Original Article

Vasomotor reactivity comparison in multiple sclerosis patients with white matter lesions and nonmultiple sclerosis subjects with white matter lesions in brain magnetic resonance imaging

Fariborz Khorvash, Ali Masaeli[1], Vahid Shaygannejad, Mohammad Saadatnia

Isfahan Neurosciences Research Center, Alzahra Hospital, [1]Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: It has been recognized a close relationship between multiple sclerosis (MS) lesions and the cerebral vasculature. In this study, we observed cerebrovascular vasomotor reactivity difference between the MS patients and the non-MS migraine individuals.

Materials and Methods: This prospective study was conducted on 40 patients with MS referring to Neurology Clinic of Isfahan Al-Zahra Hospital in 2012. The patients were compared with the same number of non-MS migraine individuals. Both groups had white matter lesions in brain magnetic resonance imaging. To evaluate the rate of cerebral artery vasomotor reactivity, transcranial Doppler device was used, and breath-holding index (BHI) was separately calculated for each middle cerebral artery. Main flow velocity (MFV) was determined by continuously recording of a period of 5 min of breathing the air in the room. The obtained data were analyzed using SPSS software version 18 and *t*-test, Chi-square and analysis of variance tests.

Results: The mean values of MFV at rest was not significantly different between cases and control groups (46.21 ± 4.20 vs. 44.69 ± 4.34, $P = 0.115$) but difference between cases and control groups in MFV apnea was significant (59.11 ± 5.10 vs. 55.35 ± 6.03, $P = 0.004$). BHI in the control group was 0.79 ± 0.26 and in the case group was 0.93 ± 0.20 and these differences was found to be significant ($P < 0.05$).

Conclusion: The mean of BHI and cerebral vasomotor reactivity in MS patients was more than the non-MS migraine individuals, although the mechanism of this process still remains unknown.

Key Words: Brain magnetic resonance imaging, multiple sclerosis, white matter lesions

Address for correspondence:
Dr. Ali Masaeli, Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: ali_dmd18@yahoo.com
Received: 04.02.2014, **Accepted:** 14.06.2015

INTRODUCTION

Multiple sclerosis (MS) is primarily considered as an inflammatory demyelinating disease; however the role of the vasculature in MS pathogenesis has received much interest. MS lesions often develop along blood vessels and alterations in blood brain barrier structure and function which in association with changes in the basement membrane, are pathological features.[1]

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.175916

How to cite this article: Khorvash F, Masaeli A, Shaygannejad V, Saadatnia M. Vasomotor reactivity comparison in multiple sclerosis patients with white matter lesions and nonmultiple sclerosis subjects with white matter lesions in brain magnetic resonance imaging. Adv Biomed Res 2016;5:23.

A close relationship between MS lesions and the cerebral vasculature has been recognized for a long time and some studies have been revealed that vascular endothelial cell activation can be an early event in MS evolution, and demyelination may have an ischemic basis in this condition. Breath holding (BH) results in hypoxia caused by bin autoregulatory vasodilatation, and an increase in cerebral blood flow (CBF) to the cortex. The increased (CBF) can be evaluated by brain magnetic resonance imaging (MRI), and can provide information about the vascular integrity.[2]

Cerebral vasoreactivity assessment can provide information regarding the reserve capacity of cerebral circulation, which its reduction has been found in association with situations predisposing one toward cerebrovascular disease.[3]

During the changes in CO_2 concentration, the relationship between flow velocity and volume flow within a large cerebral artery is linear showing that the CO_2 level does not affect directly on the diameter of large proximal arterial segments. Cerebral vasomotor reactivity can be easily studied by measuring the flow velocity changes in response to vasodilatory stimuli such as CO_2 inhalation, breath holding or acetazolamide administration. Cerebral vasoreactivity assessment can provide information regarding the reserve capacity of cerebral circulation as the possible response of vessels to adapt with systemic modification or brain metabolic activity in the need of increasing or decreasing the CBF. Reduction of this property has been showed in association with situations predisposing one toward cerebrovascular disease. It is possible that vasomotor reserve become exhausted if the resistance vessels of brain areas with low perfusion pressure be already maximally dilated. In this state, the resistance vessels are refractory to any further vasodilatory stimuli.[4-7]

