



Cerebral Vasomotor Reactivity in Medically Stabilized Patients with Takayasu's Arteritis

Takayasu Arteritinde Stabil Hastalık Döneminde Serebral Vazomotor Reaktivite

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Abstract

Objective: Takayasu arteritis (TA) is a large vessel vasculitis that affects the aorta and its main branches in the young population. Although data about the effects of controlling disease activity with immunosuppressive treatments on cerebral circulatory capacity are limited, these treatments might stabilize the cerebrovascular hemodynamic status, regardless of the severity of proximal arteriopathy. One of the causes might be the normalization of cerebral autoregulation by the treatment.

Materials and Methods: Cerebral vasomotor reactivity (cVMR) was calculated using the breath holding index (BHI) after bilateral middle cerebral artery (MCA) flow pattern was detected using transcranial Doppler ultrasound (TCD) in six patients with TA who were stabilized with treatment (age: 29±7 years, 5 female). A total of 28 measurements were performed. The control group included 18 healthy volunteers, except for migraine (29±6 years, 12 female). Bilateral MCA mean flow rates (Vmean, cm/s), pulsatility indexes (PI) and BHI were compared using non-parametric statistical methods.

Results: Middle cerebral artery Vmean and PI values were lower in patients with TA (48.3±17.2 cm/s and 0.31±0.16, respectively) compared with the controls (62.2±11.3 and 0.70±0.11, respectively) (both p<0.001). BHI was measured as 0.92±0.63 in the TA group and 0.93±0.38 in the controls (p=0.97). Additionally, in the TA group, TCD parameters measured in the occluded carotid artery territory (11 tests) did not differ from those measured in the non-occluded parent carotid artery territory.

Conclusion: It seems that cVMR can be stabilized at least in the medium range in patients with TA. A protected or improved cerebral microcirculation in patients with TA, unlike in patients with atherosclerotic cervicocephalic artery occlusions, might be an explanation.

Keywords: Takayasu's arteritis, cerebral vasomotor reactivity, breath holding test

Öz

Amaç: Takayasu arteriti (TA) genç yaşlarda arkus aorta ve dallarının tutulumu ile karakterize bir büyük damar vaskülitidir. İmmünoşüpresif tedaviler ile hastalık aktivitesinin kontrol altına alınmasının serebral dolaşım üzerine etkisi konusunda yayınlar oldukça sınırlı olup, bu tip tedaviler ile proksimal arteriopati sekeline karşın serebrovasküler hemodinamik status stabilize edilebilmektedir. Bunun nedenlerinden biri serebral mikrosirkülatuar otoregülatuar kapasitenin tedavi ile normale dönüşü olabilir.

Gereç ve Yöntem: Tedavi ile kontrol altında TA tanısı olan 6 hastada [yaş (ortalama ± standart sapma): 29±7 yıl; 5 kadın] transkraniyal Doppler ultrasonografi (TCD) ile her iki orta serebral arter (OSA) akım paterni tespit edildikten sonra nefes tutma indeksi (NTI) ile serebral vazomotor reaktivite (sVMR) çalışıldı. Altı hastada toplam 28 sVMR ölçümü yapıldı. Kontrol grubu migreni olması dışında sağlıklı olan 18 kişiden oluşturuldu (yaş: 29±6 yıl; 12 kadın). Her iki taraf OSA ortalama akım hızı (Vortalama, cm/s), pulsatilite indeksi (PI) ve NTI değerleri non-parametrik istatistiksel yöntemlerle karşılaştırıldı.

Bulgular: OSA Vortalama ve PI değerleri sırasıyla, TA grubunda 48,3±17,2 cm/s ve 0,31±0,16 olup kontrol grubundan (62,2±11,3 cm/s ve 0,70±0,11) düşük olarak saptandı (her iki; p<0,001). NTI TA grubunda 0,92±0,63 ve kontrollerde ise 0,93±0,38 olarak ölçüldü (p=0,97). Ek olarak TA grubunda oklüde ana karotid arter sahasında (11 test) çalışılan TCD ölçümleri ana karotis arteri oklüde olmayan hastalara ait ölçümlerden farklılık göstermedi.

Sonuç: TA olan hastalarda, sVMR tedavi sonrası en azından orta erimde stabil hale gelmektedir. Serebral mikrosirkülatuar, aterosklerotik servikoserebral arter oklüzyonlarındakinin aksine, korunmuş olması veya tedavi sonrası düzelmesi bu durumun açıklaması olabilir.

