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Increased Arterial Stiffness in Behcet's Disease Patients

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ABSTRACT

Background and Objectives : Pulse wave velocity (PWV) is an ideal indicator of arterial stiffness. This study investigated arterial stiffness of different vascular regions in patients suffering with Behcet's disease (BD), and we assessed whether arterial stiffness was affected by the clinical parameters of BD. **Subjects and Methods :** This study included 53 BD patients (mean age: 38±8 years) and 65 healthy controls (mean age: 38±8 years) who were without any known cardiovascular diseases. After recording the clinical parameters of the BD patients, pulse wave velocity was measured with an automated device in the heart-femoral, heart-carotid, heart-brachial and femoral-ankle segments. **Results :** Patients with BD had significantly higher PWV values than did the controls in all the regional arterial segments. The PWV values were not correlated with the duration of the disease, corticosteroid use or the presence of active disease at the time of examination. The clinical variables related to severe BD manifestations, which included severe disease, male gender, vascular lesions or immunosuppressant use, were partly associated with increased PWV on the univariate analysis, but any statistical significance for these clinical variables was lost in all the regional arterial segments on multivariate analysis. In addition, multivariate regression analysis revealed that age and the mean arterial pressure were independently associated with increased PWV in most regional arterial segments for BD patients. **Conclusion :** The patients with BD had significantly increased arterial stiffness in all the regional arterial segments when compared with the healthy controls. Longitudinal studies that employ a large population are required to determine the pathophysiologic and prognostic implications of increased arterial stiffness in BD. **(Korean Circulation J 2006;36:676-682)**

KEY WORDS : Behcet's disease ; Arteries.

Introduction

Behcet's disease (BD) is a chronic inflammatory disorder that involves multiple organs. Although the exact pathogenesis for BD is not completely understood, it has been suggested that the disease is triggered in genetically susceptible individuals by environmental factors such as infectious agents. The histological hallmark of the disease is noted to be a vasculitis. A variety of vascular lesions, including venous or arterial occlusive lesions and arterial aneurysm, can occur in approximately one-third of BD patients. These venous and arterial lesions can be infiltrated by different types of inflammatory cells, including lymphocytes, monocytes, plasma cells and neutrophils.[1-3] In general, those BD patients with major vessel disease exhibit a poor prognosis.[4]

Although the definite pathogenic mechanism for the vascular lesions in BD remains unclear, endothelial dysfunction is thought to play an important role in the development of these lesions.[5][6] It has been recently demonstrated that brachial artery flow-mediated dilatation is impaired in BD.[6] Because flow-mediated dilataion is endothelium-dependent and it is largely controlled by the release of endothelial nitric oxide (NO),[7] an impairment of endothelium-dependent flow-mediated dilatation suggests that there is decreased endothelial NO activity. This lack of activity may contribute to the vascular lesions that are often seen in BD. Furthermore, endothelial NO has been found to directly regulate large artery stiffness in vivo.[8] We and other investigators have shown that potentially functional

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DNA polymorphism in the endothelial NO synthetase gene, which could cause reduced NO activity, may be associated with susceptibility to BD.[9)10)]

Arterial stiffness is a reliable and strong independent predictor of subsequent cardiovascular events and mortality, and it may be closely related to the process of atherosclerosis.[11-14)] Since stiffened arteries transmit pulse waves faster than do the more elastic blood vessels, pulse wave velocity (PWV) is an ideal indicator of arterial stiffness. In addition, arterial abnormalities may be attributed to functional changes like endothelial dysfunction and also structural alterations such as atherosclerosis.[15)16)] Acute systemic inflammation and chronic systemic vasculitis are noted to be associated with endothelial dysfunction.[17)18)] Moreover, inflammation is known to be an important risk factor for future cardiovascular events.[19)] These findings have led to the hypothesis that the acute and chronic inflammatory processes associated with BD may cause endothelial dysfunction. This can then lead to subsequent vascular damage and the increased arterial stiffness that are closely related to the clinical course of BD patients. However, any information has been rather limited regarding arterial stiffness in BD. Thus, this study investigated the arterial stiffness of different arterial regions in Korean BD patients, and we then assessed whether arterial stiffness was affected by the clinical parameters of BD.