As the pathological differences underlying the clinical disease phases in MS have been poorly characterized and there are a few studies about the vasomotor reactivity of cerebral vessels in MS patients in this study, we aimed to examine the vascular integrity and assess the vasomotor reactivity of MS patients in response to BH in comparison with non-MS migraine patients by means of MRI. The migraine patients have been selected because of similar white matter lesions with MS patients, and we want to assess the possibility of considering breath-holding index (BHI) as a differential diagnosis factor of MS. According to our knowledge, there has been no study in this issue and it can open a new window to this field.

MATERIALS AND METHODS

This prospective study was conducted on 40 patients with MS referring to Neurology Clinic of Isfahan Al-Zahra Hospital from the beginning of 2012. The patients were compared with the same number of non-MS individuals with migraine as the control group. There were white matter lesions in both groups. After obtaining written consent undergoing biography and physical examination, patients with MS suffering from central nervous system (CNS) Vasculitis and patients with MS who were eligible to enter the study were evaluated in terms of blood pressure and hyperlipidemia and then evaluated using Doppler transcranial sonography with regard to the rate of middle cerebral artery (MCA) blood flow. All the patients were matched in disease characteristics such as duration of disease, type of disease, expanded disability status score, type of treatment and presenting symptoms. The control group was selected in a way that they were similar to the study group in terms of age and sex. Inclusion criteria were patients with MS whose disease were confirmed, age over 18 years old and no previous brain injury such as the history of trauma to the brain or injury in the brain arteries.

Patients unwilling to continue their participation in the study, with the history of previous stroke, with diabetes mellitus, smoking more than one pack per year, congestive heart failures (CHF), chronic obstructive pulmonary, cerebrovascular diseases, transient ischemic attack, carotid artery occlusion more than 30% and intracranial obstruction approved by transcranial Doppler (TCD), hematological diseases or cancer and patients treated with hormonal drugs, beta-blockers, calcium channel blockers, anticoagulants, and vessel dilator drugs were excluded from the study.

Furthermore, the control group, was selected in the way similar to the study group in terms of age and sex and those who had white matter lesions in their brain MRI and did not suffer from MS. To evaluate the rate of cerebral artery vasomotor reactivity, TCD device was put on 20% to 35% and the depth of signal was set on 40–45 and activity was determined by calculating BHI as follows.

BHI was separately calculated for each MCA. Main flow velocity (MFV) was determined by continuously recording of a period of 5 min of breathing the air in the room. After a period of 30 s of BH, MFV was again determined. To do BH, Capnogram was used, and pCO_2 reached 60 cm Hg.

To determine the relationship between cerebral artery vasomotor reactivity and other factors of the study objectives, the MRI of the patients' brain was used.

In this study, Z1 as the confidence coefficient was 95%, that is, 1.96 and Z2 as the test power coefficient was 0.80 that is, 0.84 and the significant level was considered as 0.5. The obtained data were analyzed using SPSS software (version 18.0; SPSS Inc., Chicago, USA). and *t*-test, Chi-square and analysis of variance (ANOVA) tests.

RESULTS

In this study, 40 patients with MS and white matter lesions in brain MRI were compared with the same number of non-MS with migraine and also white matter lesions in brain MRI. The case group of this study (patients with MS and white matter lesion in brain MRI) were included 28 females (70%) and 12 (30%) males and the control group (non-MS patients with migraine and also white matter lesion in brain MRI) were included 26 females (65%) and 14 (35%) males; also the mean age patients in the case group were 33.35 ± 7.01 years and in the control group was 36.43 ± 7.16 years.

There was no statistically significant difference between the groups in terms of age and sex. In other words, the two groups were matched for age and sex ($P > 0.05$) [Table 1].