Anahtar Kelimeler: Takayasu arteriti, serebral vazomotor reaktivite, nefes tutma testi

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Introduction

Takayasu arteritis (TA) is a large vessel vasculitis characterized by inflammatory involvement of the aorta and its branches that affects the young population (1). Neurologic symptoms and signs secondary to involvement of large vessels such as internal carotid artery and subclavian artery can be seen in 50% of patients with TA (2). In the course of TA, secondary to the presence of proximal arteriopathy, indirect intracranial vascular pathologic changes have also been demonstrated (3,4,5). There are small studies about the partial stabilization of this cerebrovascular haemodynamic effect with immunosuppressive-biologic agents currently used in TA treatment or various surgical treatment options (5,6,7,8), but the response of this situation in terms of cerebral vasomotor reactivity (cVMR) is not clearly known. In our study, we investigated whether cVMR values measured using the breath-holding test (BHT) in transcranial Doppler ultrasonography (TCD) in patients with TA in the stable period after treatment were different from those of healthy adults (control group).

Materials and Methods

Patients

All patients with TA who were aged >18 years, followed up and stable under treatment, and were referred to our neurosonology laboratory for evaluation with the BHT for cerebrovascular risk for various reasons (e.g. drug discontinuation, periprocedural risk) between 2016-2020 in Hacettepe Medical Faculty Vasculitis Diagnosis and Treatment Research and Application Center, were included in this retrospective analysis. Vascular examinations such as neuroimaging and digital subtraction angiography, computed tomography angiography, magnetic resonance angiography, and demographic data, additional diseases, and medications used were obtained from the hospital's electronic data system. The control group consisted of adults with normal neurologic examinations and without any additional disease other than migraine (9). BHT of both groups was performed using TCD in the Neurosonology Laboratory of Hacettepe University. This retrospective analysis of a previous study in which a control group was included (9) was approved by the Hacettepe University Ethics Committee (project no: 20/903, decision no: 2020/16-24).

TCD Breath-holding Test

The TCD examination was performed using the MultiDop® (DWL Compumedics, Singen, Germany) device and its 2 MHz head stabilized monitoring probes. During the evaluation, patients were kept in a 30° supine position. Middle cerebral artery monitoring was fixed at a depth of 45-50 mm. BHT was performed by repeating 30-second breath-holding periods at least twice. Normal inspiratory-expiratory cycles were allowed before each BHT series so that the apnea period during BHT and the effect of Valsalva did not disturb the second phase of the other BHT episodes. BHT measurements were considered valid if the apnea time was >24 sec. Triphasic TCD waveforms were evaluated throughout the BHT (9).

The normal BHT response includes the phase of transient flow velocity increase usually occurs in 5 seconds at the beginning of the test (phase 1), phase 2 where a decrease (negative) in maximum flow velocity occurs during apnea (pit response), and phase 3 in which the flow velocity increases immediately within 2-4 seconds

after the cessation of apnea and continues normally for a long time (apnea response) (9). Peak systolic velocity (PSV), end-diastolic velocity (EDV), mean flow velocity [Vmean=EDV+(PSV-EDV)/3], pulsatility index [PI=(PSV-EDV)/Vmean] and time between pit and apnea response phases (breath-holding period) were determined. The BHT was calculated as the percentage increase of apnea mean velocity relative to the baseline value divided by the duration of the breath-hold in seconds [BHT=(Vmean apnea-Vmean baseline) x 100/Vmean baseline x duration of breath-hold] (Figure 1, 2).

Statistical Analysis

The data were analyzed using the SPSS 23 IBM® package provided free of charge by Hacettepe University Faculty of Medicine. The mean values of the groups were appropriately

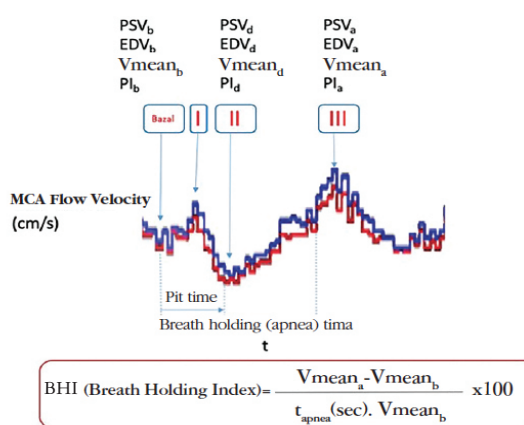


Figure 1. MCA flow-time graph and BHI Formula in TCD recording during the Breath-holding test

MCA: Middle cerebral artery, BHI: Breath-holding index, TCD: transcranial Doppler ultrasound, Vmean: Mean flow rates, PSV: Peak systolic velocity, EDV: End-diastolic velocity

