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Hyperbaric Oxygen Therapy Decreases QT Dispersion in Diabetic Patients

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Diabetes mellitus is frequently associated with the malignant ventricular arrhythmias and sudden death. The QT dispersion is the difference between the longest and shortest QT interval calculated from the standard 12-lead electrocardiogram. The QT dispersion is suggested as an index of myocardial electrical activity. An increase in QT dispersion is associated with the malignant ventricular arrhythmias and sudden cardiac death. Diabetic patients receive hyperbaric oxygen (HBO) therapy for non-healing lower extremity ulcers. The aim of this study was to determine the effect of HBO therapy on QT dispersion in diabetic patients. Thirty diabetic patients (18 male and 12 female, 59.9 ± 10 years), who were planning to undergo ten sessions of HBO therapy in two weeks for non-healing lower extremity ulcers, were consecutively enrolled into the study. The 12-lead resting electrocardiography recordings were taken before the first HBO therapy and after the 10th HBO-therapy session. QT intervals were measured on electrocardiogram. QT intervals were corrected for heart rate by using Bazett's formula (corrected QT [QTc] = QT/$\sqrt{R}$ – R [seconds]). QTc dispersion was significantly decreased from 59.8 ± 17.4 msec to 52.2 ± 15.5 msec after ten sessions of HBO therapy ($p < 0.05$). However, maximum QTc, minimum QTc and mean QTc did not change significantly after HBO therapy. We have concluded that HBO therapy may reduce the risk of malignant ventricular arrhythmia and sudden cardiac death in diabetic patients when applied repetitively. ——— hyperbaric oxygenation; diabetes mellitus; QT interval; electrocardiography.
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Diabetes mellitus is a systemic disease associated with profound morbidity and mortality (Ford et al. 2002). After a prolonged period of diabetes it is commonly accompanied with multiple cardiovascular complications such as coronary artery disease, diabetic cardiomyopathy, and cardiac autonomic neuropathy (Ali Raza and Movahed 2003). Myocardial ischemia can lead to electrophysiological heterogeneity and asynchronism in ventricular myocardium (Roukema et al. 1998). In addition, altered sympathovagal balance in the presence of cardiac autonomic neuropathy may contribute to electrophysiological heterogeneity of the myocardium (Ewing et al. 1991). The abnormalities in myocardial repolarization are a risk factor for the occurrence of the rhythm disturbances and sudden death in diabetic patients. The QT interval on the standard 12-lead electrocardiogram (ECG) shows the depolarisation and repolarisation duration of the left ventricular myocardium. QT dispersion, which is the difference between the longest and shortest QT interval, is an index of myocardial electrical activity. It was demonstrated that an increase in QT dispersion is associated with the malignant ventricular arrhythmias and sudden death in diabetic patients (Christensen et al. 2000).

Hyperbaric oxygen (HBO) therapy involves the inhalation of 100% oxygen at a pressure higher than 1 atmosphere absolute (ATA). Diabetic patients receive HBO therapy for non-healing lower extremity ulcers. HBO favorably increases the amount oxygen delivered to the tissues. Recently, it was demonstrated that HBO therapy improves cardiac neural regulation in patients with diabetic autonomic dysfunction (Sun et al. 2006). To the best of our knowledge, the effect of HBO therapy on QT dispersion in diabetic patients has not been studied before. This study aimed to evaluate the alterations of QT interval and QT dispersion in diabetic patients after ten repetitive HBO therapy sessions.

Subjects and Methods

Thirty diabetic patients (59.9 ± 10 years), who were planning to undergo HBO therapy for non-healing lower extremity ulcers, were consecutively enrolled into the study. The study was approved by the Gulhane Military Medical Academy Ethical Committee, and informed consent was obtained from each patient before enrollment.

Patients diagnosed with coronary artery disease, acute coronary syndrome, congestive heart failure (either compensated or not), dilated cardiomyopathy, left ventricular ejection fraction lower than 55%, chronic renal failure, poor clinical condition, or complicated extensive diabetic ulceration and patients using chronic beta blocker treatment were excluded at the onset of the study.

