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Effect of Hyperbaric Oxygen on Ophthalmic Artery Blood Velocity in Patients With Diabetic Neuropathy

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Abstract: To assess the relationship between blood flow and the complications of diabetes mellitus, we investigated the changes in the velocity of blood flow in the ophthalmic artery before and after hyperbaric oxygen therapy (HBO), one of the treatments for diabetic neuropathy. Color Doppler imaging was used before and after HBO. Seven diabetic neuropathy patients, 3 diabetics without neuropathy, and 7 normal, control subjects were enrolled. The patients were subjected to breathing 100% oxygen at 2.0 atmosphere absolute (ATA) for 1 hour. Hyperbaric oxygen therapy resulted in an average decrease in blood velocity by 15.0 ± 9.0% (mean ± SD) in normal subjects and 10.7 ± 8.6% in diabetics without neuropathy. Blood velocity returned to the baseline level 4 hours after discontinuation of HBO. In contrast, blood velocity increased by 20.6 ± 9.5% in diabetic patients with neuropathy irregardless of the severity of the diabetic retinopathy. The resistance index of the ophthalmic artery was not changed during HBO in the group with diabetic neuropathy, indicating that other mechanisms may be implicated, leading to the compensatory changes of blood flow. These results suggest that the increase in the blood velocity in the ophthalmic artery after HBO in diabetic neuropathy patients could be attributed to an imbalance in autonomic nervous function. **Jpn J Ophthalmol 1998;42:406–410** © 1998 Japanese Ophthalmological Society

Key Words: Blood velocity of ophthalmic artery, color doppler imaging, diabetic neuropathy, hyperbaric oxygen therapy.

Introduction

In clinical ophthalmology, hyperbaric oxygen therapy (HBO) has been used to treat retinal artery occlusion, ischemic optic neuropathy, acute retinal necrosis syndrome, cystoid macular edema as a complication of postoperative cataract surgery, diabetic retinopathy, and retinal vein occlusion. However, a plausible mechanism of how hyperbaric oxygen therapy (HBO) improves these diseases has not been fully ascertained.[1–4] Dollery et al[5] reported that HBO contributed to an increase of oxygen supply from the choroid, thereby increasing the supply of oxygen to the inner retina, even in cases with decreased retinal circulation. Flower and Patz[6] reported that HBO would improve the ischemia of the inner retina in cats and dogs with impaired retinal circulation. However, another study on retinal circulation revealed that oxygen breathing induced a local constriction of blood vessels resulting in a decrease of blood flow.[7]

Color Doppler imaging (CDI) has been used to diagnose retinal circulatory disorders, including ischemic ocular syndrome due to internal carotid artery occlusion.[8–12] Recently, CDI was employed to monitor drug-induced changes in ophthalmic circulation.[13,14]

In the present study, we used CDI to determine the blood flow velocity in the ophthalmic artery after

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HBO. The effects of HBO on ophthalmic artery circulation were documented in patients with diabetic neuropathy who are sometimes treated with HBO as an effective intervention.

Subjects and Methods

This study was performed at Kure National Hospital between September 1995 and April 1996. The subjects enrolled in this study consisted of 7 diabetic patients (14 eyes) with diabetic neuropathy requiring HBO for pain relief (age 53.6 ± 20 years, mean ± SD), 3 diabetic patients (6 eyes) without diabetic neuropathy requiring HBO for treatment of idiopathic deafness and facial paralysis (age 52.3 ± 5.1 years, mean ± SD), and 7 healthy volunteers (14 eyes) age 45.3 ± 17.5 years). Diabetic neuropathy was diagnosed based on the patient's complaints and a physical examination. Patients with neuropathy are usually annoyed by sensory disturbances in the extremities indicative of a glove-and-stocking type of pain distribution. None of these subjects had a history of cardiovascular disease. Informed consent was obtained from all subjects after the purpose and procedure of HBO were fully explained.

There were no significant differences in the demographics such as age, duration of diabetes, fasting blood sugar, or hemoglobin A1c between the two diabetic groups (Table 1). Ophthalmoscopic examination revealed that none in the group without neuropathy (6 eyes) had diabetic retinopathy, whereas 5 in the group with neuropathy (10 eyes) had retinopathy (simple diabetic retinopathy in 4 eyes, preproliferative diabetic retinopathy in 2 eyes, and proliferative diabetic retinopathy in 4 eyes).

To assess the effects of HBO on ophthalmic circulation, we determined the peak systolic blood flow velocity in the ophthalmic artery of each subject before, upon completion of HBO, and at 1-hour intervals for up to 4 hours after HBO for a total of six measurements. Systolic blood pressure, pulse rate, and partial oxygen pressure detected by a skin saturation monitor, were also measured at each monitoring time.

