Does Hyperbaric Oxygen Therapy have a Role in Diabetic Autonomic Neuropathy?

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ABSTRACT

Objectives: To determine if hyperbaric oxygen therapy could benefit patients with diabetic autonomic neuropathy treated at our hospital.

Methods: Thirty-one consecutive patients, who were treated at Princess Haya Hospital and Prince Hahim Bin Abdullah II hospital from January 2012 to April 2014, were included. Four tests of autonomic function were carried out on all patients before and after treatment in the hyperbaric recompression chamber. Data analyzed using Statistical Package for the Social Sciences version 17 and stata version 10.

Results: Twenty male and eleven female patients were included, with a mean age of 53.6 years. About 84% had Type II diabetes. Seventy-one percent of patients were found to have greater than or equal to three abnormal tests prior to treatment, and the risk of autonomic neuropathy was found to be independent of patients' sex, age, type or duration of diabetes. A statistically significant improvement was found in all tests after hyperbaric oxygen therapy. The improvement in parasympathetic function was found to be more likely affected by the number of sessions than sympathetic function (*P* value 0.001 and 0.07, respectively)

Conclusion: Hyperbaric oxygen therapy is a promising technology in the treatment of diabetic autonomic neuropathy. Further research which includes a control group is needed.

Key words: Hyperbaric oxygen therapy, Diabetic autonomic neuropathy, Diabetic foot ulcer.

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Introduction

Diabetic autonomic neuropathy (DAN) is a disorder of the autonomic nervous system in the setting of diabetes or metabolic derangements of pre-diabetes after the exclusion of other causes.[1] Major clinical manifestations of DAN include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, hypoglycemic autonomic failure and incontinence.[2,3] The prevalence is estimated to be approximately 20%–70%, depending on the test's cohort.[4] Among the most serious DAN is cardiovascular autonomic neuropathy (CAN), which encompasses damage to the autonomic

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nerve fibers that innervate the heart, affecting heart rate and blood pressure control and vascular dynamics. CAN is associated with increased mortality, silent myocardial ischemia, and may even predict the development of stroke.[5] Many studies showed a 50% increase in 5 year-mortality risk in diabetic patients with autonomic neuropathy compared to those without.[6]

Given the complexity of the autonomic system, there is no single test that precisely reflects function of a specific branch of this system. Most of the tests are based on evaluation of the cardiovascular reflexes triggered by performing specific provocative manoeuvres. The current evidence suggests that these tests reflect autonomic nervous damage not only in the heart but also elsewhere in the body.[7] Traditionally, batteries of autonomic tests have been introduced, with the Ewing battery being the most popular. It is widely used in diagnosis of diabetic autonomic neuropathy and it comprises Valsalva maneuver, response to deep breathing, orthostatic testing and isometric exercise.[8]

Therapeutic intervention with a range of vasoactive drugs improves nerve function in animal models. Promising results in diabetic patients have also been achieved using a range of therapies, including large - vessel revascularization, ACE inhibitors, g-linoleic acid, and lipoic acid.[9] Response to these therapies emphasizes the vascular mechanism in the pathogenesis of DAN, and since hyperbaric oxygen therapy (HBOT) is known to improve tissue perfusion and reverse hypoxia,[10] it is hypothesized that it may have a role in management of DAN. Indeed, few studies have been done on the subject and reported a beneficial effect of HBOT.[9,11]

The aim of this study was to examine the effect of HBOT on patients with DAN seen in the department of HBOT at Princess Haya Hospital and Prince Hashim Bin Abdullah II Hospital.

Methods

Thirty one consecutive diabetic patients were included in this study. Inclusion criteria included all patients referred to HBOT department from January 2012 to April 2014 for the treatment of diabetic foot ulcers and have no contraindication for HBOT. They were treated in the HBOT department at Princess Haya Hospital and Prince Hashim Bin Abdullah II Hospital. All treatments were provided in a multiplace recompression chamber at 2.4 atmospheric absolute pressures where patients breathe 100% oxygen for 90 minutes with intervals of air breathing.