Subjects and Methods

Subjects

This study included 53 BD patients who fulfilled the International Study Group (ISG) criteria,[20)] and 65 healthy controls who were matched to the BD patients for their age, gender, blood pressure, heart rate, height, cholesterol and glucose levels. The frequency of smokers, if any, was also taken into account. Those subjects who had hypertension, diabetes mellitus or a previous history of coronary artery disease or myocardial infarction were excluded.

At the time of examination, the presence of more than two of the following Behcet's clinical features was considered as active disease: oral ulceration, genital ulceration, skin lesions, ocular lesions, active major vessel disease and active major organ involvement, including active gastrointestinal or neurological lesions. During the course of the disease, the presence of one or more of the following clinical features was regarded as severe disease:[9)] posterior uveitis or retinal vasculitis, gastrointestinal ulcerations with bleeding or perforation, major organ involvement and major vessel involvement. In addition, those BD patients with venous or arterial occlusive diseases or arterial aneurysm were considered to have vascular lesions, but those patients with superficial thrombophlebitis were not considered to have vascular lesions. The duration of the disease in the BD group was calculated from the time when the patients fulfilled the ISG criteria to the time of their examinations. The mean of this time period was 4.7 ± 4.8 years.

Patient information was obtained on any corticosteroids treatment and immunosuppressants use for the three months before the start of this study. Using standard laboratory methods, the levels of total cholesterol, triglyceride and glucose were measured from the fasting blood samples that were taken from all the subjects. The study was approved by the Hospital Ethics Committee. An informed, written consent was obtained from each subject.

Measurements of PWV

PWV was measured in the morning with the patient in a supine position after 15 minutes of bed rest in a quite room, following 12-hour abstinence from smoking, alcohol and coffee consumption. A single trained observer performed all the measurements. PWV measurements were taken using an automated device (VP-2000, Colin Co. Ltd., Japan).[21)] This device simultaneously records the PWV, the brachial and tibial arterial blood pressures, and the ECG and heart sounds. In brief, ECG electrodes were placed on both wrists, and a heart sound microphone was placed on the left sternal border. Occlusion cuffs, which were connected to both plethysmographic and oscillometric sensors, were wrapped around both upper arms and the ankles. The brachial and tibial arterial blood pressures were measured simultaneously. The brachial and tibial arterial pulse waves were acquired using oscillometric sensors. The carotid and femoral arterial waves were acquired using tonometric sensors that were placed at the left carotid artery and the left femoral artery.

The heart-carotid pulse transit time was measured from the second heart sound to the notch of the carotid pulse wave. The heart-brachial pulse transit time was taken from the second heart sound to the notch of the brachial pulse waves. The heart-femoral pulse transit time (from the aortic orifice to the femoral artery) was calculated by summing the carotid-femoral pulse transit time and the heart-carotid pulse transit time. The femoral-ankle pulse transit time was measured by the foot-to-foot method, from the foot of the femoral arterial pulse waves to the tibial arterial pulse waves. Path lengths of the heart-femoral, heart-carotid, heart-brachial and femoral-ankle segments were calculated automatically with using the patient's height. The heart-femoral (hfPWV), heart-carotid (hcPWV), femoral-ankle (faPWV), and heart-brachial (hbPWV) PWV levels were calculated for each arterial segment by dividing the path lengths by the corresponding pulse transit times, and they were expressed as m/sec.

Statistical analysis

The data were analyzed using the SPSS statistical package program version 11.5 for Windows (SPSS Inc., Chicago, IL, USA). Differences of the continuous variables between groups were compared using independent t tests, and the results we obtained were re-evaluated using multiple regression analysis to exclude the confounding effects of the clinical variables of BD and also for excluding the confounding effects of the other risk factors on the PWV values. The bivariate correlations between two continuous variables were evaluated using Pearson's correlation coefficient when indicated. P less than 0.05 were considered to be statistically significant.