We used a SSA-260A Color Doppler Imaging unit (Toshiba, Tokyo) and a PLF-703 NT linear probe specifically designed to examine superficial blood vessels (7.5 MHz). For HBO, patients breathed 100% oxygen via a face mask for 1 hour in a chamber (KHO-300, Kawasaki Engineering, Kawasaki) at 2.0 ATA. Subjects entered the study after lunch and were instructed to refrain from eating, smoking, and drinking beverages containing caffeine for at least 4 hours after HBO.

Peak systolic velocity and end-diastolic velocity in the ophthalmic artery were measured. For better interpretation, a resistance index (RI) ratio indicating a relative alteration of the peak systolic velocity ([peak systolic velocity − end-diastolic velocity] / peak systolic velocity) was calculated.

The significance of the differences in the observed effects of HBO on hemodynamic parameters between the study groups was tested by analysis of variance (ANOVA). Post-hoc comparisons were conducted with paired *t*-test using Bonferroni's correction for multiple comparisons; a P value of < 0.05 was regarded as statistically significant.

Results

Significant differences were not found in the systolic blood pressure, pulse rate, or oxygen partial pressure in the three groups at baseline and at subsequent times after HBO. In addition, no significant differences were observed in the peak systolic velocities in the ophthalmic artery in the three groups before HBO. The mean of the peak velocity was 0.37 ± 0.08 m/s (mean ± SD) for the healthy volunteer group, 0.28 ± 0.07 m/s for the diabetics without neuropathy, and 0.32 ± 0.09 m/s for the diabetics with neuropathy.

Table 1. Clinical Characteristics of Patients in the Study Group

	Normal (n = 7)	DN (−) (n = 3)	DN (+) (n = 7)	*P* value
Age (y)	45.3 ± 11.5	52.3 ± 5.1	53.6 ± 20	n.s
Duration of diabetic (y)		6.3 ± 3.2	4.7 ± 2.6	n.s
FBS (mg/dL)		130.7 ± 12.0	196.3 ± 64.6	n.s
HbA1c (%)		8.5 ± 2.0	10.5 ± 3.0	n.s

DN(−): diabetic patients without neuropathy, DN(+): diabetic patients with neuropathy, n.s: not significant. Mean ± SD.

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In the normal subject group, the peak systolic velocity in the ophthalmic artery decreased significantly immediately after HBO, and the decrease was maintained for up to 3 hours after HBO. The maximum decrease was 21.0 ± 8.7%, and the value returned to the pre-HBO level after 4 hours. The mean blood velocity decreased by 15.0 ± 9.0% after HBO (Figure 1).

The end-diastolic velocity in normal subjects decreased significantly immediately after HBO and the decrease was maintained for 3 hours after HBO (Figure 2). Nevertheless, RI was not significantly different in the neuropathy group over this period (Figure 3).

In the diabetic group without neuropathy, a decrease in the blood peak systolic velocity was noted immediately after HBO but it did not become statistically significant until 1 hour after HBO. The value returned to the pre-HBO level after 2 hours. In contrast, the peak systolic velocity in the ophthalmic artery increased by 20.6 ± 9.5% in the diabetic neuropathy group, with a maximum increase of 22.3 ± 8.2%. The increase remained statistically significant for up to 4 hours after HBO. After HBO in the diabetics without neuropathy, the average decrease in blood velocity was 10.7 ± 8.6% with a return to the baseline level 4 hours after completion of HBO. These results showed that the difference in the decrements of the peak systolic velocities between the group without diabetic neuropathy and the healthy group turned out to be significant 1 hour after HBO (Figure 1). The end-diastolic velocity in the group without neuropathy increased significantly immediately after HBO; however, it returned to the baseline level 1 hour after HBO (Figure 2). Resistance index decreased significantly in the same patient group immediately after HBO, and returned to the baseline level 1 hour after HBO (Figure 3).

