Hyperbaric Oxygen Therapy Improves Myocardial Diastolic Function in Diabetic Patients

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Myocardial diastolic dysfunction is the relaxation abnormality of ventricles that limits the diastolic filling and generally precedes diastolic heart failure. Diastolic dysfunction is a common finding in diabetes. Diabetic patients receive hyperbaric oxygen (HBO) therapy for non-healing lower extremity ulcers, and exposure to HBO therapy is known to influence cardiovascular functions. This study was designed to evaluate the effect of HBO therapy on myocardial diastolic function in diabetic patients. Thirty diabetic patients (18 male and 12 female, 59.9 ± 10 years old), who were planning to undergo HBO therapy, were consecutively enrolled. Myocardial diastolic function was evaluated by pulsed wave Doppler echocardiography and tissue Doppler echocardiography before the first HBO therapy and after the tenth HBO therapy session. HBO therapy improved the relaxation capability of left ventricular myocardium, which was reflected by reduction in E wave deceleration time of mitral valve inflow (286.1 ± 65.8 msec vs 214.3 ± 32.1 msec, $p < 0.05$). HBO therapy also affected favorably the diastolic filling dynamics of right ventricle, which was partially reflected by the changes in E wave peak velocity of tricuspid valve inflow (0.48 ± 0.07 m/sec vs 0.46 ± 0.09 m/sec, $p < 0.05$). Tissue Doppler parameters of mitral lateral annulus, which are better correlated with ventricular relaxation, tended to be improved after HBO therapy, but the degree of improvement was not statistically significant. In conclusion, we suggest that HBO therapy may improve the myocardial diastolic function of diabetic patients when applied repetitively. —————— echocardiography; tissue Doppler; diabetes mellitus; hyperbaric hyperoxia; diastolic dysfunction.
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Diabetes is associated with a markedly increased prevalence of coronary artery disease, which affects 55% of adult diabetic patients compared to 2-4% of adults in the general population (Fein and Scheur 1990). High levels of metabolic derangements, insulin resistance, endothelial dysfunction, abnormal inflammatory response, and hypercoagulability promote the development and progression of atherosclerosis (Hink et al. 2001; Yan et al. 2003) and also adversely impact left ventricular systolic and diastolic function (Hink et al. 2001). Furthermore, specific patterns of coronary vascular disease observed in diabetes such as narrow vessel caliber, impaired collateral development, diffuse endothelial, and micro vascular dysfunction have been described (Goraya et al. 2002). Consequently, myocardium in diabetic patients is adversely affected by local and systemic factors that are induced by diabetes. The impairment of systolic function and particularly diastolic function is inevitable in diabetic patients (Airaksinen et al. 1984). Currently, a concept of diabetic cardiomyopathy or diabetic heart disease is also proposed. It describes the independent development of left ventricle (LV) dysfunction (diastolic and/or systolic dysfunction) in the absence of hypertension, coronary artery disease, etc. (Fang et al. 2004). It was reported that a primary functional abnormality in the diabetic heart was the impairment of LV diastolic function, which may or may not be associated with an overt cardiac disease (Zabalgoitia et al. 2001).

M-mode echocardiography as well as the Doppler echocardiography are still the most applicable, reproducible and widely available methods of evaluating myocardial function in symptomatic and asymptomatic diabetics. Non-invasive assessment of diastolic function relies mainly on the measurement of parameters of mitral and tricuspid valve inflow and annuluses using pulsed wave Doppler and tissue Doppler.

