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VASOMOTION CHANGES AFTER HYPERBARIC OXYGEN THERAPY IN DIABETIC PATIENTS

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ABSTRACT

Backround: Aim of this study was to assess changes in vasomotion during post-occlusive reactive hyperaemia in patients after hyperbaric oxygen therapy (HBOT).

Methods: 38 patients with type 2 diabetes mellitus underwent 15 sessions of HBOT consisting of 90 minutes of breathing 100 % oxygen at 2.5 atm. We used laser Doppler flowmetry (LDF) to assess vasomotion during post-occlusive reactive hyperaemia.

Results: We observed significant increase in endothelial (3.22 [2.07 – 5.31] vs. 4.91 [2.9 – 6.57], $p < 0.05$), neurogenic (0.64 [0.44 – 1.01] vs. 0.85 [0.53 – 1.63], $p < 0.05$), cardiac (9.22 [7.21 – 13.79] vs. 12.74 [8.66 – 16.83], $p < 0.05$) and total spectral activity (20.93 [15.97 – 27.88] vs. 27.96 [17.45 – 37.99], $p < 0.05$) after HBOT. No significant changes were observed in myogenic and respiratory spectral activity

Conclusion: Our study demonstrated vasomotion changes measured by LDF after HBOT.

KEYWORDS : hyperbaric oxygen therapy, vasomotion, post-occlusive reactive hyperaemia

BACKROUND

Hyperbaric oxygen therapy (HBOT) involves breathing 100 % oxygen in a pressurized room or tube and is a well-established first choice treatment for decompression sickness and gas poisoning. Although HBOT is widely used for the treatment of various clinical diseases, multiple studies indicated its benefit in conditions of vascular pathology with confirmed effect on healing of chronic wounds, prevention of minor or major amputations especially in diabetic patients [1, 2], improving the outcome of stroke [3], myocardial infarction [4, 5], acute peripheral extremity ischaemia [6] and reduced atherosclerotic plaques in animal models [7, 8]. Exact mechanisms that are involved in the actions of therapy with HBOT are mostly unknown, nevertheless its effects have been documented clinically and in experimental models [8, 9]. Studies suggest changes of vascular activity conducted by endothelial function as well as HBOT-induced promoting signalling pathways capable of changing protein expression and changes in concentrations of physiological mediators such as nitric oxide [NO], acetylcholine and metabolites of arachidonic acids [10, 11].

Microvascular dysfunction in diabetic patients is associated with longer duration of diabetes and chronic hyperglycaemia and it has been noted even in prediabetic subjects [12]. Changes in the blood flow condition and the vessel properties that are causing kidney, retina, neurological pathology [2] have been implicated in lower limbs in the development of foot complications and poor wound healing [13, 14]. The crucial role in a development and progression of diabetic complications has endothelial dysfunction related to the synthesis and function of NO. Moreover diabetic sensory and autonomic neuropathy is associated with worsening of functional capacity of microcirculation caused by capillary steal syndrome, diminished flow through capillaries and increased flow through arteriovenous shunts [15]. These changes result in impaired microcirculation and deterioration of tissue capacity for injury response. Measurement of microvascular function can aid the early detection of diabetes-induced microcirculatory damage and searching for high risk patients. .

Vasomotion is a product of multiple intracellular and intercellular systems, which seemingly interact with each other in variable combinations [16]. Vasomotion is a rhythmic contraction and dilation of arterioles leading to blood flow oscillations, specifically to blood flowmotion [17] controlled by autonomic nervous system, circulating substances, mechanical stimulation of vessels, myogenic, shear-dependent or metabolic response conducted along the vessels [18]. It is initiated when asynchronous cytosolic calcium concentration oscillations become synchronous within smooth muscle cells along the vascular wall through voltage-dependent Ca^{++} channels [16, 18, 19]. Vasomotion and subsequent flowmotion controls the local microvascular perfusion; maintain appropriate tissue blood flow despite the changes in arterial pressure and changes in nutrient concentrations. Flowmotion in patients with peripheral arterial disease and severe ischaemia is abolished as a consequence of impaired tissue dialysis and oxygen delivery [20]. Analysis of the flowmotion measured by laser Doppler flowmetry (LDF) revealed a broad spectrum of oscillation frequencies. High-frequency oscillations derived from the heart and respiratory movements are followed by several distinct bands of lower frequencies [16]. Further pharmacological intervention subdivided these frequencies into groups that are primarily dependent on the vascular endothelium, adrenergic activity and intrinsic smooth muscle activity. Many aspects of vasodilatation and vasomotion are still not fully recognised, causing that the use of vasomotion monitoring are in clinical practice limited.