Results of analysis the distribution of MFV at rest and 30s apnea and BHI with Kolmogorov–Smirnov Z-test showed that all three variables follow a normal distribution ($P > 0.05$) and, therefore, parametric tests were used in this study [Figure 1].

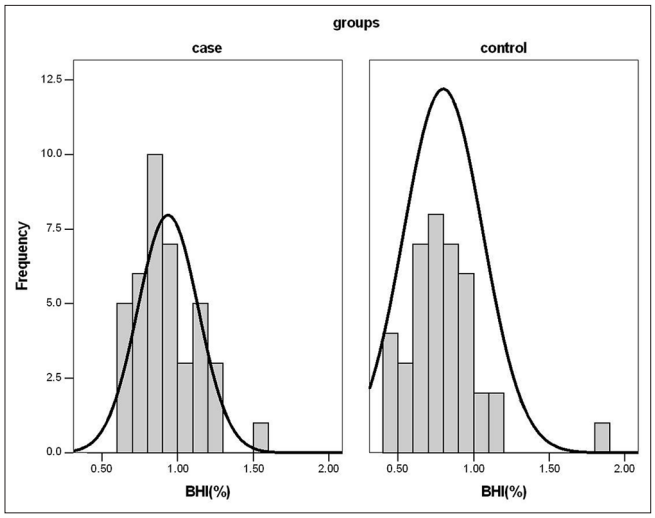

Figure 1: Breath holding index histogram for each of the two study groups

The mean MFV at rest in the case group were 46.67 ± 5.62 and 46.02 ± 3.53 in males and females, respectively and in the control group were 44.41 ± 4.06 in males and 58.74 ± 4.68 in females. The mean MFV at 30 s apnea in the case group were 59.96 ± 6.10 and 46.02 ± 3.53 in males and females, respectively and in the control group were 55.48 ± 5.34 in males and 55.28 ± 6.47 in females. The mean BHI in males and in females in the case group were 0.92 ± 0.21 and 0.96 ± 0.18, respectively and in the control group were 0.83 ± 0.12 and 0.78 ± 0.31 in males and females, respectively.

These differences in both groups in terms of sex factor was not statistically significant using *t*-test (independent sample *t*-test) ($P > 0.05$), also the mean MFV at rest and 30s apnea and BHI in each of the two groups in terms of age groups using ANOVA was not significant difference between groups ($P > 0.05$) [Table 2 and Figure 2].

The mean values of MFV at rest was not significantly different between cases and control groups (46.21 ± 4.20 vs. 44.69 ± 4.34, $P = 0.115$), but difference

Table 1: The consistency between the two groups in terms of gender and age

Groups	Age		
	Mean	SD	*P*
Case	33.35	7.01	0.060
Control	36.43	7.16	
	Sex		
	Female (%)	Male (%)	*P*
Case	28 (70)	12 (30)	0.406
Control	26 (65)	14 (35)	

These differences in both groups in terms of sex factor was not statistically significant using *t*-test (independent sample *t*-test) (*P*>0.05), also the mean MFV at rest and 30s apnea and BHI in each of the two groups in terms of age groups using ANOVA was not significant difference between groups (*P*>0.05) [Table 2 and Figure 2]

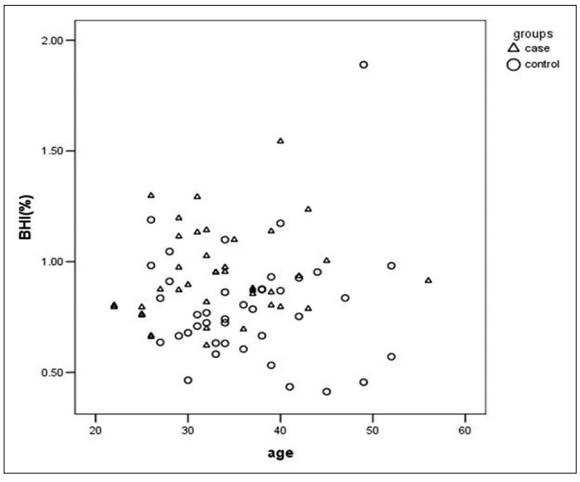

Figure 2: Scatter diagram of breath holding index means in terms of age in the case and control groups

between cases and control groups in MFV apnea was significant (59.11 ± 5.10 vs. 55.35 ± 6.03, $P = 0.004$).

