

# An Assessment of Flow-Mediated Dilatation in Behçet's Disease

## Behçet Hastalığında Akım Aracılı Dilatasyonun Değerlendirilmesi

Ruken YÜKSEKKAYA,<sup>1</sup> Fatih ÇELİKAY,<sup>1</sup> Fatih KOÇ,<sup>2</sup> Çağlar DENİZ,<sup>1</sup> Erkan GÖKÇE,<sup>1</sup>

Mehmet Murat FIRAT,<sup>1</sup> Jale YÜKSEK<sup>3</sup>

<sup>1</sup>Department of Radiology, Medical Faculty of Gaziosmanpaşa University, Tokat, Turkey;

<sup>2</sup>Department of Cardiology, Medical Faculty of Gaziosmanpaşa University, Tokat, Turkey;

<sup>3</sup>Department of Dermatology, Medical Faculty of Gaziosmanpaşa University, Tokat, Turkey

**Objectives:** This study aims to evaluate the early development of atherosclerosis in patients with Behçet's disease (BD) using flow-mediated dilatation (FMD) method under Doppler ultrasonography (US).

**Patients and methods:** Thirty patients with BD and 25 healthy volunteers were included. Doppler US was used to measure the basal and post-reactive hyperemic diameters, peak systolic velocities, resistivity indices, and blood flow volumes of the brachial arteries. Flow-mediated dilatation was defined as the percentage of difference between the post-reactive hyperemic and basal diameters.

**Results:** The mean FMD value of the BD group (10.8±12.7%) was significantly lower compared to the control group (26±18.6%). No statistically significant difference in other parameters was found between the groups.

**Conclusion:** Flow-mediated dilatation under Doppler US is simple and effective non-invasive method for predicting the early development of atherosclerosis in patients with BD.

**Key words:** Behçet's disease; Doppler ultrasonography; flow-mediated dilatation.

**Amaç:** Bu çalışmada Behçet hastasında erken ateroskleroz gelişimi, Doppler ultrasonografisi (US) eşliğinde girişimsel olmayan akım aracılı dilatasyon (FMD) yöntemi ile değerlendirildi.

**Hastalar ve yöntemler:** Otuz Behçet hastası ve 25 sağlıklı gönüllü çalışmaya dahil edildi. Brakiyal arterde bazal ve reaktif hiperemi sonrası arter çapları, akım hızları, rezistivite indeksleri ve akım miktarlarını göstermek amacıyla Doppler US kullanıldı. Akım aracılı dilatasyon, bazal ve reaktif hiperemi sonrası ölçülen brakiyal arter çapları farkının yüzdesi olarak tanımlandı.

**Bulgular:** Behçet hastalığı grubunda ortalama FMD değeri (%10.8±12.7) kontrol grubundan (%26±18.6), anlamlı derecede düşük bulundu. Diğer parametreler açısından gruplar arasında istatistiksel anlamlı farklılık bulunamadı.

**Sonuç:** Behçet hastalarında erken ateroskleroz gelişimini göstermek amacıyla Doppler US eşliğinde FMD değerlendirilmesi basit ve girişimsel olmayan etkili bir yöntemdir.

**Anahtar sözcükler:** Behçet hastalığı; Doppler ultrasonografisi; akım aracılı dilatasyon.

Behçet's disease (BD) is a multisystem, inflammatory vasculitic disorder, characterized by oral and genital ulcers, ocular and mucocutaneous lesions, gastrointestinal and central nervous system lesions, and arthritis. In addition, vascular lesions

have been reported in about 25% of the patients. This disease affects arteries and veins of all sizes. The types of vascular involvement include superficial thrombophlebitis, deep venous and arterial thrombosis, and arterial aneurysm formation.<sup>[1,2]</sup>

**Received:** November 22, 2011 **Accepted:** April 13, 2012

**Correspondence:** Ruken Yüksekaya, M.D. Gaziosmanpaşa Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, 60030 Tokat, Turkey.  
Tel: +90 356 - 212 95 00 / 1273 e-mail: rukenyuksekkaya@yahoo.com

Presented at the 31<sup>st</sup> National Congress of Radiology, November 7-12, 2010, Antalya, Turkey.

©2012 Turkish League Against Rheumatism. All rights reserved.

