (22.2) 10.88 (19.2) -3.07 (20.6)	15.25 (18.0) 25.31 (24.7)	17.57 (22.0) 40.29 (28.8)
AI@75bpm	Diabetic Non-diabetic Healthy control	9.33 (22.2) 13.93 (19.2) -7.25 (21.2)	15.33 (18.0) 22.72 (24.7)	16.89 (22.0) 33.67 (28.8)
IGF-I	Diabetic Non-diabetic	118.6(37.0) 89.4 (25.9)	110.8 (37.1) 90.1 (24.6)	106 (27.3) 94.8 (21.4)

At baseline a significant correlation was found between AI and systolic blood pressure (tau = 0.33 , P = 0.04) in the group with diabetes. A significant correlation between AI and heart rate was found in the group without diabetes (tau = -0.38, P = 0.04). No other correlations were found.

IGF-I

Shapiro-Wilk test showed normally distributed IGF-I values in both groups (P = 0.65 and P = 0.62). Significant baseline differences were found in IGF-I between the group with and without diabetes (P = 0.01) (see data in Table 2). A paired *t*-test showed no significant difference in the group with diabetes from baseline to the 30th treatment (P = 0.24). However, highly significant difference was observed from baseline to 90-day follow up (P = 0.001). No changes were found from baseline to the 30th treatment or 90-day follow-up in the group without diabetes (P = 0.44 and P = 0.79 respectively). No correlations were found between IGF-I and the other measured variables in either groups.

Discussion

We used the non-invasive peripheral arterial tonometry for measurements of endothelial function in patients undergoing sessions of HBOT.

In contrast to our hypothesis, we did not find any significant differences in endothelial function at baseline between the group with diabetes, the group without diabetes or the healthy controls. This surprising result might be a consequence of small sample sizes and high variabilities in RHI. Moreover, some regional anatomic disparities in PAD might exist. The lower extremities are more vulnerable to

the development of PAD[6] and a direct correlation to upper extremity RHI remains unproven. Even though several of the persons with diabetic foot ulcers in this cohort were likely suffering from severe PAD of their lower extremities, this was not mirrored by the measured RHI of the upper extremities (i.e., fingers) in this patient cohort as several patients had near normal RHI values at inclusion.

The baseline RHI values in the group with diabetes were on the threshold for classification as abnormal and this might complicate the evaluation of our second hypothesis – that courses of HBOT might improve RHI in persons with diabetes. The lack of significant baseline abnormality might help explain why no significant changes in RHI were observed. Although not registered in our trial files, the current cohort also consisted of some type 2 diabetes patients, whereas previous reports have described RHI index changes primarily in type 1 diabetes patients. Although PAD is a well-established complication for both groups, the predictive value of RHI index may vary between type 1 and type 2 patients.[27]

Peripheral arterial tonometry is well evaluated especially in relation to cardiovascular risk-factors and the prediction of adverse effects.[28,29] In patients with type 2 diabetes and microalbuminuria the method has been shown to be an independent predictor of coronary artherosclerosis.[30]

In a cohort of persons with diabetes (n = 123) the non-invasive test used here showed good reproducibility without significantly variations in RHI when assessed twice a day.[31] Furthermore, in 20 metabolic patients the technique has shown good test-retest reliability in a setup of five examinations separated by a minimum one-week period.[32]

It is well known that type 2 diabetes is associated with an increased risk of hypertension[33] and antihypertensive treatment in persons with diabetes significantly reduces cardiovascular risk.[34] We found elevated systolic blood pressure in the group with diabetes compared to the group without, however mean systolic blood pressure in the group with diabetes was almost 140 mmHg which is borderline normal and might be a result of rigorous antihypertensive treatment.

As alluded to above, the mean RHI values in the present cohort of persons with diabetes may be interpreted as representing borderline endothelial dysfunction; the tonometer manufacturer suggests that this state is defined by an index below 1.68.[35] In contrast to our study, others have shown significantly impaired endothelial function comparing to healthy individuals.[21,22] RHI values among persons with diabetes in those studies were not substantially different to values in the present study. However, due to lower RHI-values in the present cohort of healthy individuals and greater RHI variability among the persons with diabetes no significant differences were found in this study.