Cerebral artery vasomotor reactivity BHI in the control group was 0.79 ± 0.26 and in the case group was 0.93 ± 0.20 and these differences was found to be significant ($P < 0.05$) using *t*-test (independent sample *t*-test) [Table 3 and Figure 3]. In other words, the mean of BHI in MS patients was more than the non-MS patients.

Table 2: Comparing MFV at rest and 30 s apnea and BHI in terms of age and sex in each of the case and control groups

Groups	Variable	Mean±SD	*P*
Case	MFV rest		
	Male (*n*=12)	46.67±5.62	0.658
	Female (*n*=28)	46.01±3.53	
	MFV apnea		
	Male (*n*=12)	59.96±6.10	0.496
	Female (*n*=28)	58.74±4.68	
	BHI		
	Male (*n*=12)	0.96±0.18	0.611
	Female (*n*=28)	0.92±0.21	
	MFV rest		
	≤30 years (*n*=14)	47.08±5.08	0.344
	Above 30 years (*n*=26)	45.74±3.66	
	MFV apnea		
	≤30 years (*n*=14)	59.61±6.54	0.653
	Above 30 years (*n*=26)	58.84±4.26	
	BHI		
	≤30 years (*n*=14)	0.89±0.19	0.295
	Above 30 years (*n*=26)	0.96±0.20	
Control	MFV rest		
	Male (*n*=14)	44.41±4.06	0.768
	Female (*n*=26)	44.84±4.55	
	MFV apnea		
	Male (*n*=14)	55.48±5.34	0.924
	Female (*n*=26)	55.28±6.47	
	BHI		
	Male (*n*=14)	0.83±0.12	0.586
	Female (*n*=26)	0.78±0.31	
	MFV rest		
	≤30 years (*n*=9)	44.32±5.05	0.780
	Above 30 years (*n*=31)	44.79±4.19	
	MFV apnea		
	≤30 years (*n*=9)	55.06±4.99	0.875
	Above 30 years (*n*=31)	55.43±6.37	
	BHI		
	≤30 years (*n*=9)	0.82±0.23	0.761
	Above 30 years (*n*=31)	0.79±0.27	

MFV: Main flow velocity, BHI: Breath holding index, SD: Standard deviation

Table 3: Comparing the means of MFV at rest and 30 s apnea and BHI in the two study groups

Variable	Case	Control	*P*
MFV rest	46.21±4.20	44.69±4.34	0.115
MFV apnea	59.11±5.10	55.35±6.03	0.004
BHI	0.93±0.20	0.79±0.26	0.011

MFV: Main flow velocity, BHI: Breath holding index

DISCUSSION

MS is believed to be an immune-mediated neurodegenerative disorder of the CNS which usually affects younger adults. The causes and cure for MS remain elusive. The three prevailing concepts on the pathogenesis of MS include viral, immunological, and vascular hypotheses.[1]

Patients with MS have global cerebral hypoperfusion and widespread decrease in perfusion in normal-appearing white matter and grey matter in MS seems might be a result of reduced axonal activity, reduced astrocyte energy metabolism, and perhaps increased blood concentrations of endothelin-1. The underlying mechanism vascular dysfunction have been described in MS is unknown, but might involve endothelial dysfunction secondary to inflammatory disease activity.[2]

Several studies have shown that endothelial function may have a role to the incidence of neural events in MS.[3,4]

Study of Alexander *et al*.[8] showed that MS as a neuroinflammatory disease with a significant vascular component and emphasized the role of cerebral endothelial cell dysfunction in the pathogenesis of this progressive CNS disorder.[5] Some studies have proposed that the activation of vascular endothelial cells might be an early event in the demyelination process in MS, and it may have an ischemic basis in the evolution of MS.[6]

CBF is regulated by changing in arterioles resistance[6,8] that is, with their dilatation and constriction.