Systemic inflammatory rheumatic diseases are associated with an increased risk of cardiovascular diseases.<sup>[3-6]</sup> Atherosclerosis is widely accepted as a low-grade chronic inflammatory disorder,<sup>[3,7]</sup> and previous studies have reported a predisposition to its development in BD.<sup>[8-10]</sup> By the time clinical findings of atherosclerosis appear, the disease is at an advanced stage, and treatment is palliative.<sup>[11]</sup> Endothelial cell dysfunction (ECD) is an important marker of atherosclerosis, and it also plays an important role in the development of vascular involvement in BD.<sup>[12,13]</sup> When systemic involvement of atherosclerosis is considered, the assessment of the peripheral arteries using a non-invasive method such as flow-mediated dilatation (FMD) provides accurate information, and this method is now used for the evaluation of ECD of the brachial artery with Doppler ultrasonography (US).

We aimed to report the results of FMD assessed by Doppler US in patients with BD, which could prove to be helpful in predicting atherosclerosis.

## PATIENTS AND METHODS

The study group consisted of 30 patients with BD who were monitored at the Departments of the Dermatology and Urology at Gaziosmapasa University Hospital. The patients had been diagnosed with BD at our clinics and other hospitals. All of the patients fulfilled the criteria of the International Study Group for BD.<sup>[14]</sup> The control group included 25 healthy volunteers who were recruited from the hospital staff. Atherosclerotic risk factors including hypertension, hypercholesterolemia, smoking, diabetes mellitus (DM), and relevant family history were recorded. In the study group, patients were questioned regarding the clinical characteristics, duration of illness, and medical treatments received at the time of the examination and during the previous month (Table 1). Patients with BD were divided into two subgroups according to the median duration of the disease and disease activity state (active and inactive). At the time of examination, patients were included in the active group if they had at least two of the following clinical criteria: oral ulcers, genital ulcers, ocular involvement, arthralgia, or vascular complications.<sup>[15]</sup>

The local ethics committee of our hospital approved the study, and all participants gave their written informed consent prior to the investigation.

Each participant's blood pressure was measured with a mercury sphygmomanometer, the heights and weights were recorded, and the body mass index (BMI) values were calculated. The data concerning

the most recent blood total cholesterol, high- (HDL), and low-density (LDL) lipoprotein cholesterol levels, and triglyceride measurements were retrieved from the hospital files.

The mean FMDs of the brachial artery of both groups were assessed by a non-invasive method previously used by Brinkworth and et al.<sup>[16]</sup> in their study. Doppler US examinations were performed with a 10 MHz linear array transducer and a Logiq 9 US system (GE Medical Systems, Milwaukee, Wisconsin, USA). The measurements were taken in the morning after a fasting period of between eight and 12 hours. Afterwards, the patients took a rest in a supine position for 20 minutes in a quiet and temperature controlled (22-23°C) room where they were not allowed to smoke or use alcohol or caffeine. Then the basal systolic blood pressures of the groups were measured, and the parameters of the brachial artery were assessed from the left forearm 3-4 cm above the antecubital fossa while the patients were still in the supine position. Both the anterior and posterior walls of the brachial arteries were observed, and the basal diameters, peak systolic velocities, resistivity indices, and blood flow volumes of the brachial arteries were measured. In order to induce stagnation of blood flow within the brachial artery and subsequent ischemia, the sphygmomanometer was inflated to a systolic pressure of 250 mmHg for five minutes. Finally, the cuff was rapidly deflated to induce a reactive hyperemia, and the above-mentioned values were recorded within one minute. All measurements were taken from the greatest diameter of the brachial artery. The FMD was determined as the percentage difference between the post-reactive hyperemic and basal diameters of the brachial artery. It is calculated by using following equation:

$$\text{FMD} = \left[ \frac{\text{diameter after reactive hyperemia} - \text{basal diameter}}{\text{basal diameter}} \right] \times 100$$

The mean systolic and diastolic blood pressures, BMI, and blood total cholesterol as well as the HDL and LDL cholesterol levels, triglyceride measurements, and FMD values were compared between the two groups. The mean FMD values were also compared between the subgroups of the patients with BD with the median duration of illness and disease activity state (active and inactive) taken into consideration.