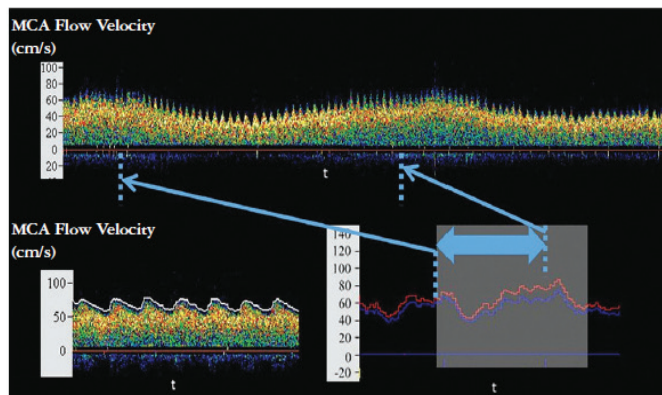


Figure 2. Original BHI Study Example (top: Compressed MCA flow-time graph, Bottom left: MCA PSV and EDV values in uncompressed MCA flow-time graph, Bottom right: Basal, pit and apnea response phases of BHT)

BHI: Breath-holding index, MCA: Middle cerebral artery, PSV: Peak systolic velocity, EDV: End-diastolic velocity

expressed as mean ± standard deviation or median ± interquartile range. Student t-test or the Mann-Whitney U test was used for parametric data for comparisons between groups, and the chi-square/Fisher's exact test was used for categorical data. A value of p<0.05 was considered statistically significant.

Results

The data of six patients with TA (Table 1, 2) and 18 healthy volunteers were analyzed. The mean age of the TA group was 29±7 years (five women), and the control group was 29±6 years (12 women). The MCA Vmean and PI values were 48.3±17.2 cm/s

and 0.31±0.16 in the TA group, 62.2±11.3 cm/s and 0.70±0.11 in the control group, respectively (both p<0.001). No difference was found between the two groups in terms breath-holding (BHI) measurements (0.92±0.63 vs. 0.93±0.38, p=0.97) (Table 3).

When the TA patient group was evaluated according to whether the parent artery was occluded [O (+) vs. O (-)], 11 out of a total of 28 measurements were found to be studied on the side of the occlusion of the parent artery. In these measurements, there was no difference between the groups in terms of PSV, EDV, Vmean, PI, and BHI values (Table 4).

Table 1. Individual TCD measurements of patients with TA

	PSV (cm/s)	EDV (cm/s)	Vmean (cm/s)	PI	BHI	% Decrease
1	23.2±1.2	19.5±0.5	20.7±0.6	0.18±0.05	0.83±0.12	25.8±12.1
2	62.5±8.1	51±9.4	54.8±9	0.21±0.06	1.59±1.12	9.2±10.3
3	63.5±17.9	43.2±9.1	50±12	0.39±0.09	0.60±0.52	23.5±5
4	83.2±10.5	48.2±4.9	59.9±6.8	0.58±0.02	0.51±0.27	27.8±8
5	70±16.4	48±16	55.3±15.1	0.41±0.21	1.09±0.88	0.6±6.9
6	65.5±8.1	54.5±5.9	58.1±6.6	0.18±0.03	1.06±0.40	3.1±9.9

TA: Takayasu arteritis, TCD: Transcranial Doppler ultrasound, PSV: Peak systolic velocity, EDV: End-diastolic velocity, Vmean: Mean flow rates, PI: Pulsatility indexes, BHI: Breath-holding index

Table 2. General data of patients with TA

	1	2	3	4	5	6
Age/age at diagnosis (years)	32/31	28/27	25/14	40/20	29/25	18/15
Gender	Female	Female	Male	Female	Female	Female
Complaint/finding at admission	Hemiparesis	Epileptic seizure	Headache	Amaurosis fugax	Hemiparesis	Vertigo
Imaging	CTA	CTA	MRA	DSA	CTA	CTA
Vascular involvement	Bi. CCA Left cor Left sub	Right CCA Left CCA Bi. sub	Right CCA SMA	Right ICA Bi. sub SMA	Bi. CCA Right sub IMA	Bi. CCA Bi. sub
TA subtype	1+c	2a	1.4	1.4	2b	2a
Treatment	Mycophenolate Mofetil	Tocilizumab	Azathioprine	Methylprednisolone	Methylprednisolone	Tocilizumab
Large vessel occlusion	Left ICA	Right ICA, Left ICA	Right CCA	-	-	-

TA: Takayasu arteritis, CTA: Computed tomography angiography, CCA: Common Carotid Artery, cor: Coronary artery, DSA: Digital subtraction angiography, ICA: Internal carotid artery, MRA: Magnetic resonance angiography, S/I MA: Superior/inferior mesenteric artery, Sub: Subclavian artery, Bi: Bilateral