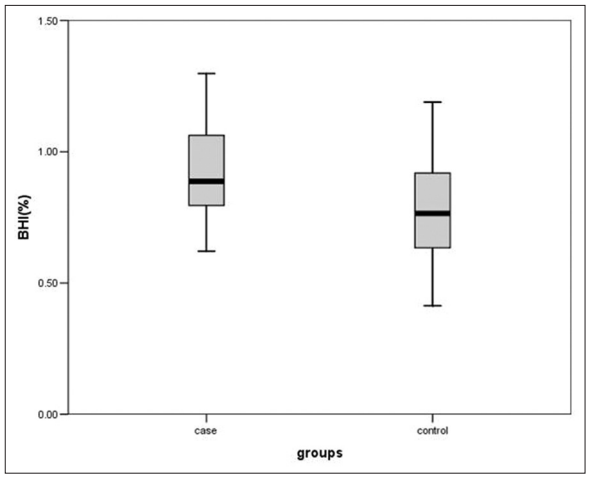

Figure 3: Box plot diagram of breath holding index in the two study groups

Vasomotor reactivity can help the cerebral vessels get their maximum dilatation when a severe decrease in cerebral perfusion occurred and can prevent the brain.[9,10] Hypercapnia is the most powerful stimulant when the brain vessels don't respond to any vasodilator stimulant.[11] Cerebrovascular reactivity is a hemodynamic parameter representing the increase in normal cerebral artery blood flow in response to a vasodilator stimulus such as hypercapnia.[12,13] An early preclinical detection of cerebrovascular complications in individuals with MS can help to timely treatment and prevention of future disabilities.

Despite the growing incidence of MS in the world and in Iran, few studies have evaluated cerebral vasomotor reactivity in patients with MS.

In study of Uzuner *et al*.[14]. on 12 patients with clinically diagnosed MS and 11 healthy subjects (control group) that examined by TCD, blood flow velocities of the patients were recorded during 30 s of normal breathing and 15 s BH and vasomotor reactivity was calculated as a ratio of difference of cerebral flow velocities during BH. Results of this study showed there were no significant differences between the controls (55.7%) and the patients during attacks (46.5%) in vasomotor reactivity, as well as after treatment (48.3%) and during attack-free periods (50.9%). There were also no significant changes amongst the patients groups throughout the study. Results of their study also showed that there were nonsignificant cerebrovascular vasomotor reactivity difference between the relapsing-remitting MS patients and the healthy controls in different disease activity stages of MS, although it was slightly lower in the MS patients.[15]

Results of our study showed that the cerebral artery vasomotor reactivity measured with BHI in the MS patients with white matter lesion was more than the non-MS migraine patients with white matter lesion (0.93 ± 0.20 vs. 0.79 ± 0.26) and these differences was significant ($P < 0.05$). The difference between the results of our study and Uzuner *et al*. could be due to controls of Uzuner *et al*. study that were healthy subjects whereas the control group in our study was the migraine patients. In our study, 40 patients with MS were compared with the same number of non-MS with migraine.

In another study of Uzuner *et al*. the blood flow velocity (BFv) changes to visual stimuli was assessed using TCD in patients with MS during an exacerbation period. The study was conducted on 84 patients and 45 healthy subjects. Both posterior cerebral arteries (PCAs) were simultaneously monitored by TCD sonography during 10 cycles of 20 s eyes open observing complex moving visual images, and 20 s eyes closed at the end of every cycle. Mean cerebral BFv throughout the procedure, velocity at rest, and velocity at stimulation on both PCAs were significantly lower in patients than controls. However, BFv changes to visual stimulation on both sides were significantly higher in patients compared to controls. Results of their study suggested that patients with MS during exacerbation have more reactive vessels in the posterior circulation.[16]