Continuous data was expressed as the mean  $\pm$  standard deviation (SD), and categorical data was given as numbers with related percentages (n, %). Differences in continuous data were analyzed using

**Table 1.** Clinical characteristics, family history of Behçet's disease, duration of illness and history of medical treatment at the time of the Doppler examination in patients with Behçet's disease

Patient number	Oral ulcers	Genital ulcers	Artralgia	Skin lesions	Ocular involvement	Vascular complications	Family story of BD	Duration of BD	Story of medical treatment
1	+	+	+					15	+
2	+			+				1	+
3	+	+	+	+				6	+
4	+	+	+	+				13	+
5	+	+						1	+
6	+	+	+					4	+
7	+	+	+				+	2	+
8	+				+			3	+
9	+		+	+			+	4	+
10	+		+					12	+
11	+	+	+					10	+
12	+		+					15	+
13	+		+					30	+
14	+	+		+				2	+
15								3	+
16	+		+	+	+			8	+
17	+	+	+	+	+			12	+
18	+		+	+				8	+
19	+	+	+	+				4	+
20			+					4	+
21	+		+					4	+
22	+		+		+	+		27	+
23	+	+		+				1	+
24	+	+	+	+		+		8	+
25	+	+	+	+				21	+
26	+							20	+
27	+		+	+	+			2	+
28								8	+
29	+	+	+	+				3	+
30	+	+		+	+			7	+

BD: Behçet's disease.

Student's t-test, and a chi-square test was used to compare categorical data. A two-tailed p-value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS version 11.0 software program (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

The control subjects and patients with BD were comparable in terms of age ( $35\pm 10$  versus  $38\pm 11$ , respectively;  $p=0.35$ ) and gender (15 males and 10 females versus 16 males, and 14 females, respectively;  $p=0.785$ ). No statistical differences were seen in the atherosclerotic risk factors between the two groups (Table 2).

All patients were under medical treatment at the time of the Doppler US examination (Table 1). The mean

duration of illness in the BD group was  $8.6\pm 7.7$  years. The groups demonstrated no statistically significant differences in terms of blood pressure, BMI values, blood total cholesterol, HDL and LDL cholesterol levels, or triglyceride measurements (Table 3). Twenty-five patients with BD were in the active subgroup (15 males, 10 females; mean age  $39\pm 12$  years; range 15 to 59 years), and five patients were in the inactive subgroup (1 male, 4 females; mean age  $35\pm 7$  years; range 23 to 43 years). The mean FMD value of the BD group ( $10.8\pm 12.7\%$ ) was lower than the control group ( $26\pm 18.6\%$ ), which was statistically significant ( $p=0.01$ ). The other measurements did not differ between the both groups (Table 4). There was also no statistical difference in the FMD values between the subgroups of BD patients with respect to the duration of the illness. The FMD values of the active and inactive

**Table 2.** Demographic and baseline characteristics of the study groups

	Behçet's disease (n=30)			Control (n=25)			p
	n	%	Mean±SD	n	%	Mean±SD	
Gender							
Male	16			15			0.785
Female	14			10			
Age (years)			38±11			35±10	0.35
Hypertension	2	7		0	0		0.495
Diabetes mellitus	1	3		0	0		1
Hyperlipidemia	1	3		0	0		1
Family medical history	4	13		0	0		0.117
Smoker	9	24		6	30		0.764

SD: Standard deviation.

BD subgroups were  $10.83\pm 12.62\%$  and  $10.85\pm 14.90\%$ , respectively.

## DISCUSSION

There are known associations between atherosclerosis and chronic inflammatory diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).<sup>[3-6,17-19]</sup> Previous studies have reported a predisposition toward the development of atherosclerosis in BD,<sup>[8-10]</sup> and in these disease states, hardening of the arteries generally occurs at a younger age.<sup>[3-6]</sup>

Many changes occur in the arterial wall before the clinical findings of atherosclerotic diseases become evident. In the early subclinical stages, intima media thickness (IMT) and ECD are important markers of atherosclerosis.<sup>[20]</sup> Endothelial cell dysfunction is widely accepted as an initial lesion in atherogenesis<sup>[4]</sup> and can be reversed with effective treatment.<sup>[11]</sup> It is known that cardiovascular risk factors such as smoking, hypertension, hyperlipidemia, DM, and obesity can cause ECD before the clinical findings of atherosclerosis are manifested.<sup>[11]</sup> Many authors have proven that inflammation is also an independent

risk factor for this disease.<sup>[3-7,17-19]</sup> Indeed, ECD can be demonstrated in more than one vascular bed, and this is related to focal inflammation. Suppression of the immune inflammatory process may result in the reversal of ECD.<sup>[4]</sup> Flow-mediated dilatation is a non-invasive method used for the evaluation of ECD of the brachial artery with Doppler US.

In the literature, ECD in BD has been investigated by IMT, arterial distensibility, arterial stiffness, peak systolic and end-diastolic velocities, and FMD.<sup>[8-10,21-26]</sup> Increased values of IMT with BD have been reported in some studies.<sup>[7-9]</sup> Alan et al.<sup>[8]</sup> also proved the existence of decreased arterial distensibility in BD, and Rhee et al.<sup>[22]</sup> detected increased arterial stiffness in BD. Akçar et al.<sup>[26]</sup> reported lower peak systolic and end-diastolic flow velocities throughout internal carotid artery. Oflaz et al.,<sup>[9]</sup> Chambers et al.,<sup>[21]</sup> and Ulusoy et al.<sup>[25]</sup> detected a decrease in the FMD values in BD.