Hyperbaric oxygen (HBO) therapy involves the inhalation of 100% oxygen at a pressure higher than 1 atmosphere absolute (ATA). HBO therapy has been extensively used as an adjunctive therapy for non-healing ulcers in diabetic patients for the last two decades. The use of HBO therapy for myocardial protection via improved oxygen availability and various cellular mechanisms is still under investigation. HBO therapy has recently been proposed as a promising therapy for cardiovascular diseases (Yogaratnam et al. 2006). From the viewpoint of new areas of application for HBO, we focused on evaluating the probable effects of HBO therapy on myocardial diastolic function in diabetic patients. In support of this goal, we performed transthoracic echocardiography, pulsed wave Doppler and tissue Doppler echocardiography on the diabetic patients before the first HBO therapy and after tenth HBO therapy session in order to assess the systolic and diastolic function of the left and right ventricles. Molénat et al. (2004) conducted an echocardiographic and Doppler study and reported hemodynamically negative effects of acute hyperbaric hyperoxia, however their study group was composed of healthy and relatively young volunteers without any cardiac or diabetic disease. Also, the above-mentioned issue was the acute effect developed over a short period of time ranging from 15 min to 5 hrs (Molénat et al. 2004). Consequently, our protocol for HBO therapy was strictly different and could be an objective model for exploring whether HBO therapy can be used for myocardial protection in diabetics.

SUBJECTS AND METHODS

Patients

Diabetic patients admitted to the department of hyperbaric medicine for non-healing lower extremity wounds were consecutively enrolled into the study. The study was approved by the Institutional Ethical Committee, and informed consent was obtained from each patient before enrollment.

Exclusion criteria

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.

Hyperbaric oxygen therapy

HBO treatments were performed in a multiplace hyperbaric chamber that accommodates 16 patients at the same time. Patients were compressed to 2.5 ATA in 10 min 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 for 10 min. The total duration of each HBO therapy was 120 min. Patients received HBO treatments once a day from Monday to Friday. In total, 10 sessions of HBO therapy were performed as five weekly sessions. Standard echocardiography, pulsed wave Doppler echocardiography, and tissue Doppler imaging were performed on patients before the first session of HBO and one day after the 10th session of HBO therapy.

Transthoracic Echocardiography

Transthoracic echocardiography was performed by VingMed System Five with a 2.5 MHz probe (GE Medical System, Hortan, Norway). From the parasternal long-axis view, left ventricular end-diastolic (LVDD) and end-systolic diameters (LVDS), left ventricular ejection fraction (LVEF) and left atrial diameter (LAD) were measured by M-mode echocardiography. The measurements were performed according to the recommendations of the American Society of Echocardiography (Lang et al. 2005).

Pulsed wave Doppler echocardiography

Pulsed Doppler velocity profiles, the peak early (E wave) and late (A wave) diastolic flow velocities and their ratio (E/A) as well as the velocity time integrals (VTI) of E and A wave (E wave-VTI and A wave-VTI) were measured from the mitral and tricuspid inflow. Transmitral and transtricuspid pulsed wave Doppler peak velocities were recorded from the apical four chamber or apical long axis views. Because the mitral valve is funnel-shaped, the velocities increased progressively across the mitral valve apparatus towards the outlet of the mitral funnel. Accordingly, all PW Doppler flow measurements were performed through the sample volume located in the same position at the outlet of the mitral and tricuspid valve funnel in order to eliminate the inter- and intra-measurement variability.

Tissue Doppler imaging

Tissue Doppler parameters of mitral and tricuspid lateral annuluses (Garcia et al. 1998), which were rela-

tively preload-independent measurements of diastolic function (Sohn et al. 1997), and peak velocities of systolic (S), early (É), and late (Á) diastolic waves were recorded using tissue Doppler imaging before and after the last session of HBO therapy.

Transthoracic echocardiography, pulsed wave Doppler echocardiography, and tissue Doppler imaging were performed and recorded by one investigator blinded to all clinical data as well as the purpose of the study.