HBO therapy was performed in a multiplace hyperbaric chamber (Galeazzi Co., Livorno, Italy) that accommodates 16 patients at the same time. Patients were compressed to 2.5 ATA in 10 minutes and then began breathing 100% oxygen via a tight fitting face mask. Patients were exposed to 100% oxygen for three oxygen periods (30 min each) interspersed with two air breaks (5 min each). The patients were then decompressed in 10 min. The total duration of each HBO therapy was 120 min. Patients received HBO therapy once a day from Monday to Friday. In total, 10 sessions of HBO therapy were performed as five weekly sessions.

All patients were evaluated by using transthoracic echocardiography before the initiation of HBO therapy. Systolic and diastolic blood pressures were measured. Fasting serum glucose levels, HbA_1c levels, and serum K^+ levels were measured from the blood samples obtained at a fasting state before the first and after the tenth HBO therapy. The 12-lead surface electrocardiography recordings at 50 mm/sec and 10 mm/mV for an optimum analysis (Glancy et al. 1996) were obtained with Kenz-Cardico 1210 Electrocardiograph (Suzuken Co., Nagoya) before the first HBO therapy and after the tenth HBO therapy.

ECG recordings were analyzed digitally on computer by one individual blinded to the clinical data in a disorganized sequence. QT interval was measured from the beginning of the QRS complex to the end of the T wave. Corrected QT (QTc) intervals were calculated by using Bazett's formula ($QTc = QT/\sqrt{R\text{-}R[\text{seconds}]}$). Properties of QTc interval such as minimum QTc (min QTc), maximum QTc (max QTc), mean QTc were measured. Min QTc and max QTc are the minimum and the maximum QTc intervals among all QTc intervals which were calculated from each surface derivation of 12 lead electrocardiograms. QTc dispersion was calculated as the difference between the longest (max) and shortest (min) QTc intervals (QTc dispersion = QTc max – QTc min).

Data were presented as mean ± standard deviation (S.D.). Pre-treatment and post-treatment values were

compared by using Wilcoxon signed rank test. A $p < 0.05$ was regarded as statistically significant. Statistical analyses were performed using SPSS for Windows 10.0 (SPSS Inc., Chicago, IL, USA).

Results

The study group consisted of 30 diabetic patients (mean age 59.9 ± 10 years). Of these patients, 18 were male and 12 were female. The diabetic age of the patients were 10.3 ± 6.3 years. Mean echocardiographic left ventricular ejection fraction was 66.5 ± 7.2% and left ventricular end-diastolic diameter was 50.5 ± 5.4 mm. Systolic and diastolic blood pressures, fasting serum glucose levels, serum HbA_1c levels and serum potassium levels which measured before and after the whole HBO therapy were not significantly different ($p > 0.05$).

Changes in QTc interval and QTc dispersion are presented in Table 1. QTc dispersion significantly decreased after ten HBO therapy sessions ($p < 0.05$). However, max QTc, min QTc and mean QTc did not change significantly after HBO therapy. In addition, there was not any significant change in heart rate of the patients after HBO therapy.

Discussion

QT dispersion is a strong predictor of cardiac death in patients with diabetes mellitus (Naas et al. 1998). It was also suggested that QTc dispersion could be a better predictor of mortality than microalbuminuria in diabetics (Darbar et al. 1996; Sawicki et al. 1996). Our study results demonstrated that HBO therapy decreased QTc dispersion in diabetic patients when applied repetitively for two weeks.

Ischemic myocardium may play a significant role as an arrhythmic substrate due to intracardiac inhomogeneities of repolarization (Roukema et al. 1998). Asymptomatic myocardial ischemia is of a high prevalence among diabetic patients even in the lack of significant coronary artery stenosis (Koistinen 1990). Although we induced the diabetic patients with documented coronary artery disease, we could not strictly clarify the absence of ischemia or coronary artery disease in our study group by invasive methods. Ischemia refers to lack of oxygen due to inadequate perfusion, which results from an imbalance between oxygen supply and demand. HBO therapy favorably increases oxygen content of plasma. Also HBO leads hyperoxia even in poorly perfused tissues. So improvement of silent ischemia induced by HBO may be one of the probable explanatory mechanisms for improved QT dispersion.