On the other hand, in this study we evaluated the role of BHI as a functional parameter of impaired cerebrovascular reactivity (intracranial small vessel wall dysfunction). The BHI is a measure of the vasomotor reactivity of the brain, which can be measured with the TCD. BHI also is used to test subclinical atherosclerotic changes in recognizing patients who are at risk for developing cognitive impairment[14,17] and also can evaluate risk factors of atherosclerosis (obesity) as an independent factor for altered cerebrovascular reactivity.[18]

The study Hradílek *et al*.[17] blood flow in the ophthalmic artery was assessed in acute and chronic optic neuritis in MS patients by color Doppler ultrasonography. Blood flow, vascular resistance and heart rate in these patients compared with normal subjects showed a significant difference ($P < 0.05$), but there was no difference between the two groups of patients.[19]

The results above studies are consistent with the results of the present study. Cerebral artery vasomotor reactivity in patients with MS was more than the healthy individuals.

In study of Mousavi *et al*.[18] 289 healthy individuals (without hypertension, diabetes mellitus, obesity, smoking, CHF, coronary heart disease) were divided into four groups, according to age and sex (women >30 and men <30). After determination of each patient's flow velocity of MCA by mean of a TCD instrument, before and after 30 s apnea, BHI was calculated. BHI was significantly higher in women than men (0.918 ± 0.40 vs. 0.637 ± 0.22; $P < 0.001$). BHI was significantly lower in older (age >30) women (0.812 ± 0.31) than in younger (≤30 years) women (0.995 ± 0.44; $P < 0.001$) but there was no significant difference between older (age >30) men (0.62 ± 0.23) and younger (≤30 years) men (0.65 ± 0.20; $P > 0.05$). Results of this study showed that the average of BHI was lower in men than in women in total and in all age subgroups, and vasomotor reactivity remains relatively constant in

men but decreases in women. Results of the study suggested that changes of cerebrovascular vasomotor reactivity in healthy subjects may be related to aging, but they are probably mainly influenced by sex.[7] In our study, there was no statistically significant difference between the groups in terms of age and sex because the two groups were matched for age and sex.

Study of Ozkan *et al*. showed significant changes in CBF volume with a nonsignificant increase in vascular reactivity after treatment with intravenous high-dose methylprednisolone in patients with exacerbations of MS.[19]

A variety of tests were introduced to evaluate intracranial hemodynamics using the phenomenon of vasomotor reactivity, including carbon dioxide reactivity with TCD ultrasonography, CBF scanning techniques, and the BHI. Hypoxia caused by BH results in autoregulatory vasodilatation, and an increase in CBF to the cortex and it can be evaluated by TCD. According to the above one of the most important results of this study comes from further recommends the use of TCD is in the early stages of MS patients and also it can use as a differential diagnosis factor of MS against non-MS migraine patients with similar white matter lesions in brain MRI. Because TCD is an available method to assessment of cerebrovascular reactivity and is a safe, noninvasive, and low-cost technique, which neurologists utilize it for imaging the large intracranial vessels and it can provide information about the vascular integrity.[7] Also recommended to be performed the future studies to evaluate cerebrovascular reactivity in MS patients to help in understanding the etiology of MS.