Statistical analyses

Data were presented as mean ± standard deviation (S.D.). Alterations in echocardiographic parameters after HBO therapy were evaluated by using Wilcoxon's signed rank test. A p value < 0.05 was regarded as statistically significant. Statistical analyses were performed using SPSS for Windows 11.0 (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 was 10.3 ± 6.3 years. Systolic and diastolic blood pressure, heart rate, LVEF, LVDD and LVDS did not change after ten HBO treatments compared with pretreatment values (Table 1). HBO significantly improved the E wave deceleration time of mitral valve inflow (286.1 ± 65.8 msec, vs 214.3 ± 32.1 msec, $p <$ 0.05) and peak velocity of E wave of tricuspid valve inflow (0.48 ± 0.07 m/sec vs 0.46 ± 0.09 m/sec, $p < 0.05$) (Table 2). Additionally, HBO therapy induced favorable changes in the remaining pulsed wave Doppler parameters of mitral and tricuspid inflow ($p > 0.05$) (Table 2). It was also noticed that HBO therapy induced a considerable improvement in the tissue Doppler parameters of mitral and tricuspid lateral annuluses ($p > 0.05$) (Table 3).

DISCUSSION

Cardiovascular diseases are the leading cause of morbidity and mortality, especially among diabetic patients (Wingard and Barrett-Connor 1995). Pathophysiological abnormalities associated with diabetes, such as existing metabolic derangements, insulin resistance, endothelial dysfunction, inflammatory response, and hyperco-

TABLE 1. Comparison of clinical and echocardiographic features of patients obtained before and after hyperbaric oxygen (HBO) therapy.

	Before HBO therapy	After HBO therapy
SBP (mmHg)	126.7 ± 18.8	128.5 ± 19.3
DBP (mmHg)	72.4 ± 11.5	73.2 ± 10.8
Heart rate (beats/min)	76.0 ± 6.8	75.3 ± 5.9
LVIDD (mm)	50.5 ± 5.4	50.9 ± 4.8
LVIDS (mm)	31.9 ± 6.2	31.8 ± 6.2
IVS (mm)	11.2 ± 0.4	11.1 ± 0.6
LV EF (%)	66.5 ± 7.2	65.8 ± 5.7
E/A	1.06 ± 0.79	1.12 ± 0.57

SBP, systolic blood pressure; DBP, diastolic blood pressure; LVIDD, left ventricular internal diameter-diastolic; LVDDS, left ventricular internal diameter-systolic; IVS, interventricular septum; LVEF, left ventricular ejection fraction; E/A, ratio of peak velocity of E wave to peak velocity of A wave.

TABLE 2. Comparison of pulsed wave Doppler echocardiography parameters referring to diastolic function of left and right ventricle measured from the mitral and tricuspid valve inflows before and after hyperbaric oxygen (HBO) therapy.

	Before HBO therapy	After HBO therapy
E_{MV} velocity (m/sec)	0.78 ± 0.23	0.87 ± 0.14
E_{MV} TVI	11.3 ± 4.2	15.6 ± 5.3
E_{MV} deceleration time (msec)	286.1 ± 65.8	214.3 ± 32.1*
A_{MV} velocity (m/sec)	0.90 ± 0.31	0.87 ± 0.25
A_{MV} TVI	11.3 ± 5.1	10.1 ± 2.6
$IVRT_{MV}$ (msec)	119.4 ± 27.7	117.1 ± 25.0
E_{TV} velocity (m/sec)	0.48 ± 0.07	0.46 ± 0.09*
E_{TV} TVI	8.34 ± 2.15	8.52 ± 2.43
E_{TV} deceleration time (msec)	260.5 ± 95.8	311.5 ± 88.8
A_{TV} velocity (m/sec)	0.45 ± 0.09	0.61 ± 0.49
A_{TV} TVI	5.93 ± 1.33	6.36 ± 1.92

MV, mitral valve; TV, tricuspid valve; E_{MV}, E wave of mitral valve inflow; E_{TV}, E wave of tricuspid valve inflow; TVI, time-velocity integral; IVRT, isovolumic relaxation time.
*Statistically significant, $p < 0.05$.