Results

Table 1 summarizes the clinical features of the 53 BD patients. Major vascular lesions were detected in nine patients: inferior vena cava occlusion was found in three patients, superior vena cava occlusion was found in one patient, deep vein thrombosis at the lower extremities was found in three patients, cavernous sinus thrombosis was found in one patient and femoral arterial aneurysm was found in one patient. Immunosuppressive agents and corticosteroids were used by 15 (azathioprine in 10 and cyclosporine in 5) and 38 patients, respectively. No differences between the BD patients and the controls were found in terms of age, the gender ratio and the other parameters that are known to affect the PWV, including height, blood pressure, heart rate and the total cholesterol levels. The BD patients had significantly higher PWV values did the controls in all the regional arterial segments, including the heart-femoral, heart-carotid, heart-brachial and femoral-ankle segments (Table 2).

Table 3 shows the relationship between the PWV values and the clinical parameters of BD in the different regions. Male BD patients exhibited a tendency towards elevated PWV values in all the four regions when compared to the female patients. However, significantly higher levels of PWV were observed in only the heart-femoral and femoral-ankle segments. It's interesting that the patients without genital ulcerations had a tendency to have higher PWV levels than did

Table 1. Clinical features of 53 patients with Behcet's disease

Clinical features	Number of patients (%)
Oral ulcerations	53 (100)
Genital ulcerations	32 (60.4)
Erythema nodosum-like lesions	21 (39.4)
Papulopustular lesions	44 (83.0)
Positive pathergy reaction	28 (52.8)
Ocular lesions	12 (22.6)
Intestinal lesions	6 (11.3)
Peripheral arthritis	14 (26.4)
Vascular lesions	9 (17.0)
Central nervous system lesions	2 (3.8)
Positive HLA-B51	22 (42.3)
Active disease	16 (30.2)
Severe disease	19 (35.8)
Immunosuppressant use	15 (28.3)
Corticosteroid use	38 (71.7)

Table 2. Comparisons of the demographic data, laboratory values and cardiovascular parameters between patients with Behcet's disease and the controls

Parameters	Behcet's group (n=53)	Controls (n=65)	p
Age (years)	38.1±8.1	38.2±8.0	NS
Men (% of total)	50.9	49.2	NS
Height (cm)	164.7±8.5	163.8±8.2	NS
Body mass index (kg/m^2)	22.1±2.9	22.7±2.7	NS
Systolic blood pressure (mmHg)	119.2±11.1	117.2±9.6	NS
Diastolic blood pressure (mmHg)	73.8±8.3	72.5±7.9	NS
Mean arterial pressure (mmHg)	90.9±9.0	88.4±8.1	NS
Pulse pressure (mmHg)	45.4±8.0	46.3±6.1	NS
Heart rate (bpm)	65.2±7.8	65.5±9.9	NS
Smoker (% of total)	15.1	13.8	NS
Serum glucose (mg/dL)	85.3±8.3	85.8±9.9	NS
Serum total cholesterol (mg/dL)	163. 4±31.7	171.1±22.1	NS
Serum triglyceride (mg/dL)	103.2±52.2	99.7±48.3	NS
Pulse wave velocity (m/s)			
Heart-femoral	7.9±1.1	7.2±0.6	<0.001
Heart-carotid	6.8±1.5	6.2±1.0	0.035
Heart-brachial	5.4±0.7	5.1±0.6	0.004
Femoral-ankle	10.4±1.3	10.0±0.9	0.034

Data are expressed as means±SD

the patients with genital ulcerations. Significantly higher levels were observed only in the femoral-ankle segment for the patients without genital ulcerations. In the case of the other clinical features of BD, no significant differences were found between the patients with and without the individual features of Behcet's disease, with the exception that the patients with vascular lesions had significantly higher PWV values in the heart-brachial segment than did the patients without vascular lesions. In addition, the PWV levels did

