ORIGINAL RESEARCH

N-terminal pro-B-type natriuretic peptide levels increases after hyperbaric oxygen therapy in diabetic patients

Senol Yildiz¹

Gunalp Uzun¹

Omer Uz²

Osman Metin Ipcioglu³

Ejder Kardesoglu²

Omer Ozcan³

Departments of ¹Underwater and Hyperbaric Medicine, ²Cardiology, ³Clinical Biochemistry, Gulhane Military Medical Academy Haydarpasa Teaching Hospital, 34668, Uskudar, Istanbul, Turkey

Manuscript submitted 5th March, 2008

Manuscript accepted 5th July, 2008

Clin Invest Med 2008; 31 (5): E231-E235.

Abstract

Purpose: Diabetic patients receive hyperbaric oxygen therapy for non-healing lower extremity ulcers. Exposure to hyperbaric hyperoxia during hyperbaric oxygen therapy may affect cardiovascular functions by different mechanisms. Patients may experience serious problems such as pulmonary edema and death during hyperbaric oxygen therapy. The effect of hyperbaric oxygen therapy on cardiovascular functions in diabetic patients is not well documented. N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been suggested as powerful biochemical marker of cardiac function. The aim of this study was to investigate the effect of hyperbaric oxygen therapy on NT-proBNP levels in diabetic patients.

Methods: Twenty-five diabetic patients (19 male and 6 female, 64.7 ± 10.2 yr), who were planning to undergo hyperbaric oxygen therapy for non-healing lower extremity ulcers, were prospectively enrolled into the study. All patients were evaluated with echocardiography before the study. Heart rate and arterial blood pressure of patients were measured, and venous blood samples were drawn from each patient for NT-proBNP analysis before and immediately after the hyperbaric oxygen therapy.

Results: NT-proBNP levels increased from 815 ± 1096 pg/ml to 915 ± 1191 pg/ml after HBO₂ therapy ($P < 0.05$). Heart rate and arterial blood pressure did not change with HBO₂ therapy ($P > 0.05$).

Conclusion: Hyperbaric oxygen therapy induces considerable ventricular wall stress in diabetic patients. Care should be taken when a diabetic patient with cardiovascular disease is treated with hyperbaric oxygen therapy.

Hyperbaric oxygen (HBO₂) therapy is frequently used in the treatment of foot complications in diabetic patients. During HBO therapy, patients are exposed to 100% oxygen at a pressure between 2 to 3 atmospheres absolute (ATA). Diabetes mellitus is associated with various kinds of cardiovascular problems including coronary artery disease, left ventricular systolic and diastolic dysfunction and congestive heart failure.¹ Exposure to hyperbaric hyperoxia may affect cardiovascular function by different mechanisms. HBO₂ therapy increases systemic vascular resistance, induces bradycardia and reduces cardiac output.²⁻⁴ The effects of HBO₂ therapy on cardiovascular homeostasis are well tolerated in patients without cardiovascular pathology. However, patients with underlying cardiac disease may experience serious problems such as pulmonary edema and death during HBO₂ therapy.⁵

B-type natriuretic peptide (BNP) is a cardiac neurohormone. It is synthesized as a 108-aminoacid-long prohormone termed proBNP, which is stored in secretory granules in ventricular myocytes. On secretion into circulation, proBNP is cleaved in equal proportions into biologically inactive N-terminal pro-BNP (NT-proBNP; 76 amino acids) and biological active BNP (32 amino acids). The cardiac production and plasma concentration of NT-proBNP is very low in healthy subjects.⁶ A small amount of proBNP is stored in myocytes and gene expression is the main regulator of peptide secretion. The proBNP gene expression increases very rapidly in response to an appropriate stimulus.⁷ The main stimulus for increased BNP and NT-proBNP synthesis and secretion is myocardial wall stress as a result of ventricular volume expansion and pressure overload.^{8,9} Both peptides, therefore, have been suggested as powerful biochemical markers of myocardial stress/dysfunction.^{9,10}

Little is known about the influences of environmental factors on plasma levels of BNP and NT-proBNP. In a recent study, Grassi et al.¹¹ investigated the effect of HBO₂ therapy on BNP levels in healthy subjects and reported no change after HBO₂ therapy. The effect of HBO₂ therapy on plasma NT-proBNP levels in diabetic patients has not been evaluated previously.