agulability, contribute to cardiovascular diseases by promoting the development and rapid progression of atherosclerosis (Hink et al. 2001; Yan et al. 2003). In addition, the new concept of diabetic heart disease, independent from hypertension, coronary artery disease and etc, also contributes to morbidity and mortality (Fang et al. 2004). This new concept of heart disease is characterized initially by diastolic (Zabalgoitia et al. 2001) and subsequently systolic dysfunction of myocardium (Yu et al. 2002). These may precede further diastolic or systolic heart failure (Kitzman et al. 2001). Unfortunately, diastolic dysfunction may develop despite an adequate metabolic control (Zabalgoitia et al. 2001) and is actually accepted as an earlier indicator of poor prognosis in diabet-

TABLE 3. Comparison of Tissue Doppler echocardiography parameters; referring to diastolic function of left and right ventricles measured from the mitral and tricuspid lateral annuluses before and after hyperbaric oxygen (HBO) therapy.

	Before HBO therapy	After HBO therapy
S_{MV} (cm/sec)	8.22 ± 2.21	9.61 ± 2.58
$É_{MV}$ (cm/sec)	8.18 ± 3.54	8.61 ± 2.94
$Á_{MV}$ (cm/sec)	9.80 ± 3.23	11.04 ± 6.21
S_{TV} (cm/sec)	13.35 ± 2.81	11.11 ± 1.28
$É_{TV}$ (cm/sec)	10.60 ± 2.37	9.26 ± 2.70
$Á_{TV}$ (cm/sec)	13.61 ± 5.98	12.10 ± 3.09

MV, mitral valve annulus; TV, tricuspid valve annulus; S, peak velocity of systolic wave of annular myocardial motion; É, peak velocity of early diastolic wave of annular myocardial motion; Á, peak velocity of late diastolic wave of annular myocardial motion.

ic patients (Melchior et al. 2001; Bella et al. 2002).

Non-invasive assessment of myocardial diastolic dysfunction could easily be done by pulsed wave Doppler imaging. E wave deceleration time, isovolumic relaxation time, peak velocities of E and A wave and the ratio of E/A are measured from the early diastolic and late diastolic waves of mitral and tricuspid inflows (Nishimura and Tajik 1997). Additionally, tissue Doppler echocardiography was introduced into daily practice. Doppler echocardiography assesses myocardial motion characteristics within the tissue of mitral and tricuspid annuluses. It characterizes the systolic (S), early diastolic (É) and late diastolic (Á) waves of myocardial motion and is a relatively preload-independent method (Sohn et al. 1997). It also allows the early diagnosis of diastolic dysfunction in hypertrophic myocardial disease (Nagueh et al. 2001) as well as in heart failure with preserved ejection fraction (Kasner et al. 2007). The role of tissue Doppler imaging for detection of silent myocardial dysfunction in patients with type 2 diabetes mellitus was studied by Von Bibra et al.(2005). They reported that tissue Doppler imaging was an easily applicable and effective tool in the identification and management of either systolic or diastolic myocardial dysfunction preceding overt diabetic heart disease (Nagueh et al. 2001).

The presence of diastolic dysfunction in dia-

betic patients can easily be detected by Doppler echocardiography (Galderisi 2006), and myocardial diastolic function were confidently evaluated in our study population, which was composed of diabetic patients. Previous studies that investigated the role of HBO therapy on myocardial function mainly focused only on left ventricular function, while, the effect of diabetes on right ventricular function was not thoroughly investigated. Nunoda et al. (1985) performed a histopathological study on the right ventricle and reported increased fibrosis in diabetic patients. Since the adverse effects of diabetes on both the right and left ventricles were documented, we aimed to concomitantly evaluate the effects of HBO therapy on both the left and right ventricular functions.