The diabetes and non-diabetes groups were different in other ways. The diabetes group consisted of more men, were older and had (on average) higher systolic blood pressure and increased BMI compared to the group without diabetes; all significant risk factors for impaired endothelial function. Therefore, it was unexpected that no difference in endothelial function was found between these groups at baseline.

Contrary to a study evaluating endothelial function by peripheral arterial tonometry in patients with diabetes undergoing coronary angiography[36] and in adolescents with uncontrolled type 1 diabetes,[37] we did not find any correlation between RHI and HbA1c in our cohort of persons with diabetic foot ulcers.

AI has shown to be associated with cardiac risk factors and coronary artery disease and may be a useful instrument to evaluate the overall risk for coronary artery disease.[38] A study evaluating microvascular endothelial function in persons with type 1 and type 2 diabetes showed significantly lower AI in persons with type 1 diabetes than healthy controls, while persons with type 2 diabetes were comparable to controls.[21] We did not observe any significant differences in AI between our cohort of subjects with diabetes (both type 1 + 2) and healthy controls. However, after standardizing AI to a heart rate of 75 bpm we did find differences between the persons with diabetes and the healthy controls. Perhaps surprisingly, the patient group without diabetes also varied significantly from healthy controls, which might draw attention to this group's overall morbidity; a group primary comprised of subjects with delayed radiation injury following cancer therapy including the use of chemotherapy. Unexpectedly, we observed a significant increase in AI among the subjects without diabetes over the course of HBOT, however after adjustment to AI@75bpm the difference became non-significant.

IGF-I, a pro-insulin like growth factor, is related to insulin resistance[39] and has shown to stimulate keratinocyte proliferation in the basal layer of epidermis.[40] A lack of IGF-I expression may be important in the delayed wound healing in diabetic foot ulcers. In a cohort of subjects with diabetes, IGF-I was shown to increase with sessions of hyperbaric oxygen therapy and to be a predictive factor of wound healing.[18] However, the present study demonstrated decreasing IGF-I levels over a course of HBOT which was statistically significant at the 90-day follow up.

To our knowledge, this is the first study to monitor endothelial function by peripheral arterial tonometry in subjects with diabetes undergoing a course of HBOT. Some certain limitations to this study consist. First, the combination of small sample sizes and high variability in RHI might have prevented finding any correlations and significant differences between groups. Second, the ulcers were not scored using acknowledged methods such as PEDIS or Wagner ulcer grading[41,42] which preclude assessment of the association between ulcer severity and endothelial function. Third, we

did not measure transcutaneous oxygen tension (TCOM), a quantitative assessment of oxygen availability and indirect measure of periwound microcirculatory bloodflow. The TCOM test is generally accepted as one of the most useful for prediction of failure to respond to HBOT. A comparison and evaluation of the linkage between peripheral endothelial function and periwound microcirculatory blood flow are needed. Finally, the subjects with diabetes treated with HBOT at our centre represents a group of patients with significant wound healing delay, often previous and multiple minor- and/or major amputations as well as a high degree of comorbidities with a median Charlson comorbidity index value of 5.[43]

Future studies should aim to evaluate the relationship between endothelial function in subjects with diabetic foot ulcer assessed by peripheral arterial tonometry and specific growth factors for neovascularization, such as VEGF. Future studies could aim to investigate the correlation between TCOM and peripheral arterial tonometry. Furthermore, studies investigating the association between endothelial dysfunction and the prediction of wound healing in subjects with diabetic foot ulcer are wanted.

Conclusions

This study demonstrated borderline impaired endothelial function measured by peripheral arterial tonometry among subjects with diabetic foot ulcers, however, no significant differences were found when compared to either a patient group without diabetes undergoing HBOT or healthy controls. There was no significant improvement in endothelial function during courses of HBOT in either patient cohort. However, given the baseline lack of substantial endothelial dysfunction (and therefore reduced scope for improvement) and the possibility that tonometry in the upper limb may not accurately reflect endothelial function in the lower limb, we cannot confidently exclude a positive effect of HBOT on lower limb endothelial dysfunction in subjects with diabetes.

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