We hypothesized that changes in NT-proBNP levels could provide additional information about how hyperbaric hyperoxia (HBO₂ therapy) effects the ventricular function in diabetic patients. The aim of this study was to evaluate the effect of HBO₂ therapy on NT-proBNP levels in diabetic patients.

Materials and Methods

The study was approved by the Institutional Ethics Committee of the Gulhane Military Medical Academy, and all patients gave written informed consent before participation. The study group consisted of 26 diabetic patients with non-healing lower extremity ulcers referred to our department for HBO₂ therapy

between May 2007 and September 2007. Patients with pulmonary emboli, cirrhosis, pulmonary hypertension, renal failure, malignity, tuberculosis, acute coronary syndrome, and acute pulmonary edema were excluded from the study.

Echocardiography (Vivid 3, General Electrics) was performed before the first HBO₂ therapy in all patients. Left ventricular, left atrial and aortic diameters, ejection fraction, left ventricular wall thickness, and left ventricular diastolic function were evaluated. Arterial blood pressure and heart rate was measured after 30 min rest before entering the hyperbaric chamber. Arterial blood pressure and heart rate measurements were repeated within 15 minutes after the HBO therapy.

Venous blood sample was drawn from each patient for NT-proBNP measurement at resting position before the first HBO₂ therapy. Patients received routine hyperbaric treatment including three 30 min oxygen periods with two 5 min air breaks at 2.4 atmospheres absolute (ATA) in a multiplace hyperbaric chamber. Together with compression (10 min) and decompression periods (10 min), the total duration of the HBO₂ therapy was 120 min. Just after the treatment, a second venous blood sample was drawn for NT-proBNP measurement. Blood samples were sent immediately to the biochemistry laboratory. Serum was separated and stored at -80 °C until the all samples were collected. NT-proBNP was measured using Elecsys ® proBNP assay (Roche Diagnostics, Basel, Switzerland) according to the manufacturer's guidelines.

Statistical analyses were performed using commercially available software (SPSS Inc. 10.0, Chicago, IL). Pre- and post-HBO₂ values were compared using Wilcoxon signed rank test. A *P* value < 0.05 is regarded as statistically significant.

Results

Twenty-six patients were included in the study. One patient did not come for HBO₂ therapy and was excluded from the study. The clinical characteristics of

TABLE 1. Clinical characteristics of patients (mean $\pm$ SD).

Age (yr)	64.7 $\pm$ 10.2
Sex (M/F)	19/6
Diabetic age (yr)	12.0 $\pm$ 9.0
Hypertension (n)	21 (84%)
Smoking (n)	12 (48%)
Fasting blood sugar (mg/dl)	157 $\pm$ 45
Hemoglobin A1c (%)	8,5 $\pm$ 1,9
Body mass index (kg/m ²)	25,4 $\pm$ 3,5
Cholesterol (mg/dl)	149 $\pm$ 20
Triglyceride (mg/dl)	126 $\pm$ 70
HDL cholesterol (mg/dl)	42 $\pm$ 37
LDL cholesterol (mg/dl)	94 $\pm$ 25
VLDL cholesterol (mg/dl)	25 $\pm$ 14

the remaining 25 patients (19 male, 6 female) are presented in Table 1. Mean age of the patients was 64.7 $\pm$ 10.2 yr (range: 45 to 78 yr) and the mean duration of diabetes was 12.0 $\pm$ 9.0 yr (range: 1 to 26 yr).

Echocardiographic characteristics of patients are presented in Table 2. Mean left ventricular ejection fraction was 57.9 $\pm$ 8.8% and left ventricular end-diastolic diameter was 46.2 $\pm$ 7.2 mm. None of the patients had decompensated heart failure. Systolic dysfunction was detected in two patient and diastolic dysfunction in three patients. Right ventricular diameter and function were in the normal range in all patients. NT-proBNP levels, arterial blood pressure and heart rate of patients before and after HBO₂ therapy are presented on Table 3. Heart rate and arterial blood pressure of patients did not change with HBO₂ therapy. However, NT-proBNP levels increased 12.9 $\pm$ 13.1 % after HBO₂ therapy (915 $\pm$ 1191 pg/ml) compared with the pretreatment values (815 $\pm$ 1096 pg/ml) (P <0.05). None of the patients experienced a complication related to HBO₂ therapy during the study period.