Hyperbaric oxygen therapy is a new promising adjunctive therapy in the current cardiovascular era. It was reported that chronic application of HBO therapy improved myocardial performance through various mechanisms in diabetic patients (Sun et al. 2006) as well as other patients (Swift et al. 1992; Sharifi et al. 2004); however, Frobert et al. (2004) documented that acute hyperoxia may induce negative effects on myocardial functions in normal males by tissue Doppler echocardiography. It was proposed that when HBO was applied chronically, it could beneficially affect myocardium by mimicking ischemic preconditioning, thus inhibiting inflammation and trigger-

ing neo-vascularization via production of reactive oxygen species at a plausible level (Becker 2004; Yogaratnam et al. 2006).

Patients had neither the symptoms nor the signs of coronary artery disease, previous myocardial infarction, hypertension, congestive heart failure, and left ventricular hypertrophy; however, elderly patients were not excluded from the study. Elderly patients may have disturbed diastolic function earlier even in the absence of myocardial hypertrophy. The main pathophysiologic factors that affect LV diastolic function are the relaxation rate and compliance of LV in mid-late diastole, which are determined by LV fibrosis/scar, the extent of relaxation and ventricular interaction modulated by pericardium (Gilbert and Glantz 1989). As we will mention in the following paragraphs, our findings suggest that HBO therapy improved the diastolic function by promoting diastolic suction in early diastole; however, the mechanisms should be clarified by further investigations.

During myocardial relaxation, the pressure cross-over between the left atrium and left ventricle causes the mitral valve to open and rapidly fill (E_{MV} wave). The area under the E wave, the time velocity integral (E_{MV} TVI), reflects the contribution of the rapid filling phase to the LV diastolic filling. The deceleration time (DT) of the E wave is a measure of how rapidly diastolic filling stops. The A wave, an important index of diastolic function, is associated with atrial contraction. The area under the A wave, the time velocity integral (A_{MV} TVI), reflects the contribution of the atrium to LV diastolic filling (Nishimura and Tajik 1997).

LV compliance exhibited a significant improvement, which was represented by shortening of the abnormal DT of E_{MV} wave following 10 sessions of HBO therapy (286.1 ± 65.8 vs 214.3 ± 32.1, $p < 0.05$). Furthermore, increased TVI of E_{MV} wave due to HBO therapy revealed the enhancement in LV diastolic filling (11.3 ± 4.2 vs 15.6 ± 5.3, $p > 0.05$). These changes reflect that the contribution of the rapid filling phase to LV diastolic filling increased following HBO therapy. As the LV diastolic filling improved, the demand for the contribution of the left atrium decreased

and caused the peak velocity of A_{MV} waves to decrease. These changes suggest that chronic HBO therapy based on this protocol induces an improvement in LV diastolic function; however, it is not clear whether this improvement is limited to diastolic dysfunction associated with diabetes. Isovolumic relaxation time, the interval between aortic valve closure and mitral valve opening, did not change following the HBO therapy. It was probably determined by factors unaffected by HBO therapy.

Improvement in myocardial relaxation and thus, diastolic filling, suggest that the LV and LV end-diastolic pressures, and thus pulmonary capillary wedge pressure, normalize. This may be interpreted as improvement in LV diastolic filling and may induce reduction in RV afterload and, subsequently, preload. An insignificant reduction in peak velocity of E waves of tricuspid valve inflow (0.48 ± 0.07 vs 0.46 ± 0.09, $p < 0.05$) reflected that RV preload may or may not have been partially reduced. Increased contribution of the rapid filling phase to RV filling, reflected by increased TVI of E_{TV} waves (8.34 ± 2.15 vs 8.52 ± 2.43, $p > 0.05$), represents the improvement of RV diastolic function induced by HBO therapy.