The aim of this study was to investigate the effect of HBOT on vasomotion in diabetic patients using provocation test post-occlusive reactive hyperaemia (PORH) using LDF in patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

Participants

38 patients with type 2 diabetes mellitus (DM) were recruited and

underwent 15 HBOT sessions. The participants had neuropatic foot ulcer (n = 12, Wagner grade 2 - 3) or neuropathy (n = 26) without foot ulcer which was confirmed by electromyography. Neuropathy without the presence of foot ulcer is an off-label indication for HBOT therapy, therefore each patient was individually evaluated by hyperbaric specialist before study enrolment. Patients with foot ulcer underwent HBOT therapy following Undersea and hyperbaric medical society indication - enhancement of healing in selected chronic wounds. The exclusion criteria for subjects were oncology disease, severe hepatopathy, hypothyroidism or other known endocrinopathies, pregnancy, use of oral contraceptives or corticosteroids, treatment with vasodilator agents in past 6 months, surgery or endovascular intervention in past 6 months, HBOT in past 12 months. All subjects were informed, signed an informed consent and filled in a questionnaire about medical history. They were instructed not to change their daily regimen during the study period of 15 days (including diet or physical activity). The study was approved by the local ethics committee of University Hospital Bratislava and was conducted in accordance with the Declaration of Helsinki.

STUDY DESIGN

Protocol of HBOT therapy

HBOT was conducted in a hyperbaric oxygen chamber (Haux, Starmed, Germany) for 12 sitting patients. HBOT treatment (7 days per week) consisted of a 15-minute compression period to 2.5 atm, followed by 90 minutes of 100% oxygen inhalation at 2.5 atm with 2 pauses of 5 minutes without inhalation of 100 % hyperbaric oxygen, followed by a 15-minute decompression period. The total treatment time was 120 minutes for one session. 38 participants underwent 15 HBOT sessions. No subject discontinued the therapy.

Measurement of microcirculation

Measurements were conducted in morning hours in a quiet, temperature-controlled room (23-24 °C). Subjects were fasting, caffeine, alcohol and smoking was prohibited to consume 12 hours prior examination. Microcirculation was measured non-invasively by LDF system (Periflux 5000, Perimed, Stockholm, Sweden) equipped with a laser thermostatic probe (Probe 457, Perimed, Stockholm, Sweden) fixed on lateral side of right leg (10 cm above ankle) before administering HBOT and after 15 hyperbaric dives. The optimal cutaneous temperature was reached with light-weighted blanket covering the site while subject rested in supine position for 15 – 20 minutes before the test. We did not apply local skin heaters at 33°C in our protocol typical for physiologic studies because many patients had severe neuropathy which caused skin temperature above 33 °C at the baseline. Therefore, we wanted to avoid potential effect of cooling which could influence the results. The baseline skin temperature between the first and second visit did not differ more than 0.3 °C. The LDF signal has been recorded continuously by a computer equipped with acquisition software (PC Notebook, Lenovo, China). PORH measurements consisted of 3 minute monitoring of baseline skin perfusion, followed by inflation and occlusion of pressure cuff to 200 mmHg placed 15 cm above laser probe. After 3 minutes of occlusion and reduction of flow confirmed on the screen, cuff was abruptly released with continuous measuring of the post-occlusion flux followed by return to the baseline flux. Flux was measured in arbitrary perfusion unit. Vasomotion measurements were evaluated from LDF signals during PORH. Arterial blood pressure and respiratory rate were measured before and after each test.