Discussion

Our results demonstrated that serum NT-proBNP levels increases after HBO₂ therapy in diabetic patients without overt cardiovascular disease. HBO₂ therapy favourably increases the amount of oxygen dissolved

TABLE 2. Echocardiographic characteristics of patients (mean $\pm$ SD)

Ejection fraction (%)	57.9 $\pm$ 8.8
Left atrial dimension (mm)	37.2 $\pm$ 8.4
Aorta dimension	28.1 $\pm$ 4.5
IVS diastole	10.7 $\pm$ 2.1
IVS systole	12.5 $\pm$ 2.1
LV end-diastolic dimension (mm)	46.2 $\pm$ 7.2
LV end-systolic dimension (mm)	34.8 $\pm$ 10.1

IVS: Intraventricular septum; LV: left ventricular

TABLE 3. Heart rate, arterial blood pressure and NT-proBNP levels before and after hyperbaric oxygen (HBO₂) therapy in diabetic patients (mean $\pm$ SD).

	Before HBO ₂	After HBO ₂	P
Heart rate (min ⁻¹)	84.6 $\pm$ 10.5	82.8 $\pm$ 9.7	0.398
Systolic blood pressure (mmHg)	129.0 $\pm$ 17.9	127.0 $\pm$ 18.2	0.690
Diastolic blood pressure (mmHg)	73.1 $\pm$ 12.5	75.8 $\pm$ 10.6	0.713
NT-proBNP (pg/ml)	815 $\pm$ 1096	915 $\pm$ 1191	<0.001

in the arterial blood and leads to hyperoxia even in poorly perfused tissues.¹² HBO₂ induced hyperoxia increases systemic vascular resistance by peripheral vasoconstriction.^{2,4} In addition, it has been shown that acute exposure to hyperbaric hyperoxia increases left ventricular wall stress.⁴ We suggest that increased systemic vascular resistance induced left ventricular wall stress in diabetic patients and augmented secretion of NT-proBNP.

Since this is the first study to investigate the effect of HBO₂ therapy on NT-proBNP levels in diabetic patients, it is not possible to compare our results with others. However, Grassi et al. investigated the effect of HBO₂ therapy on BNP levels in a small group of healthy volunteers.¹¹ The HBO₂ therapy protocol in their study was very similar to our protocol. Eight subjects were exposed to %100 O₂ at 2.5 ATA for 90 min in a hyperbaric chamber. BNP levels were measured at three time points: before the HBO₂ therapy, immediately at the end of the therapy, and at 5 hours from the beginning of the therapy. In contrast to our findings, they found that BNP levels did not change with HBO₂ therapy. The differences between the study

of Grassi et al. and our study may explain the discrepancy in the results. While our study group consisted of diabetic patients, they included healthy volunteers who are also relatively younger than our study group (32.3 yr vs. 64.7 yr; respectively). Grassi et al.¹¹ reported that BNP levels were within normal values at all times in their study subjects. Although none of the patients had decompensated heart failure or experienced acute myocardial ischemia during the study period, NT-proBNP levels were higher than normal in most of the patients. Similar results have been reported by Magnusson et al.¹³ who found increased levels of NT-proBNP in diabetic patients without overt cardiovascular disease. The myocardium in diabetic patients is adversely affected by local and systemic factors induced by diabetes. Currently, a concept of diabetic cardiomyopathy or diabetic heart disease has been proposed. This describes the development of left ventricle dysfunction (diastolic and/or systolic) that is independent of hypertension and coronary artery disease.¹⁴ It may be speculated that ventricular myocardium is more vulnerable to release NT-proBNP in the presence of an appropriate stimulus in diabetics than normal subjects. In addition, cardiac autonomic neuropathy may also contribute to the release of NT-proBNP from myocardium in diabetic patients. Taken together, we postulate that the acute effects of HBO₂ therapy on cardiovascular homeostasis is well tolerated in healthy young subjects but in diabetics with a degree of cardiovascular pathology, HBO₂ may exert significant effects.