Additionally, diabetes may lead increased pro-inflammatory response due to endothelial

Table 1. Clinical, laboratory and electrocardiographic data before and after hyperbaric oxygen (HBO) therapy.

	Before HBO therapy	After HBO therapy
Heart rate (beats/min)	79.6 ± 6.3	78.8 ± 6.5
Systolic blood pressure (mmHg)	126.7 ± 18.8	128.5 ± 19.3
Diastolic blood pressure (mmHg)	72.4 ± 11.5	73.2 ± 10.8
K^+ (mEq/l)	3.94 ± 0.14	4.11 ± 0.24
Fasting serum glucose (mg/dl)	165.4 ± 63.6	157.1 ± 82.8
HbA_1c concentration (%)	8.1 ± 2.4	7.9 ± 2.1
Minimum QTc (msec)	380.8 ± 31.5	383.3 ± 23.2
Maximum QTc (msec)	440.7 ± 24.7	435.5 ± 19.1
Mean QTc (msec)	410.7 ± 26.9	409.4 ± 19.8
QTc dispersion (msec)	59.8 ± 17.4	52.2 ± 15.5*

Data are presented as mean ± S.D.
*$p < 0.05$

dysfunction, increased oxidative stress, aggravated platelet, and coagulation hyperactivity (Hink et al. 2001). QTc abnormality was also suggested as a surrogate indicator of subclinical atherosclerosis, increased carotid intima media thickness, and future strokes in Type II diabetic patients (Cardoso et al. 2003). Diabetes may also affect myocardial microvasculature negatively by inducing neutrophil and increasing cellular adhesion molecules (ICAM-1 and P-selectin) in circulation (Niwa et al. 1996; Buras et al. 2000). HBO may improve endothelial cell function, proliferation, and neovascularization by inducing reactive oxygen species at a plausible level. HBO induced those cardio-protection mechanisms may alleviate the tissue ischemia (Yogaratnam et al. 2006). HBO treatment given prior to and during ischemic insult increased the survival of myocardium and ATP preservation (Yogaratnam et al. 2006). This was a significant finding which suggested that undamaged integrity of cellular structure and tissue was a prerequisite to gain the greatest benefit from HBO (Yamada et al. 1995; Chen et al. 1998). We suggest that improvement in QT dispersion may be associated with various myocardial protection effects induced by HBO therapy.

Early deterioration of cardiac neural regulation in diabetic patients is inevitable because of lack of tight glycemic control (Kempler et al. 2002). Myocardial repolarization is under neural control and the heterogeneity might be affected by changes in cardiac neural activity induced by diabetes (Perkiomaki et al. 1996). Sun et al. (2006) reported that HBO therapy improved cardiac neural regulation in patients with diabetic autonomic dysfunction. They concluded that the vagotonic effect induced by HBO therapy improved cardiac neural regulation (Sun et al. 2006). Improvement of QTc dispersion of our study group might be ascribed to favorable effects of HBO therapy on diabetic autonomic dysfunction. Moreover improvement in QT dispersion may be resulted by summing of the vagotonic effects induced by a whole consecutive HBO therapy sessions (Lund et al. 1999, 2000).

Additionally, Earle et al. (2000) reported that urinary albumin excretion positively correlated with QT dispersion in type I diabetic patients. Importantly, they suggested that QT abnormalities can occur independently of autonomic dysfunction or myocardial ischemia in diabetic patients. Similarly, our study group is of high probability of having abnormal QTc dispersion due to diabetes and independently of ischemia or autonomic dysfunction. So HBO therapy may have been improved QTc dispersion in a study group similar to Earle et al. (2000) by cardio-protective effects of which the exact mechanisms could not be clarified yet.

In this study we excluded the diabetic patients with documented coronary artery disease, but we did not strictly evaluate the absence of myocardial ischemia in study group. Also we did not evaluate the presence of autonomic dysfunction in study group. Those are the limitations of our study.

We concluded that HBO therapy may improve the myocardial electrical homogeneity and reduce the risk of malignant ventricular arrhythmia and sudden cardiac death in diabetic patients. Further research is needed to better define the role of HBO therapy in myocardial protection in diabetics.

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