Four tests of autonomic function were done for each patient twice: before starting treatment and after the last session. These tests included:

A. Two tests for parasympathetic function:

1. Valsalva Ratio (VR): the patients were asked to blow into a semiclosed mouthpiece for 15 seconds and the heart rate (HR) is recorded. Then they release and the HR is recorded again. In normal subjects, during the Valsalva maneuver the HR rises and after release it slows. By dividing the highest rate by the lowest it gives the VR. Normally it is >1.21 but this response is decreased in DAN which results in lower VR.
2. Inspiratory-Expiratory Rate (IE rate): The patients were asked to take 6 deep breaths in a minute and the HR was measured during inspiration and expiration and the difference was recorded. Normally there will be >15 beats difference, but in DAN this response is decreased (sometimes there will be no difference at all).

B. Two tests for sympathetic function:

1. Fall in systolic blood pressure (SBP) on standing: the blood pressure was measured with patient in supine position then on stand up and the drop in SBP was recorded. In normal subjects this drop is <10mmHg, while in patients with DAN it is higher.
2. Rise in diastolic blood pressure (DBP) on sustained handgrip: The blood pressure reading was taken and then the patients were asked to grip on a sphygmomanometer cuff for 5 minutes and blood pressure was taken again before release. Normally DBP rises on handgrip by >16mmHg but in patients with DAN it is lower.

Table I: Patients demographics

Age(years)	
Mean	53.6
Range	16-75
Sex	
Male	20 (64.5%)
Female	11(35.5%)
Type of Diabetes	
Type I	5 (16.1%)
Type II	26 (83.9%)
Duration of Diabetes(years):	
Median	15
Range	2-23
Number of HBOT sessions:	
Mean	14.3
Range	8-20
Pre-treatment DAN tests results:	
One abnormal test	9 (29%)
Two abnormal tests	0 (0%)
Three abnormal tests	4 (12.9%)
Four abnormal tests	18 (58.1%)

Table II: The results of 4 tests of DAN* before and after treatment with HBOT** (Wilcoxin signed rank test)

	VR‡		**IE Rate†**		**SBP‡‡ Drop on standing**		**DBP†† increase on handgrip**	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Mean	1.1677	1.3097	12.48	16.81	12.71	11.13	8.77	11.32
Median	1.1000	1.3000	12.00	17.00	11.00	10.00	8.00	11.00
Range	1.00-1.60	1.10-1.70	4-24	7-26	2-40	2-33	5-20	7-22
P value	<0.001		<0.001		<0.006		<0.001	

*DAN: Diabetic Autonomic Neuropathy **HBOT: Hyperbaric oxygen therapy ‡VR: Valsalva Ratio
†IE Rate: Inspiratory –Expiratory Rate ‡‡SBP: Systolic Blood Pressure ††DBP: Diastolic Blood Pressure

Data analyzed using Statistical Package for the Social Sciences (SPSS) version 17 and stata version 10. Descriptive statistics were used for patient's characteristics. Regression analysis was used to determine the effect of sex, age, duration and type of diabetes on the prevalence of DAN. To compare and follow the changes in the four tests, Paired samples t test, repeated measure ANOVA test and Wilcoxon signed rank test were used. *P* values <0.05 were considered statistically significant.

Results

Twenty males and eleven females were included; with a mean age of 53.6 years. Patients demographics are shown in Table I. All patients had type II diabetes mellitus except four patients with type I. The mean duration of diabetes was 12.7 years. Before treatment; all patients had at least one abnormal test of autonomic function, while 71% had more than or equal to three abnormal tests. Regression analysis showed that the risk of DAN did not differ significantly with patient age, sex, duration or type of diabetes.

The patients received a mean of 14.3 HBOT sessions. After the post-treatment autonomic evaluation was done; paired samples t test, repeated measure ANOVA and Wilcoxin signed rank tests were run. These tests showed a statistically significant improvement in all the 4 tests of autonomic function, results are shown in Tables II and III and represented in Fig. 1. The improvement in parasympathetic function was found to be more likely affected by the number of sessions than sympathetic function (*P* value was 0.001 and 0.07 respectively). Patients received more than 15 sessions showed a more significant improvement (*P* value 0.01).