Table 3. Comparison between patients with TA and controls

	TA	Control	p
N	6	18	-
Year (year)	29±7	29±6	0.91
Gender (F)	5	12	0.62
MCA Vmean (cm/s)	48.3±17.2	62.2±11.3	<0.001
MCA PI	0.31±0.16	0.70±0.11	<0.001
BHI	0.92±0.63	0.93±0.38	0.97

BHI: Breath holding Index, MCA: Middle cerebral artery, PI: Pulsatility index, TA: Takayasu arteritis, Vmean: Mean flow rates

Table 4. Comparison of measurements results between the occluded parent artery side and non-occluded parent artery side in the TA group [O (+) vs. O (-)]

	O (+)	O (-)	p
Number of measurements	11	17	-
PSV (cm/s)	52.3±21.5	63.2±22.8	0.14
EDV (cm/s)	41.6±17.3	44±14.5	0.63
MCA Vmean (cm/s)	45.2±18.6	50.4±16.6	0.43
MCA PI	0.23±0.09	0.36±0.18	0.08
BHI	1.2±0.7	0.85±0.5	0.26

EDV: End-diastolic velocity, BHI: Breath holding index, PI: Pulsatility index, PSV: Peak systolic velocity, MCA: Middle cerebral artery, Vmean: Mean flow rates

Discussion

In the literature, “pulseless spectrum” ipsilateral with extracranial pathology, decreased flow velocity and PI, microembolic signal, and collateral flow reorganization were described in TCD examinations in patients with TA (10), and in our series, “pulseless spectrum”, decreased flow velocity, and decreased PI were found, in accordance with the literature.

When evaluated in terms of treatment, it has been shown that the “pulseless” condition can disappear in half of all patients with TA after steroid treatment (6). In patients with TA, stabilization or reduction in vessel wall thickness and diameter can be demonstrated in carotid Doppler examinations after treatment with immunosuppressive agents such as azathioprine and mycophenolate mofetil (11). In addition, flow velocity and PI normalizations in TCD in patients with TA after surgical treatment of large vessels were described at the case report level (5,7,8).

It is striking that there are not many studies in the literature regarding sVMR in patients with TA. When the literature is reviewed in this respect, case reports are showing decreased cVMR after acetazolamide administration in patients with TA (with and without neurologic involvement) (5,12,13). No study or case report evaluating cVMR with BHT in patients with TA could be identified.

Although both are manifestations of large vessel involvement, cerebral hemodynamics in the course of TA do not follow the pattern observed in large vessel atherosclerosis. In patients with an increased degree of atherosclerotic carotid artery stenosis, cVMR evaluated by triggering hypercapnia (5% CO₂) was found to be lower than in patients with atherosclerotic carotid artery disease without stenosis (14). In another study, significantly lower cVMR and BHI values were found in patients with >70% atherosclerotic carotid stenosis than in patients with 50-69% stenosis, regardless of whether they were symptomatic (15). When the stenosis worsened and became occlusive, the CO₂-induced cVMR and dynamic cerebral autoregulatory measurements were found to be lower than the non-occluded hemispheric measurements (16). In light of these data, it can be concluded that in patients with stable TA under treatment, at least in the middle range after treatment, sVMR is normal or normalized, despite the persistence of parent large artery pathology.

Conclusion

In our study, cVMR was evaluated using the BHT in six clinically stable patients with TA with neurologic involvement, who were not surgically treated, and who were receiving immunosuppressive or biologic agents, and the relevant values were not found to be different from healthy controls. This appears to be secondary to the preservation of cerebral microcirculation in patients with TA due to the effect of treatment or regardless of treatment, possibly in contrast to atherosclerotic cervicocerebral artery occlusions.

The main limitation of our study was the small number of patients examined. The reason for this was that it was limited only to the requests made by the physicians of the patients to evaluate the risk of stroke. It was thought that it would be appropriate to report this as a pre-study considering the presence of very similar changes in all patients and the importance of these changes on drug selection. There is a need for large-scale and preferably multi-center studies that will show the temporal course of cerebral hemodynamic changes in TA starting from the earliest period and in long-term follow-up, and investigate the effect of the treatments on cVMR.

Ethics

Ethics Committee Approval: Hacettepe University Ethics Committee (project no: 20/903, decision no: 2020/16-24).

Informed Consent: Informed consent was waived due to retrospective nature of study in Takayasu patients, while informed consent was obtained in control group.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Y.P., E.M.A., M.A.T., Concept: Ö.K., E.M.A., M.A.T., Design: Ö.K., E.M.A., M.A.T., Data Collection or Processing: M.Y.P., S.R., E.Ç.B., F.K., Analysis or Interpretation: M.Y.P., E.M.A., M.A.T., Literature Search: M.Y.P., E.K., E.M.A., M.A.T., Writing: M.Y.P., E.M.A., M.A.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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