DATA COLLLECTION AND STATISTICAL ANALYSIS

Data were analysed by Perisoft for Windows 2.5.5 software. Spectral analysis of LDF signals was performed using the fast Fourier transform analysis. Spectral power of skin vasomotion was calculated from spectral analysis curve as area under curve (AUC) [21]. The frequency spectrum was divided into five frequency intervals in hertz (Hz): 0.00095–0.021 Hz – endothelial, 0.021–0.052 Hz sympathetic activity, 0.052–0.145 Hz myogenic activity of the vessel walls, the band of 0.145–0.6 Hz consistent with respiration, 0.6–1.8 Hz due to transmission to cutaneous microcirculation of the haemodynamic modifications synchronous with heart [22]. Total vasomotion was obtained by the sum of considered intervals.

Statistical analysis was performed by using GraphPad Prism 5 software for Windows. The Kolmogorov-Smirnov test was used to verify the normal distribution of parameters in the cohort. The normally distributed data were analysed by paired t-test. Wilcoxon signed-rank test was used for abnormal distribution. Results are reported as the mean ± standard deviation or median and interquartile range. A two-tailed probability level $p < 0.05$ was considered significant. There were no concerning gender differences in measured data, therefore we analysed female and male data together.

RESULTS

38 patients (27 males, 11 females) with type 2 diabetes mellitus were enrolled to this study. Mean age of subjects was 62.4 ± 7.1 years with average duration of DM was 12.9 ± 8 years (Tab 1.).

Variables	Study group (n = 38)
Age (years)	62.4 ± 7.1
Gender - male, n (%)	27 (71.1%)
Duration of diabetes mellitus (years)	12.9 ± 8.0
BMI (kg/m2)	30.8 ± 5.5
Waist circumference (cm)	107.3 ± 15.5
Arterial hypertension	32 (82.1%)
Dyslipidaemia	26 (66.7%)
Periphery arterial disease	11 (28,94 %)
Neuropathy	38 (100 %)
Retinopathy	12 (30.8%)
Presence of ulcer (Wagner 2. – 3.)	9 (23.1%)
Smoking	6 (15,8 %)

Table 1. - Basic characteristics of the cohort. BMI – body mass index

There were no significant changes in arterial blood pressure, heart or respiratory rate (Tab. 2.).

Variables	Before HBOT (n = 38)	After HBOT (n = 38)	Significance
Fasting glucose (mmol/l)	7.73 [6.75 – 10.61]	8.01 [7.77 – 10.7]	NS
HbA1c (mol/mol IFCC)	57.1 ± 17.4	56.28 ± 16.42	NS
Creatinine (µmol/l)	77.92 ± 18.7	76.91 ± 19.99	NS
Blood pressure – systolic (mmHg)	131.2 [121.8 – 140.3]	130.4 [121.4 – 138.2]	NS
Blood pressure – diastolic (mmHg)	73.9 ± 10.3	72.7 ± 10.1	NS
Heart rate (/min)	72.4 ± 9.6	73.4 ± 9.2	NS
Respiratory rate (/min)	13.3 ± 1.6	13.9 ± 1.8	NS
RBC (1012/l)]	4.52 ± 0.42	4.51 ± 0.41	NS
Haemoglobin (g/l)	140.5 ± 13.1	139.5 ± 12.7	NS
Haematocrit	0.42 ± 0.03	0.43 ± 0.03	NS

Table 2. – Effect of hyperbaric oxygen therapy on selected parametres. HbA1c – glycated haemoglobin, RBC – red blood cell count. NS – non significant

We observed significant increase of endothelial spectral activity on ankle measured as area under curve (AUC) after HBOT; 3.22 [2.07 – 5.31] vs. 4.91 [2.9 – 6.57], $p < 0.05$ and likewise in neurogenic spectral activity; 0.64 [0.44 – 1.01] vs. 0.85 [0.53 – 1.63], $p < 0.05$ (Fig. 1.)