Table III: The results of 4 tests of DAN* before and after treatment with HBOT** (paired samples t test)

		95% Confidence interval					
		Mean	**Lower**	**Upper**	**t**	**df**	**Sig. (2-tailed)**
Pair 1	V\R‡ ratio before -V\R ratio after	-.14194	-.18713	-.09674	-6.414	30	.000
Pair 2	I-E† rate before - I-E rate after	-4.323	-5.286	-3.360	-9.167	30	.000
Pair 3	SBP‡‡ decrease on standing before - SBP decrease on standing after	1.581	.575	2.586	3.210	30	.003
Pair 4	DBP†† increase on grip before-DBP increase on grip after	-2.548	-3.197	-1.900	-8.030	30	.000

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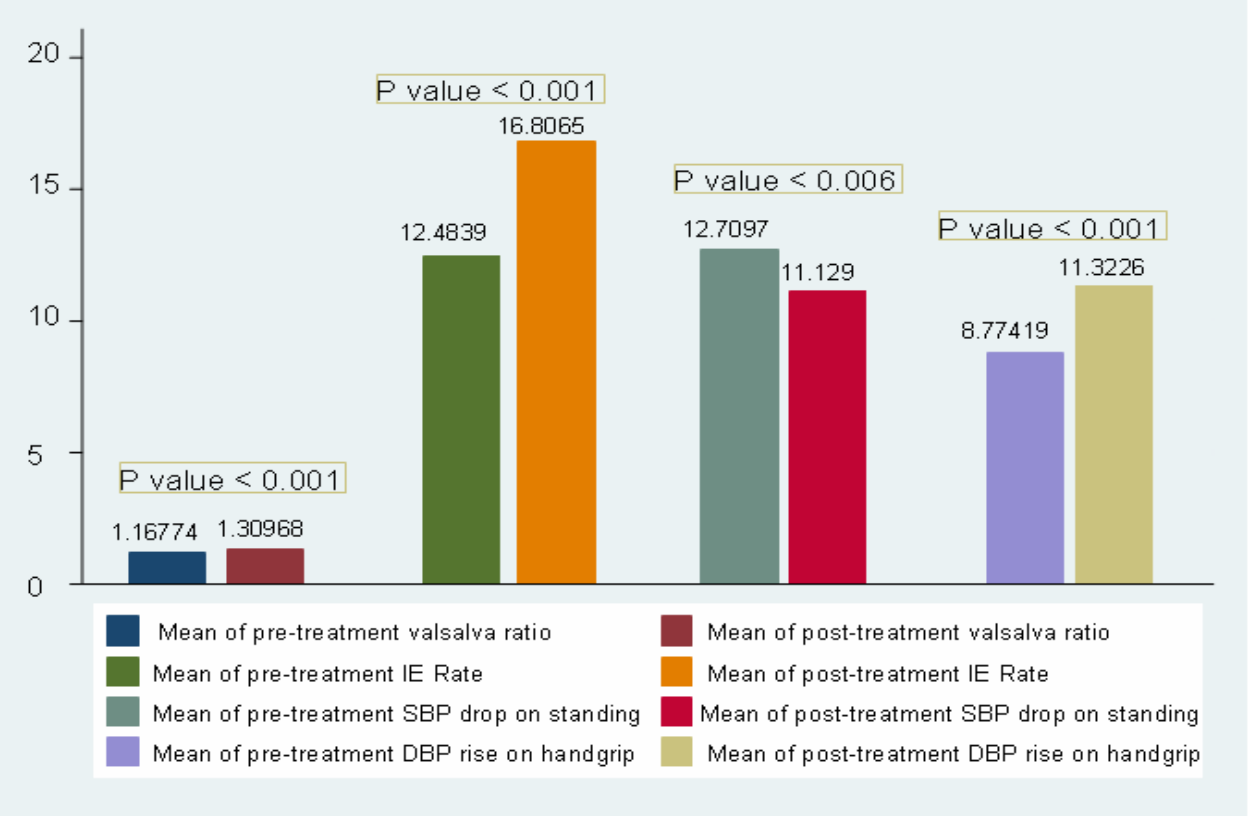

Fig. 1: Comparing changes in autonomic function tests results before and after HBOT
(IE Rate: Inspiratory-Expiratory Rate, BP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HBOT: Hyperbaric oxygen therapy)