Vlahović et al. (2004) investigated the role of HBO therapy on myocardial stiffness in patients who received thrombolytic therapy for acute myocardial infarction. They performed pulsed wave Doppler echocardiography; however, they assessed the LV diastolic function at the early post-infarction period after only one session of HBO therapy. In this case, the probability that infarcted myocardium would profit from HBO therapy would be less than expected. In our study, we documented that a total of 10 sessions of HBO therapy could be enough to trigger an improvement of myocardial diastolic function within a 2 week period. It is possible that if Vlahović et al. (2004) had applied a longer period of HBO therapy, the infarcted myocardium would have been allowed sufficient time to revive, resulting in improved outcomes.

Similarly, Molénat et al. (2004) conducted an echocardiographic and Doppler study to investigate the hemodynamic effects of hyperbaric

hyperoxia. Their study group included healthy young adults without any cardiac disease or diabetes. However, they investigated only the acute effects over a period of 15 min to 5 hrs following the HBO therapy. Frobert et al. (2004) reported that myocardial performance in healthy males was improved by hypoxia and worsened by hyperoxia. They also reported that tissue Doppler measurements of diastolic function were unaffected by either hypoxia or hyperoxia. They suggested that these changes are related to the alterations in vascular tone. In our study, the improvement of myocardial diastolic function induced by HBO therapy was documented after a period from the previous HBO applications so that our findings would realistically convey the favorable chronic effects of HBO therapy. This was important because previous studies have reported that chronic application of HBO therapy could trigger a different mechanism at the cellular level via reactive oxygen species mimicking ischemic preconditioning.

In our study, improvement of myocardial diastolic function due to HBO therapy was also documented by tissue Doppler echocardiography. While the increased velocities of S_{MV}, $Á_{MV}$, and $É_{MV}$ waves of the mitral lateral annulus were representative of improvement in LV diastolic function and also compliance, slightly decreased velocities of S_{TV}, $Á_{TV}$, and $É_{TV}$ waves of the tricuspid lateral annulus were representative of the reduced afterload and preload of the RV following HBO therapy (Table 3). In the absence of gross shape abnormalities or severe regional wall motion abnormalities, mitral annulus motion reflects the pressure difference between the LA and LV rather than volume changes. Peak velocity of the early diastolic É wave of the mitral annulus is relatively pre-load independent and correlates with LV relaxation (Sohn et al. 1997). Consequently, increased velocity of $É_{MV}$ waves may indicate an improvement in relaxation of LV induced by HBO therapy (Vlahović et al. 2004).

LV functions significantly affect the right ventricular functions. LV contributes to right ventricular systolic pressure and outflow volume with a rate of 20 to 40% (Santamore and

Dell'Italia 1998). Arinc et al. (2005) reported that peak velocities of tricuspid lateral annulus were decreased following an effective hemodialysis parallel to a reduction in preload and pulmonary artery systolic pressure. Consequently, changes in tissue Doppler parameters of tricuspid lateral annulus reflect improvement in myocardial diastolic function induced by HBO therapy.

This study has great importance because we documented the improvement of diastolic function due to HBO therapy in diabetics, by using pulsed wave and tissue Doppler echocardiography. We suggest evaluating the role of HBO therapy on myocardial diastolic function in patients with diastolic heart failure and preserved ejection fraction. One of the limitations of the study was that the data did not reach statistical significance. This may be due to the limited number of patients and the time or dose dependency of HBO exposure. It can be assumed that a longer duration of the HBO therapy may induce a pronounced improvement on LV and RV functions. Either pulmonary vein flow parameters or end-diastolic pressures of LV and LA could be estimated in order to clarify the effects of HBO on flow parameters and tissue Doppler measurements. In addition, new imaging modalities such as the strain rate of myocardium could be measured. Variability between measurements was not evaluated since the data was gathered from a study group with a limited number of patients by one echocardiographer blinded to the study project.

In our study, we documented that HBO therapy improves myocardial diastolic function in diabetic patients. Diastolic dysfunction is the most common and earliest pathology reported in a growing population of diabetic patients. Following the development of an effective HBO therapy protocol, this issue will be at the heart of the new area of HBO therapy for myocardial protection in groups of patients with and without diabetes.

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