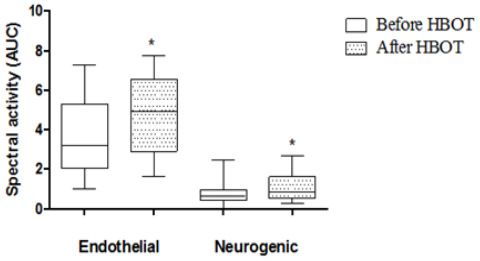


Figure 1. – Changes in endothelial and neurogenic activity. AUC – area under curve, HBOT – hyperbaric oxygen therapy.

Furthermore, changes were observed in cardiac spectral activity 9.22 [7.21 – 13.79] vs. 12.74 [8.66 – 16.83], $p < 0.05$ (Fig. 2). Total vasomotion, consisting of all frequency ranges [0.57 – 96 cycle per minute], increased significantly after HBOT; 20.93 [15.97 – 27.88] vs. 27.96 [17.45 – 37.99], $p < 0.05$ (Fig. 2., Tab. 3.).

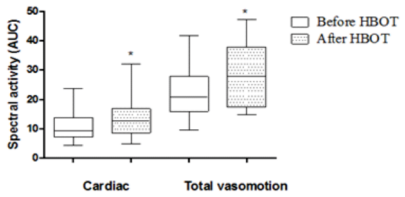


Figure 2. – Changes in endothelial and neurogenic activity. AUC – are under curve, HBOT – hyperbaric oxygen therapy.

Statistical significant changes were not observed in myogenic and respiratory spectral activity (Table 3.).

Vasomotion (AUC)	Before HBOT [n = 39]	After HBOT [n = 39]	P
Endothelial	3.22 [2.07 – 5.31]	4.91 [2.9 – 6.57]	< 0.05
Sympathetic	0.64 [0.44 – 1.01]	0.85 [0.53 – 1.63]	< 0.05
Myogenic	1.23 [0.81 – 2.2]	1.83 [1.01 – 2.61]	NS
Respiratory	3.83 [3.04 – 5.68]	4.2 [3.542 – 5.7]	NS
Cardiac	9.22 [7.21 – 13.79]	12.74 [8.66 – 16.83]	< 0.05
Total vasomotion	20.93 [15.97 – 27.88]	27.96 [17.45 – 37.99]	< 0.05

Table 3. - Spectral vasomotion activity before and after HBOT. AUC – area under curve, NS – non significant, $p < 0.05$ – significance.

DISCUSSION

This study aimed to determine changes in vasomotion after 15 sessions in hyperbaric chamber in patients with type 2 diabetes mellitus. Skin perfusion during baseline measures might not be impaired because of a compensatory mechanism related to increased endothelial, myogenic and sympathetic activities. However, during reactive testing such as post-occlusive hyperaemia these mechanisms appear to be exhausted in accordance with the reduced vasoreactivity to acetylcholine and sodium nitroprusside [23]. Previous reports have already shown that the spontaneous fluctuations in resting skin blood flow are absent or considerably reduced in diabetic patients [24] or in patients with peripheral arterial disease [23]. Therefore, we used a provocation test with post-occlusive reactive hyperaemia to assess vasomotion changes induced by HBOT.

The potentially beneficial effects of HBOT are still not completely known. On the one hand it might be mediated by oxygen supplementation trough hypoxic tissue, but on the other hand, HBOT could more importantly affect signalling cascades in cells and interact with numerous mechanisms which contribute to functional changes of blood vessels [25]. Upregulation of gap junctions with increased connexins expression leads to improved propagation of hyperpolarisation and depolarisation synchronous Ca^{2+} waves. Formation of oxygen dependant cytochrome P450 from family of the 4A omega-hydroxylases increases arachidonic acid metabolites and leads to conducted vasomotor response regulating vessel diameter. Furthermore, hyperbaric oxygenation affects formation of ROS, ATP and NO with changing expression of various proteins [11].

The vascular endothelium is a highly effective pathway for the conduction of electrical signals in the microcirculation and plays a key role in the pathogenesis of microangiopathy and neuropathy. It has been demonstrated that hyperglycaemia, acute or chronic, cause changes in vascular function, including a decrease in endothelium-dependent vasodilation and an increase in contractile response of vascular smooth muscle mediated by prostanoids [10, 26]. HBOT increases NO synthase activity leading to increase NO bioavailability with HBOT-induced vasodilatation [25]. This is consistent with our finding of significant change in endothelial function after HBOT. This result might suggest beneficiary effect on vascular function by modulating mechanism of vascular response suggesting restored vascular reactivity [11, 25].