This study revealed that FMD values decreased in BD when compared with age- and gender-matched healthy controls. The FMD values predict atherosclerosis in the subclinical period of BD. The patient and the control groups were comparable regarding gender, age, blood

**Table 3.** Baseline measurements of the study groups

	Behçet's disease (n=30)	Control (n=25)	p
	Mean±SD	Mean±SD	
Body mass index (kg/m <sup>2</sup> )	26.42±4.69	24.67±4.55	0.2
Systolic blood pressure (mmHg)	118.3±11.90	114.5±12.34	0.288
Diastolic blood pressure (mmHg)	76.38±7.43	74.25±6.74	0.311
Total cholesterol (mg/dl)	187.75±47.95	165.87±46.62	0.169
HDL cholesterol (mg/dl)	46.95±12.51	43.27±10.69	0.362
LDL cholesterol (mg/dl)	124.76±49.15	99±41.30	0.107
Triglycerides (mg/dl)	139.63±96.71	146.20±81.51	0.821

SD: Standard deviation; HDL: High density lipoprotein; LDL: Low density lipoprotein.

**Table 4.** Basal and postreactive hiperemic brachial artery measurements in study groups

	Behçet's disease (n=30)	Control (n=25)	p
	Mean±SD	Mean±SD	
Basal diameter	4.1±0.7	3.7±0.6	0.081
Basal flow value (ml/min)	89.4±49.5	73.1±41.9	0.199
Basal peak systolic velocity (cm/sec)	97.1±19.7	87.6±19.4	0.373
Basal resistivity index	0.9±0.8	0.9±0.7	0.781
Postreactive hiperemic diameter (cm)	4.4±0.6	4.6±0.6	0.275
Postreactive hiperemic blood flow amount (ml/min)	245.5±150.4	237±131.9	0.827
Postreactive hiperemic peak systolic velocity (cm/sec)	119.1±41.4	108.1±33.9	0.289
Postreactive hiperemic resistivity index	1.03±1.3	0.79±0.1	0.369
Flow-mediated dilatation (%)	10.8±12.7	26±18.6	0.01

SD: Standard deviation.

pressure, lipid profile, family medical history, and smoking status. Therefore, our findings of decreased FMD values cannot be associated with traditional atherosclerotic risk factors and can be attributed to the inflammatory nature of BD.

Oflaz et al.<sup>[9]</sup> reported decreased FMD values in BD compared with healthy individuals in a study consisting of 50 BD patients. The mean FMD values that they found were 10.41±3.85% in BD patients and 14.41±3.39% in the healthy control group. They also compared the FMD values of BD patients with and without vascular involvement and definitively found more prominent ECD in patients with vascular involvement. Ulusoy et al.<sup>[25]</sup> reported decreased FMD values in 28 BD patients. The FMD values in the BD and the control groups were 15.7±2.4% and 21.4±6.4%, respectively. The mean FMD value in our BD group (10.8±12.7%) was also similar to those obtained in the previously mentioned studies. However, our mean FMD value (26±18.6%) in the control group was higher when compared with the referenced control groups. In a study performed by Chambers et al.<sup>[21]</sup> with 19 BD patients and 21 healthy controls, the mean FMD values were quite different (0.7±0.9% in the patient group and 5.7±0.9% in the control group) from those cited in the literature. Ulusoy et al.<sup>[25]</sup> enrolled the youngest and Chambers et al.<sup>[21]</sup> the oldest groups of patients in their studies. Unlike our study with an almost balanced male/female ratio (53/47%), the study groups of Oflaz et al.<sup>[9]</sup> and Ulusoy et al.<sup>[25]</sup> consisted mainly of male participants (82% and 86%, respectively).

We found no correlation between the duration of the illness and FMD values. This condition might be explained by the fact that all patients were undergoing medical treatment at the time of the Doppler US examination.

In conclusion, measuring the brachial artery FMD with Doppler US is a simple and noninvasive method for the prediction of the early development of atherosclerosis in patients with BD. Using this noninvasive method, cardiovascular problems may be predicted and preventive measures can be taken earlier in the subclinical stage of the disease.

#### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

#### Funding

The authors received no financial support for the research and/or authorship of this article.