Discussion

Diabetic neuropathy (DN) is the most common and troublesome complication of diabetes mellitus, and accounts for more hospitalizations than all the other diabetic complications combined, and is responsible for 50% to 75% of nontraumatic amputations. DN is a heterogeneous disorder that encompasses a wide range of abnormalities affecting proximal and distal peripheral sensory and motor nerves as well as the autonomic nervous systems.[12] DAN is among the least recognized and understood complications of diabetes, whose symptoms range widely from comparatively minor pupillary and sweating problems to significant disturbances in cardiovascular, alimentary, and genitourinary function, which result in increased patient morbidity and mortality.[13]

The prevalence of autonomic neuropathy in diabetics was estimated to be approximately 20-70%. Low *et al*. (2004) reviewed the autonomic symptoms and standardized autonomic testing of

patients with diabetes mellitus (Type I and II) and of control patients, and find that 54% of patients with Type 1 diabetes, and 73% of patients with Type 2 diabetes had objective autonomic impairment (while autonomic symptoms were present more commonly in type I than in type II diabetes).[14] Elisabeth *et al*. (2012) reported that more than 56% of patients had at least one abnormal test and the prevalence was higher in type II diabetes patients than in type I diabetes patients (27.8% vs 20.6 %, respectively; P=0.02). The same study showed that duration and old age were risk factors for DAN.[15] This correlation was proved by some studies while rejected by others.[16-18] Our study showed that all patients had at least one abnormal test and 71% had three or more abnormal tests. Also we didn't found that age, sex, duration or type of diabetes to be independent risk factors for DAN. The high prevalence of DAN in our study might be related to the type of study population. All our patients had foot ulcers and, as shown by Ahmed *et al*. (1986), DAN is greater in diabetic patients with ulcers than diabetics without ulcers.[18] Relation between foot ulcers and DAN had been reported in many studies. A prospective study by Boyko *et al*. demonstrated the effect of DAN on the risk of developing a foot ulcer independent of other measures of sensory neuropathy.[19] DAN is associated with postural instability while walking and abnormal distribution of foot pressure. Also, there is decreased circulatory transit time in the foot, and this may well diminish tissue oxygenation.[17,18]

The pathogenesis of DAN remains uncertain. Hyperglycemia plays the key role in the activation of various biochemical pathways related to the metabolic and/or redox state of the cell (balance between oxidants and antioxidants), which, in concert with impaired nerve perfusion; contribute to the development and progression of diabetic neuropathies. Experimental data implicate a number of pathogenic pathways that may impact autonomic neuronal function in diabetes including: formation of advanced glycation end products, increased oxidative / nitrosative stress with increased free radical production, activation of the polyol and protein kinase C pathways, activation of polyADP ribosylation, and activation of genes involved in neuronal damage.[20-22] This impaired nerve perfusion theory inspired researchers to investigate the possible role of HBOT in management of neuropathy, and the results were in favor of HBOT in most of these studies.[23-26] Nevertheless, most these studies focused on the sensory neuropathy while few searched the HBOT role in autonomic neuropathy.[9,11,26]

Our study showed a significant improvement in all autonomic function tests after HBOT. Cihan Top *et al.* (2002) showed similar results.[9] Also, this improvement tended to be more pronounced for parasympathetic than sympathetic function which emphasized the significant vagotonic effect of HBOT as shown by Sub TB *et al*. (2006) in a randomized controlled trial.[11] In contrast to sympathetic functions, we found that improvement in parasympathetic functions depends on the number of treatment sessions, with at least 15 sessions given to gain the most benefit. A limitation of our study was the lack of a control group.

Since DAN affects most body organs and associated with increased morbidity and mortality, it seems relevant to screen diabetic patients for its presence. The above described tests should be done for patients at presentation. An easy to use handheld device(Vagus™) was developed to facilitate patients testing in a short time.[15] Also, a simple, noninvasive device, Sudoscan™, can evaluate autonomic function by measuring sweat gland function.[27] Finally, it should be stressed that near-normal glycemic control remains the most efficient way of delaying the onset of and controlling DAN.[2,21,28,29]

Conclusion

DAN cause damage to most body organs and associated with increased morbidity and mortality. HBOT is a promising technology that may result in a significant improvement in autonomic function. Further studies are needed in this field due to scarcity of studies on this subject and the lack of control group in most of these studies, including ours.

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