It is well established that vasomotion is under strong modulatory influence by sympathetic innervation and previous studies presented impairment of microvascular components in both human and experimental diabetes [27]. Altered vasomotion in diabetes has been suggested as an early index of sympathetic dysfunction [16]. Animal models revealed a natural history of diabetic microangiopathy that the perivascular nerve was affected first, followed by the endothelial and myogenic components [28]. Autonomic nervous system is controlling microcirculation by regulating the tone of precapillary sphincters and flow through arteriovenous shunts. Neuropathy leads to redistribution of blood flow through arteriovenous shunts bypassing capillary bed with decrease in effective dialyses of the tissue and an abnormal capillary leakage [16, 29]. Impaired neurogenic vasomotion is associated with sudomotor dysfunction, cardiovascular autonomic neuropathy and peripheral diabetic neuropathy in high-risk diabetics [10, 27]. Early impairment of low-frequency vasomotion in diabetic patients was noted mainly in its neurogenic and endothelial components except the smooth muscle dysfunction. Previous investigations indicated that vascular smooth muscle was relatively resistant to change with progressive diabetic involvement and showed greater vulnerability of endothelial and neurogenic elements [28, 30]. Enhancing myogenic activity is affecting blood flow oscillations through changing vessel diameter by spontaneous constriction and dilation of arteriolar smooth muscles [31]. Based on these findings we might conclude changes in endothelial and neurogenic spectrum in our study could be the first line response to HBOT induced after 15 sessions. Although, we discovered changes in other low-frequency vasomotion areas, myogenic activity seems to be more resistant. Nevertheless, more profound changes in low-frequency spectral activity could be revealed after numerous hyperbaric treatments.

High frequency ranges are often confounded by other cardiovascular signals, which are often synchronous with respiration-induced changes in heart rate, blood pressure and baroreflex-induced changes suggesting passive downstream transmission [32]. Furthermore, isolated lower frequency bands abolishment was revealed during skin anaesthesia [33]. Despite this well-known fact, study performed by Podgoreanu, et al. revealed persistence of these high frequency bands independently of cardiac contractions and respiration in patients during nonpulsatile cardiopulmonary bypass [34]. It might suggest central and also peripheral origin of vasoregulatory mechanism in high frequency ranges. Despite no change in mean arterial pressure, heart and respiratory rate after HBOT therapy, we found significant changes in a higher spectral activity of frequency ranges represented by cardiac activity and total vasomotion measured on ankle after HBOT. We assume that higher spectral activity in cardiac frequency range is a result of increased sensitivity of microcirculation on flow mediated vasodilatation caused by increased sensitivity on vasodilator metabolites. Such restored microcirculation has potential to established laminar shear stress which acts on vessel wall. Regular laminar shear stress influenced an expression of important molecules involved in regulation of vasomotion [11]. Changes in respiratory spectral activity were not observed.

We have to address some potential limitations of the present study. Our limitation was sum of only 15 hyperbaric sessions and relatively small cohort size, but despite the fact we were able to determine significant changes and emphasized differences in important physiological function – vasomotion as a potential therapeutic target.

CONCLUSION

This study demonstrated changes in vasomotion after HBOT in diabetic patients. We observed significant increase in endothelial, neurogenic, cardiac and total vasomotion. Based on these findings, we can conclude that hyperbaric oxygen induces changes in vasomotor responses and influences vascular sensitivity and reactivity. All of this is making the role of hyperbaric oxygen and vasomotion changes very interesting and the complete understanding of it very challenging. However, stepwise investigation might result in the elucidation of these interactions and targeting new therapeutic strategies for management of diabetic patients.

Abbreviations:

HBOT – hyperbaric oxygen therapy, LDF – laser Doppler flowmetry, PORH – post-occlusive reactive hyperaemia, DM – diabetes mellitus, AUC – area under curve, Hz – hertz

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