CONCLUSION

The present results indicate that the mean of BHI and cerebral vasomotor reactivity in MS patients was more than the non-MS migraine individuals, although the mechanism of this process still remains unknown. To elucidate the effect of age, sex, and other effective factors further studies with more patients may be needed. These studies help us to better understanding the disease process and its treatment.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Holley JE, Newcombe J, Whatmore JL, Gutowski NJ. Increased blood vessel density and endothelial cell proliferation in multiple sclerosis cerebral white matter. Neurosci Lett 2010;470:65-70.
2. Uzuner N, Ozkan S, Cinar N. Cerebrovascular reactivity in multiple sclerosis patients. Mult Scler 2007;13:737-41.
3. Milo R. The efficacy and safety of daclizumab and its potential role in the treatment of multiple sclerosis. Ther Adv Neurol Disord 2014;7:7-21.
4. D'haeseleer M, Cambron M, Vanopdenbosch L, De Keyser J. Vascular aspects of multiple sclerosis. Lancet Neurol 2011;10:657-66.
5. Jimenez J, Jy W, Mauro LM, Horstman LL, Ahn ER, Ahn YS, *et al.* Elevated endothelial microparticle-monocyte complexes induced by multiple sclerosis plasma and the inhibitory effects of interferon-beta 1b on release of endothelial microparticles, formation and transendothelial migration of monocyte-endothelial microparticle complexes. Mult Scler 2005;11:310-5.
6. Hafler DA, Fox DA, Manning ME, Schlossman SF, Reinherz EL, Weiner HL. *In vivo* activated T lymphocytes in the peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. N Engl J Med 1985;312:1405-11.
7. Jolink WM, Heinen R, Persoon S, van der Zwan A, Kappelle LJ, Klijn CJ. Transcranial Doppler ultrasonography co2 reactivity does not predict recurrent ischaemic stroke in patients with symptomatic carotid artery occlusion. Cerebrovasc Dis 2013;37:30-7.
8. Alexander JS, Zivadinov R, Maghzi AH, Ganta VC, Harris MK, Minagar A. Multiple sclerosis and cerebral endothelial dysfunction: Mechanisms. Pathophysiology 2011;18:3-12.
9. Moghaddasi M, Mamarabadi M, Habibi AH. A comparison of cerebral vasomotor reactivity in diabetic and nondiabetic Iranian patients. J Res Med Sci 2010;15:50-3.
10. Müller HR. Evaluation of vasomotor reactivity by transcranial Doppler and acetazolamide test before and after extracranial-intracranial bypass. Stroke 1992;23:1840.
11. Martí-Fàbregas J, Belvís R, Guardia E, Cocho D, Muñoz J, Marruecos L, *et al.* Prognostic value of pulsatility index in acute intracerebral hemorrhage. Neurology 2003;61:1051-6.
12. Diehl RR, Henkes H, Nahser HC, Kühne D, Berlit P. Blood flow velocity and vasomotor reactivity in patients with arteriovenous malformations. A transcranial Doppler study. Stroke 1994;25:1574-80.
13. Caplan LR, Reis DJ, Siesjo BK, Weir B, Welch KM. Primer on cerebrovascular disease. In: Traystman RJ, editor. Regulation of Cerebral Blood Flow by Carbon Dioxide. 1th ed. San Diego: Academic Press; 1997. p. 55-7.
14. Uzuner N, Ozkan S, Gücüyener D, Ozdemir G. Cerebral blood flow velocity changes to visual stimuli in patients with multiple sclerosis. Mult Scler 2002;8:217-21.
15. Unfirer S, Kibel A, Drenjancevic-Peric I. The effect of hyperbaric oxygen therapy on blood vessel function in diabetes mellitus. Med Hypotheses 2008;71:776-80.
16. Lipsitz LA, Mukai S, Hamner J, Gagnon M, Babikian V. Dynamic regulation of middle cerebral artery blood flow velocity in aging and hypertension. Stroke 2000;31:1897-903.
17. Hradílek P, Stourac P, Bar M, Zapletalová O, Skoloudík D. Colour Doppler imaging evaluation of blood flow parameters in the ophthalmic artery in acute and chronic phases of optic neuritis in multiple sclerosis. Acta Ophthalmol 2009;87:65-70.
18. Mousavi SA, Khorvash F, Asadi B, Karkheiran F. Evaluation of vasomotor reactivity by transcranial Doppler sonography: Age and sex related differences in breath holding index in Iranian population. J Res Med Sci 2005;10:93-6.
19. Ozkan S, Uzuner N, Kutlu C, Ozbabalik D, Ozdemir G. The effect of methylprednisolone treatment on cerebral reactivity in patients with multiple sclerosis. J Clin Neurosci 2006;13:214-7.