Table 3. Analysis of pulse wave velocity (mean±SD, m/s) in the four regions according to the clinical parameters of Behcet's disease

Variable	hfPWV	p	hcPWV	p	hbPWV	p	faPWV	p
Gender								
Male	8.3±1.0	0.009	7.0±1.6	0.359	5.4±0.7	0.063	10.9±1.3	0.003
Female	7.5±1.1		6.6±1.5		5.2±0.6		9.9±1.0	
Genital ulcerations								
Present	7.6±1.1	0.053	6.6±1.5	0.305	5.3±0.7	0.323	10.1±1.1	0.019
Absent	8.2±1.1		7.0±1.6		5.5±0.6		10.9±1.4	
EN-like lesions								
Present	7.7±1.2	0.531	7.0±1.3	0.455	5.4±0.5	0.772	10.2±1.1	0.372
Absent	7.9±1.1		6.6±1.7		5.4±0.7		10.6±1.4	
PPL								
Present	7.9±1.2	0.399	6.7±1.5	0.388	5.5±0.7	0.249	10.6±1.3	0.110
Absent	7.6±0.9		7.2±1.6		5.2±0.5		9.8±1.0	
Positive PR								
Present	7.9±1.3	0.598	6.9±1.6	0.664	5.4±0.7	0.697	10.7±1.3	0.121
Absent	7.8±1.0		6.7±1.5		5.4±0.6		10.1±1.2	
Ocular lesions								
Present	8.1±1.0	0.364	7.3±1.6	0.147	5.6±0.5	0.303	10.3±1.3	0.758
Absent	7.8±1.2		6.6±1.5		5.4±0.7		10.5±1.3	
Intestinal lesions								
Present	8.0±1.0	0.746	7.6±2.6	0.410	5.5±1.1	0.670	10.5±1.3	0.981
Absent	7.8±1.2		6.7±1.3		5.4±0.6		10.4±1.3	
Peripheral arthritis								
Present	7.8±1.1	0.707	6.4±1.0	0.311	5.4±0.4	0.948	10.2±1.4	0.436
Absent	7.9±1.1		6.9±1.7		5.4±0.7		10.5±1.2	
Vascular lesions								
Present	8.2±1.0	0.336	7.1±1.6	0.448	5.9±0.7	0.022	10.7±1.6	0.488
Absent	7.8±1.2		6.7±1.5		5.3±0.6		10.4±1.2	
Positive HLA-B51								
Present	7.9±0.8	0.798	6.8±1.5	0.768	5.3±0.5	0.334	10.6±1.0	0.496
Absent	7.8±1.3		6.7±1.6		5.5±0.7		10.3±1.5	
Active disease								
Present	8.2±1.3	0.198	7.4±1.9	0.078	5.6±0.7	0.174	10.8±1.4	0.195
Absent	7.7±1.0		6.5±1.3		5.3±0.6		10.3±1.2	
Severe disease								
Present	8.2±1.0	0.126	7.4±1.9	0.044	5.8±0.8	0.003	10.8±1.5	0.162
Absent	7.7±1.2		6.4±1.2		5.2±0.5		10.3±1.1	
Immunosuppressants								
Yes	8.5±1.0	0.016	7.3±1.4	0.157	5.8±0.4	0.008	10.8±1.3	0.154
No	7.6±1.1		6.6±1.6		5.3±0.7		10.3±1.3	
Corticosteroids								
Yes	7.8±1.1	0.774	6.9±1.6	0.430	5.5±0.6	0.207	10.6±1.3	0.105
No	7.9±1.2		6.5±1.3		5.2±0.8		10.0±1.3	