#### REFERENCES

1. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. *N Engl J Med* 1999;341:1284-91.
2. Koç Y, Güllü I, Akpek G, Akpolat T, Kansu E, Kiraz S, et al. Vascular involvement in Behçet's disease. *J Rheumatol* 1992;19:402-10.
3. Bacon PA, Stevens RJ, Carruthers DM, Young SP, Kitas GD. Accelerated atherogenesis in autoimmune rheumatic diseases. *Autoimmun Rev* 2002;1:338-47.
4. Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. *J Rheumatol* 1997;24:445-51.
5. Mutru O, Laakso M, Isomäki H, Koota K. Ten year mortality and causes of death in patients with rheumatoid arthritis. *Br Med J (Clin Res Ed)* 1985;290:1797-9.
6. Kitas GD, Banks MJ, Bacon PA. Accelerated atherosclerosis as a cause of cardiovascular death in RA. *Pathogenesis* 1998;1:78-83.
7. Oztürk MA, Oktar SO, Unverdi S, Ureten K, Göker B, Haznedaroglu S, et al. Morphologic evidence of subclinical atherosclerosis obtained by carotid ultrasonography in patients with Behçet's disease. *Rheumatol Int* 2006;26:867-72.

8. Alan S, Ulgen MS, Akdeniz S, Alan B, Toprak N. Intima-media thickness and arterial distensibility in Behçet's disease. *Angiology* 2004;55:413-9.
9. Oflaz H, Mercanoglu F, Karaman O, Kamali S, Erer B, Gencellac H, et al. Impaired endothelium-dependent flow-mediated dilation in Behçet's disease: more prominent endothelial dysfunction in patients with vascular involvement. *Int J Clin Pract* 2005;59:777-81.
10. Keser G, Aksu K, Tamsel S, Ozmen M, Kitapcioglu G, Kabaroğlu C, et al. Increased thickness of the carotid artery intima-media assessed by ultrasonography in Behçet's disease. *Clin Exp Rheumatol* 2005;23:S71-6.
11. Korkmaz H, Onalan O. Evaluation of endothelial dysfunction: flow-mediated dilation. *Endothelium* 2008;15:157-63.
12. Hampton KK, Chamberlain MA, Menon DK, Davies JA. Coagulation and fibrinolytic activity in Behçet's disease. *Thromb Haemost* 1991;66:292-4.
13. Haznedaroglu IC, Ozcebe OI, Ozdemir O, Celik I, Dündar SV, Kirazli S. Impaired haemostatic kinetics and endothelial function in Behçet's disease. *J Intern Med* 1996;240:181-7.
14. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990;335:1078-80.
15. Atasoy M, Karatay S, Yildirim K, Kadi M, Erdem T, Senel K. The relationship between serum prolactin levels and disease activity in patients with Behçet's disease. *Cell Biochem Funct* 2006;24:353-6.
16. Brinkworth GD, Noakes M, Moran LJ, Norman R, Clifton PM. Flow-mediated dilatation in overweight and obese women with polycystic ovary syndrome. *BJOG* 2006;113:1308-14.
17. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. *Am J Med* 2008;121:S9-14.
18. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol* 1997;145:408-15.
19. Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum*. 1999;42:338-46.
20. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;316:1371-5.
21. Chambers JC, Haskard DO, Kooner JS. Vascular endothelial function and oxidative stress mechanisms in patients with Behçet's syndrome. *J Am Coll Cardiol* 2001;37:517-20.
22. Rhee MY, Chang HK, Kim SK. Intima-media thickness and arterial stiffness of carotid artery in Korean patients with Behçet's disease. *J Korean Med Sci* 2007;22:387-92.
23. Seyahi E, Ugurlu S, Cumali R, Balci H, Ozdemir O, Melikoglu M, et al. Atherosclerosis in Behçet's Syndrome. *Semin Arthritis Rheum* 2008;38:1-12.
24. Kürüm T, Yildiz M, Soy M, Ozbay G, Alimgil L, Tüzün B. Arterial distensibility as determined by carotid-femoral pulse wave velocity in patients with Behçet's disease. *Clin Rheumatol* 2005;24:134-8.
25. Ulusoy RE, Karabudak O, Kilicaslan F, Kirilmaz A, Us MH, Cebeci BS. Noninvasive assessment of impaired endothelial dysfunction in mucocutaneous Behçet's disease. *Rheumatol Int* 2008;28:617-21. Epub 2007.
26. Akçar N, Göktekin F, Ozer A, Korkmaz C. Doppler sonography of ocular and carotid arteries in Behçet patients. *J Clin Ultrasound* 2010;38:486-92.