There are limitations of our study. The first one is NT-proBNP levels were measured only just after HBO₂ therapy. Therefore we do not know how NT-proBNP levels proceeded in the first 24 hours after HBO₂ therapy. Another limitation is the low number of patients recruited into the study. Our results should be confirmed in a larger study.

We conclude that HBO therapy induces significant ventricular wall stress in diabetic patients and care should be taken when a diabetic patient with cardiovascular disease is treated with HBO₂ therapy.

References

1. Ali Raza J, Movahed A. Current concepts of cardiovascular diseases in diabetic patients. *Int J Cardiol.* 2003;89:123-34.
2. Neubauer B, Tetzlaff K, Staschen CM, Bettinghausen E. Cardiac output changes during hyperbaric hyperoxia. *Int Arch Occup Environ Health.* 2001;74:119-22.
3. Abel FL, McNamee JE, Cone DL, Clarke D, Tao J. Effects of hyperbaric oxygen on ventricular performance, pulmonary blood volume, and systemic and pulmonary vascular resistance. *Undersea Hyperb Med.* 2000;27:67-73.
4. Molénat F, Boussuges A, Grandfond A, et al. Haemodynamic effects of hyperbaric hyperoxia in healthy volunteers: an echocardiographic and Doppler study. *Clin Sci (Lond).* 2004;106:389-95.
5. Weaver LK, Churchill S. Pulmonary edema associated with hyperbaric oxygen therapy. *Chest.* 2001;120:1407-9.
6. Due-Andersen R, Pedersen-Bjergaard U, Hoi-Hansen T et al. NT-proBNP during hypoglycemia and hypoxemia in normal subjects: Impact of renin angiotensin system (RAS) activity. *J Appl Physiol.* 2008;104:1080-5.
7. Mantymaa P, Vuolteenaho O, Marttila M, Ruskoaho H. Atrial stretch induces rapid increase in brain natriuretic peptide but not in atrial natriuretic peptide gene expression in vitro. *Endocrinology* 1993;133:1470-3.
8. Magga J, Marttila M, Mantymaa P, Vuolteenaho O, Ruskoaho H. Brain natriuretic peptide in plasma, atria, and ventricles of vasopressin and phenylephrine-infused conscious rats. *Endocrinology* 1994;134:2505-15.
9. Iwanaga Y, Nishi I, Furuichi S, et al. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure. Comparison between systolic and diastolic heart failure. *J Am Coll Cardiol.* 2006;47:742-8.
10. Pemberton CJ, Johnson ML, Yandle TG, Espiner EA. Deconvolution analysis of cardiac natriuretic peptides during acute volume overload. *Hypertension.* 2000;36:355-9.
11. Grassi P, Buscema G, Rinaldi A, Gobbato PE, Berlot G. B-type natriuretic peptide in healthy subjects after exposure to hyperbaric oxygen at 2.5 ATA. *Aviat Space Environ Med.* 2007;78:52-3.
12. Sheikh AY, Gibson JJ, Rollins MD, Hopf HW, Hussain Z, Hunt TK. Effect of hyperoxia on vascular endothelial growth factor levels in a wound model. *Arch Surg.* 2000;135:1293-7.

13. Magnusson M, Melander O, Israelsson B, Grubb A, Groop L, Jovinge S. Elevated plasma levels of Nt-proBNP in patients with type 2 diabetes without overt cardiovascular disease. *Diabetes Care*. 2004;27:1929-35.
14. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: Evidence, mechanisms, and therapeutic implications *Endocrine Reviews*. 2004;25:543-567.

Correspondence to:

Gunalp Uzun, MD
Department of Underwater and Hyperbaric Medicine
Gulhane Military Medical Academy, Haydarpasa Teaching
Hospital
34668, Kadikoy, Istanbul, Turkey
E-mail: gunalpuzun@yahoo.com