In contrast, the peak systolic velocity increased by about 20.6 ± 9.5% in diabetic patients with neuropa-

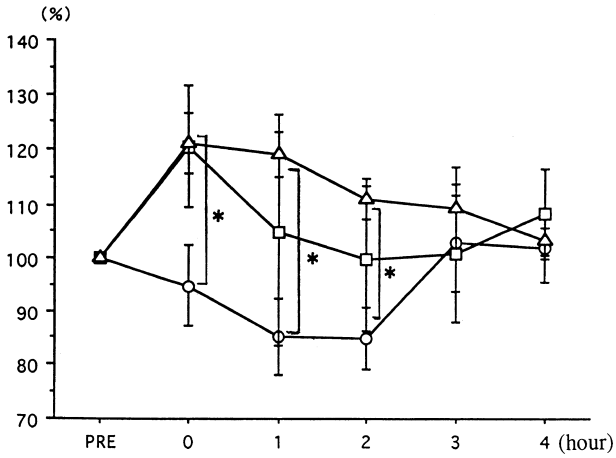

Figure 2. Time course of relative changes of end-diastolic velocities in ophthalmic artery after HBO in diabetic neuropathy patients (n = 14, △), diabetic patients without neuropathy (n = 6, □), and normal subjects (n = 14, ○). Error bars represent standard error of means. * *P* value <0.05 was considered significant.

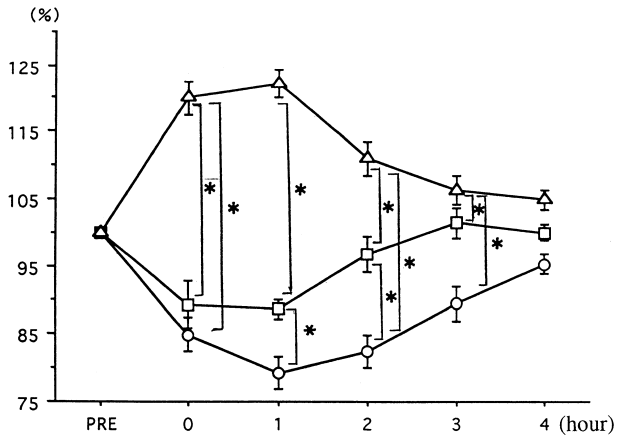

Figure 1. Time course of relative changes of peak systolic velocities in ophthalmic artery after HBO in diabetic neuropathy patients (n = 14, △), in diabetic patients without neuropathy (n = 6, □), and in normal subjects (n = 14, ○). Error bars represent standard error of means. *P value of <0.05 was considered significant.

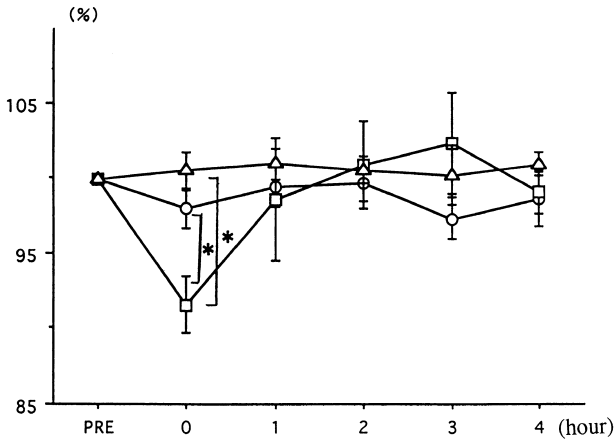

Figure 3. Time course of relative changes of RI after hyperbaric oxygen in diabetic neuropathy patients (n = 14, △), diabetic patients without neuropathy (n = 6, □), and normal subjects (n = 14, ○). Error bars represent standard error of means. *P value <0.05 was considered significant.

thy regardless of the severity of diabetic retinopathy. The difference between the diabetic neuropathy and healthy volunteer groups was significant immediately after HBO (Figure 1). End-diastolic velocity in the neuropathy patients increased significantly from immediately after HBO and then returned to the baseline level 4 hours after completion of HBO. (Figure 2). However, the RI was not significantly different in the same patient group over the period (Figure 3).

Significant differences between the study groups were verified by ANOVA, with peak systolic velocities, $P < 0.001$; End-diastolic velocities, $P = 0.02$; and RI, $P = 0.04$.

Discussion

In this study, the mean peak systolic velocity in the ophthalmic artery before HBO was within the normal values for all groups ([0.306–0.439] + [0.065–0.166] m/s, [mean ± SD]). These normal values were determined by Kaiser et al based on published normal values.[15] Tamaki et al[16] reported that the peak systolic velocity in the ophthalmic artery of diabetic patients without retinopathy (0.26 ± 0.05 m/s) was not significantly different from that of the diabetic retinopathy group. No correlation was found between the severity of diabetic retinopathy and the peak systolic velocity in the ophthalmic artery, unlike the findings in previous reports.[16–18] It should be noted, however, that they did not include patients with diabetic neuropathy in their study.