Data are expressed as means±SD. EN: erythema nodosum, PPL: papulopustular lesions, PR: pathergy reaction, hcPWV: heart-carotid pulse wave velocity, hbPWV: heart-brachial pulse wave velocity, hfPWV: heart-femoral pulse wave velocity, faPWV: femoral-ankle pulse wave velocity

not significantly differ between the patients with and without active disease at the time of examination. In contrast, the BD patients with severe disease or those BD patients who had been taking immunosuppressive agents showed a tendency towards increased PWV values in comparison with the patients without severe disease or those BD patients who had been taking immunosuppressants. Significant differences were observed in the heart-carotid and heart-brachial segments when severe disease was present; significant differences were also found in the heart-femoral and heart-brachial segments in the patients who had been exposed to immunosuppressive agents. The patients who had been treated with corticosteroids had similar PWV levels to the patients who had not received corticosteroids.

On the bivariate correlation analyses of BD patients with using Pearson's correlation coefficient, all the regional PWV levels except the femoral-ankle segment correlated well with increasing patient age. In particular, the degree of correlation was greater in the central arteries (hfPWV and hcPWV) than in the peripheral arteries (hbPWV and faPWV). The PWV values in all the regional arterial segments were positively correlated with the mean blood pressure. However, all the regional PWV values did not correlate with the duration of disease (Table 4). In addition, the regional PWV values did not correlate with height and the levels of cholesterol, glucose and triglyceride (data not shown).

Multiple regression analysis was used to adjust for any potential confounding influences of age, gender, the mean blood pressure, the duration of the disease and the clinical variables of BD. Only age and the mean blood pressure appeared to be significant factors associated with increased PWV in most of the regional arterial segments for the BD patients, except for the femoral-ankle segment in regards to age. In addition, the statistical significance was lost upon univariate analysis for some of the clinical variables associated with increased PWV in all the regional arterial segments (Table 5).

Table 4. Correlations between the regional PWV values and age, mean blood pressure and disease duration

	Age		Mean blood pressure		Disease duration	
	r	p	r	p	r	p
hfPWV	0.483	<0.001	0.472	<0.001	0.080	0.567
hcPWV	0.531	<0.001	0.547	<0.001	-0.065	0.646
hbPWV	0.423	0.002	0.560	<0.001	-0.069	0.622
faPWV	0.208	0.134	0.609	<0.001	-0.224	0.106

hcPWV: heart-carotid pulse wave velocity, hbPWV: heart-bra-chial pulse wave velocity, hfPWV: heart-femoral pulse wave velocity, faPWV: femoral-ankle pulse wave velocity

Table 5. Multiple regression analysis for the co-factors that affect regional PWV in Behcet's disease

		hfPWV	hcPWV	hbPWV	faPWV
Age	Beta	0.468	0.473	0.534	0.033
	p	0.007	0.004	0.001	0.833
Mean blood pressure	Beta	0.319	0.312	0.340	0.546
	p	0.041	0.033	0.017	<0.001
Gender	Beta	0.132	-0.083	-0.098	0.265
	p	0.386	0.552	0.473	0.069
Genital ulcerations	Beta	-0.055	0.046	0.119	0.076
	p	0.777	0.800	0.499	0.678
Vascular lesions	Beta	-0.095	-0.080	0.083	-0.318
	p	0.615	0.645	0.622	0.077
Severe disease	Beta	-0.072	0.222	0.190	0.478
	p	0.802	0.404	0.463	0.081
Immunosuppressant use	Beta	0.292	-0.076	0.080	0.107
	p	0.061	0.588	0.557	0.456

hcPWV: heart-carotid pulse wave velocity, hbPWV: heart-brachial pulse wave velocity, hfPWV: heart-femoral pulse wave velocity, faPWV: femoral-ankle pulse wave velocity