Riva et al[7] reported changes of blood flow in the retina following oxygen breathing. They measured blood flow in the retina after 5 minutes of 100% oxygen breathing in healthy subjects using a Laser Doppler Velocimeter (LDV) they constructed. They reported that the blood flow in the retina deceased by 53%, but when the vessel diameter was taken into account, the blood flow decreased by 64%. Grunwald et al[19] performed a study using LDV in healthy subjects and in 16 patients with insulin-dependent diabetes mellitus (IDDM) complicated by background diabetic retinopathy. They found that after 100% oxygen breathing the blood velocity in the retina decreased by 46% in healthy subjects and by 20% in diabetic patients.

Although our study was different from the previous studies in that the measurements were of the ophthalmic artery instead of the retinal vessels, and our patients breathed 100% oxygen for 1 hour at a pressure of 2.0 ATA instead of 1.0 ATA, similar results were obtained; that is, the blood velocity in the ophthalmic artery decreased in the diabetic group without neuropathy and in the healthy group. In contrast, the blood velocity increased in the diabetic group with neuropathy irregardless of the severity of the retinopathy.

Evans et al[20] measured the blood velocity in the ophthalmic artery under 100% oxygen breathing in 11 patients with IDDM and 11 age-matched healthy subjects. They reported that the peak systolic velocity was unchanged in the healthy group but was significantly decreased in the IDDM patient group, which is inconsistent with our findings. This disagreement may be accounted for by the fact that their subjects were younger (29.5 ± 8.6 years) and were exposed to 100% oxygen via a face mask, but not in a chamber as in HBO therapy.

RI is regarded as a better index of the downstream vascular resistance than a single parameter including either peak systolic or end-diastolic velocity. It is still open to question as to why RI decreased in only diabetics without neuropathy, particularly at the termination of HBO.

Peak systolic velocity and end-diastolic velocity in the ophthalmic artery significantly increased immediately after HBO, and then returned to the baseline level 4 hours after completion of HBO in the diabetic neuropathy group. Blood flow in the carotid artery, however, remained constant because there were no alterations in RI over that period.

Tamaki et al[16] reported that no significant difference in the RI was observed for the various stages of diabetic retinopathy. Evans et al[20] measured the blood velocity in diabetic patients and found that their blood velocities were higher than their counterparts in the healthy group. They also found that the RI remained unchanged in the healthy group but was significantly decreased in the IDDM patients following 100% oxygen. Their findings are not consistent with ours in that no differences were detected between the healthy and the diabetic groups in our study.

Blood velocity in other parts of the body has been investigated using CDI in patients with diabetic neuropathy. Best et al[21] measured pre- and postprandial blood velocity in the mesenteric artery and the celiac artery in diabetics with neuropathy, diabetics without neuropathy, and healthy subjects. They found that the preprandial blood velocities in the mesenteric artery were 0.23 ± 0.02 m/s in the healthy group, 0.23 ± 0.03 m/s in the diabetic group without neuropathy, and 0.34 ± 0.06 m/s in the diabetic group with neuropathy. Postprandial, the blood velocity decreased slightly in the diabetic neuropathy

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group but increased significantly ($P < 0.01$) in the other two groups. The change in the blood velocities at these sites in the diabetics with neuropathy was in the opposite direction than the changes in the diabetics without neuropathy and the healthy volunteers. Fujii et al[22] investigated the alteration in skin blood flow after oral intake of sugar. They found that the skin blood flow decreased transiently after 30 minutes in the healthy group, decreased less in the diabetics without neuropathy, and remained unchanged in the diabetics with neuropathy. This suggested that dermal blood flow changed in a similar manner in the diabetics without neuropathy and the healthy groups under different types of loading, whereas the diabetic neuropathy group changed in the opposite direction. However, the patterns of change in blood velocity, whether an increase or a decrease, was not identical.

In summary, the blood velocity in the ophthalmic artery decreased after HBO in the healthy volunteers and the diabetics without neuropathy, but increased in the group with diabetic neuropathy. Nevertheless, the RI of the ophthalmic artery did not change in the group with diabetic neuropathy. The alterations in blood velocity of this patient group because similar to that of the diabetics without neuropathy after HBO. The responses to various types of loads in the diabetics with neuropathy were different from those in the diabetics without neuropathy and healthy groups. The cause for these differences is still unknown. According to a study of the R-R interval of the electrocardiograms, the switching of the sympathetic nerve and parasympathetic nerve malfunctions in patients with diabetic neuropathy, indicated an autonomic imbalance.[23] Increase in blood velocity after oxygen breathing only in the diabetics with neuropathy suggests a certain disorder involved in nervous or vasomotor control in the ophthalmic artery.

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