Discussion

Behcet's disease (BD) is a chronic inflammatory disorder that's characterized by recurrent oral and genital ulcerations, ocular lesions and skin lesions. Although the exact pathogenesis of this disease remains unclear, small vessel vasculitis accounts for a considerable portion of the pathogenic process in BD. In addition, large venous or arterial lesions can occur in up to one-third of BD patients.[1)3)] Although the precise pathogenic mechanism for the vascular lesions in BD remains murky at best, endothelial dysfunction is thought to play an central role in the development of these lesions.[5)6)] Acute systemic inflammation and chronic systemic vasculitis are also known to be associated with endothelial dysfunction.[17)18)] In the present study, we measured the regional PWVs of four arterial segments in BD patients and the healthy controls. The two groups were well matched for the factors known to affect arterial stiffness. The BD patients had significantly higher PWV values in all the four arterial regions than did the controls, indicating the presence of increased arterial stiffness in the patients with BD. Such increased arterial stiffness in the BD patients may be attributed to endothelial dysfunction and the acute or chronic inflammatory processes associated with BD.

Univariate analysis showed that the BD patients with severe disease or those BD patients that had taken immunosuppressive agents exhibited a tendency towards increased PWVs. In addition, the male BD patients, who are known to have a more severe disease course as compared to female patients,[4)] also had higher PWV levels than did the female patients. In the case of the patients with major vessel lesions, which are a severe manifestation of BD, significantly increased PWV values were found only in the heart-brachial segment. Any statistical significance for the cli-

nical parameters that were noted to be related to the severe BD manifestations, which included severe disease, immunosuppressives use, male gender and vascular lesions, was lost upon multiple regression analysis for all the regional arterial segments, so further studies with a larger number of patients are needed to elucidate the relationship between the regional PWV values and those clinical parameters of BD. On the other hand, similar to the well-known effects of age and mean blood pressure on PWV,[13)22)] we found on multiple regression analysis that age and the mean blood pressure were the independent significant factors associated with increased PWV in the BD patients. With respect to age, the effect on the PWV values in BD patients was greater in the central arteries than in the peripheral arteries.

The use of corticosteroid as a risk factor for cardiovascular disease is controversial.[23-26)] In the current study, the patients who had been treated with corticosteroids had PWV values that were similar to the patients who had not received these medications. This may be explained by the double-edged nature of corticosteroids, i.e., that while patients treated with corticosteroids usually have severe disease, and these drugs can reduce arterial wall inflammation. On the other hand, the fact that the PWV values did not correlate with the duration of the disease in the present study may reflect the previous observation that the overall activity and severity of BD tend to abate with time.[27)]

It has been noted that prolonged exposure to low levels of acute-phase reactants, including C-reactive protein and amyloid A protein, may be associated with subsequent vascular injury.[19)] However, C-reactive protein is not likely to be a suitable marker for disease activity in BD patients. In the current study, no difference in the PWV values was observed between the BD patients with and without active disease, outwity determined by the presence of active lesions at the time of examination. Since the disease activity usually fluctuates in BD patients during the course of the disease, only the presence of active lesions at a single point would not result in the increased PWV levels.

Information has been limited regarding the arterial stiffness in chronic inflammatory disorders that display systemic vasculitis, such as BD. Booth et al.[28)] reported that antineutrophil cytoplasmic antibody-associated systemic vasculitis is associated with increased arterial stiffness, and that the stiffness correlated with the degree of active inflammation. Kurum et al.[29)] described that the PWV levels in 14 BD patients did not significantly differ from the PWV levels in healthy controls. When compared with our study, their study population was small and they excluded subjects with active BD. More recently, Ikonomidis et al.[30)] reported that BD patients had an increased aortic diameter, lower mean aortic strain and distensibility, and also a higher mean aortic stiffness index on echocardiographic study. However, all these investigations, including our study, employed a cross-sectional study design; thus, causality can not be established.

In conclusion, the present study showed that BD patients have significantly increased central and peripheral arterial stiffness when compared with healthy controls. Age and the mean blood pressure were the independent significant factors associated with increased PWV. Longitudinal studies with a large subject population are required to determine the pathophysiologic and prognostic implications of increased arterial stiffness in BD.

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